Comparison of the Prognostic Value of Liver Biopsy and FIB-4 Index in Patients Coinfected With HIV and Hepatitis C Virus

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Background. We compared the prognostic value of liver biopsy (LB) and FIB-4 index in patients with human immunodeficiency virus (HIV)/hepatitis C virus (HCV) coinfection.

Methods. We studied patients from the Grupo de Estudio del SIDA 3603 study cohort, in whom fibrosis was evaluated at baseline using both LB (Metavir score) and FIB-4 index. We assessed overall death (OD) and liver-related events (LREs), defined as decompensation or hepatocellular carcinoma, whichever occurred first. We used receiver operating characteristic (ROC) curves to determine the ability of LB and FIB-4 to predict outcomes. We also assessed the association between advanced fibrosis—LB (F3 or greater) or FIB-4 (≥3.25)—and outcomes using multivariate Cox regression analysis.

Results. The study sample comprised 903 patients (328 with sustained virologic response [SVR]). Baseline fibrosis by LB was as follows: F0, n = 71; F1, n = 242; F2, n = 236; F3, n = 236; F4, n = 118. Fibrosis by FIB-4 was as follows: ≤1, n = 148; >1 to <3.25, n = 597; ≥3.25, n = 158. After a median follow-up of 62 months, there were 46 deaths and 71 LREs. The area under the ROC curves for OD/LREs was 0.648 and 0.742 for LB and FIB-4, respectively ($P = .006$). Similar results were found for patients without SVR and for OD and LREs separately. The adjusted hazard ratios of OD or LRE were 1.740 (95% confidence interval [CI], 1.119–2.7.06; $P = .014$) for advanced fibrosis assessed by LB and 3.896 (95% CI, 2.463–6.160; $P < .001$) assessed by FIB-4.

Conclusions. FIB-4 outperformed LB as a predictor of OD and LRE. These findings are of relevance for clinical practice and research and call into question the role of LB as a gold standard for assessing prognosis in HIV/HCV coinfection.

Keywords. HIV; hepatitis C; interferon; follow-up studies; treatment outcome.

In patients with chronic hepatitis C, liver biopsy has long been considered the standard procedure for staging liver fibrosis, assessing prognosis, and guiding treatment [1]. However, liver biopsy has significant

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limitations, including sampling errors, observer variation, and the risk of occasional but potentially severe complications [1, 2].

In the last few years, the role of liver biopsy for staging liver fibrosis in patients with chronic hepatitis C has been challenged by the development of noninvasive methods, including serum tests and measurement of liver stiffness. Serum tests involve determination of biochemical markers of the synthesis or degradation of fibrosis that are not readily available in clinical practice and tests that are derived from routine laboratory parameters, such as the patented FibroTest/FibroSure [3], the nonpatented Forns index [4], the aspartate aminotransferase (AST)–to-platelet ratio index (APRI) [5], and the FIB-4 index [6]. In patients with chronic hepatitis C with or without coinfection by human immunodeficiency virus (HIV), liver stiffness measured by transient elastography has proven very accurate for the diagnosis of advanced liver fibrosis and cirrhosis, and accurate for discriminating between patients with no/mild fibrosis and patients with significant fibrosis [7, 8].

Although noninvasive tests have been extensively studied for staging liver fibrosis in chronic hepatitis C, less is known about their prognostic value. Serum tests and transient elastography can be used to predict mortality and liver-related events (LREs) in patients with chronic hepatitis C [9, 10]. However, few studies have compared the prognostic value of noninvasive methods with that of liver biopsy [11–14]. Our aim was to compare the prognostic value of the FIB-4 index (cutoff values derived from patients included in the AIDS Pegasys Ribavirin International Coinfection Trial [6]) with that of liver biopsy in HIV/hepatitis C virus (HCV)–coinfected patients.

SUBJECTS AND METHODS

Design and Patient Selection

The patients in this study were selected from the cohort of the Grupo de Estudio del SIDA (AIDS Study Group [GESIDA]) of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (Spanish Society of Infectious Diseases and Clinical Microbiology [SEIMC]). This cohort was composed of patients who were both naive to anti-HCV therapy and had been treated with interferon and ribavirin. In 2003, it was decided to follow HIV/HCV–coinfected patients who started therapy with these drugs between January 2000 and January 2008 at 19 institutions in Spain [15–17]; all the centers included in the cohort were monitored to verify that all the information in the database was consistent with the patient's medical records. We selected patients whose liver fibrosis histological stage was known and for whom the data necessary to calculate the FIB-4 index were available before starting therapy with interferon plus ribavirin. The study cohort received the approval of the ethics committees of the participating centers for analysis of anonymized routine clinical data with a view to scientific publication. Consequently, written informed consent was not required.

Investigations

Liver biopsy samples were scored following the criteria established by the Metavir Cooperative Study Group [18], as follows: F0, no fibrosis; F1, portal fibrosis; F2, periportal fibrosis or rare portal–portal septa; F3, fibrous septa with architectural distortion and no obvious cirrhosis (bridging fibrosis); and F4, definite cirrhosis.

Staging of liver fibrosis was also estimated at baseline using the FIB-4 index, as follows: [age (years) × AST (U/L)]/[platelet count (10^9/L) × ALT (U/L)]$^{1/2}$ [6]. The FIB-4 model was developed using 3 levels of fibrosis (Ishak score 0–1, 2–3, and 4–6). Based on the area under the receiver operating characteristic curves (AUROCs) for null to moderate fibrosis (Ishak score 0–3) and advanced fibrosis (Ishak score 4–6), 2 cutoff points were chosen to predict either the absence (<1.45) or presence (>3.25) of advanced fibrosis. Likewise, based on the AUROC for null or mild fibrosis (Ishak score 0–1) and significant fibrosis (Ishak score 2–6), 2 cutoff points were chosen to predict either the absence (<0.6) or presence (≥1.0) of significant fibrosis [6]. For the purpose of this work, significant fibrosis was defined as Metavir stage ≥F2 (equivalent to an Ishak score ≥3) or a FIB-4 value ≥1; advanced fibrosis was defined as Metavir stage ≥F3 (equivalent to an Ishak score ≥4) or a FIB-4 value ≥3.25.

Treatment Response and Follow-up

Sustained virologic response (SVR) was defined as an undetectable serum HCV RNA level 24 weeks after discontinuation of therapy. Once treatment was complete, patients were actively monitored to analyze clinical and laboratory parameters, including survival, liver decompensation, antiretroviral therapy, $CD4^+$ cell count, HIV RNA load, and HCV RNA load. The study period lasted from the date interferon plus ribavirin was stopped until death or the last follow-up visit. The administrative censoring date was 31 July 2010.

All the information related to death (death reports, autopsy reports [if available], and standard forms) was reviewed by J. B. and J. G.-G. Both authors were blind to the category of treatment response and classified deaths in accordance with the opinion of the attending clinician as follows: (1) liver-related death, when the train of events that ended in death was caused by liver decompensation or hepatocellular carcinoma (HCC); (2) AIDS-related death, when death was directly related to an AIDS-defining condition; and (3) non-liver-related, non-AIDS-related death. We also assessed LREs including ascites, hepatic encephalopathy, variceal bleeding, and HCC. Ascites was confirmed by paracentesis and/or ultrasound. Hepatic encephalopathy was established on clinical grounds after the reasonable exclusion of HIV-associated encephalopathy based on clinical findings, laboratory parameters, and neuroimaging techniques. The source of gastroesophageal bleeding was confirmed by endoscopy whenever possible. Diagnosis of HCC was based on noninvasive imaging tests or pathology findings.

Table 1. Characteristics of 903 HIV/Hepatitis C Virus–Coinfected Patients[a]

Characteristic	Without OD/LRE (n = 813)	With OD/LRE (n = 90)	Total (N = 903)
Male sex, No. (%)	602 (74.3)	76 (84.4)*	678 (75.3)
Age, y, median (IQR) (baseline)	40 (37–43)	40 (37–43)	40 (37–43)
Prior injection drug use, No. (%)	688 (85.4)	78 (86.7)	766 (85.5)
CDC HIV classification C, No. (%)[b]	184 (22.9)	23 (25.6)	207 (23.2)
$CD4^+$ nadir, cells/μL, median (IQR)	218 (120–331)	202 (90–300)	217 (116–330)
$CD4^+$ baseline, cells/μL, median (IQR)	530 (394–731)	510 (330–674)*	529 (387–727)
Undetectable HIV RNA load at baseline, No. (%)[c]	525 (66.5)	54 (62.1)	579 (66)
HCV genotype, No. (%)[d]			
1 or 4	506 (62.2)	73 (81.1)*	579 (64.1)
2 or 3	287 (35.3)	14 (15.6)	301 (33.3)
Unknown	20 (2.5)	3 (3.3)	23 (2.5)
HCV RNA ≥500 000 IU/mL, No. (%)	481 (68.2)	52 (74.3)	533 (68.8)
Metavir fibrosis score, No. (%)			
F0	65 (8)	6 (6.7)	71 (7.9)
F1	229 (28.2)	13 (14.4)*	242 (26.8)
F2	219 (26.9)	17 (18.9)	236 (26.1)
F3	213 (26.2)	23 (25.6)	236 (26.1)
F4	87 (10.7)	31 (34.4)*	118 (13.1)
FIB-4 fibrosis category			
≤1	143 (17.6)	5 (5.6)*	148 (16.4)
>1 to <3.25	552 (67.9)	45 (50)*	597 (66.1)
≥3.25	118 (14.5)	40 (44.4)*	158 (17.5)
HBsAg positive, No. (%)	30 (3.7)	4 (4.4)	34 (3.8)
Current alcohol intake >50 g/d, No. (%)	29 (3.9)	9 (11)*	38 (4.6)
Current methadone use, No. (%)	88 (11.7)	20 (23.5)*	108 (12.9)
Sustained virologic response	321 (39.5)	7 (7.8)*	328 (36.3)

Abbreviations: CDC, Centers for Disease Control and Prevention; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; LRE, liver-related event; OD, overall death.

[a] Baseline assessment of fibrosis by both liver biopsy (Metavir) and FIB-4 index, stratified according to the presence or absence of OD or LREs, whichever occurred first.

[b] A, asymptomatic HIV or persistent generalized lymphadenopathy; B, symptomatic non-C conditions; C, AIDS-defining conditions.

[c] Baseline HIV RNA load was determined in 883 patients using commercial assays with different lower limits of detection (HIV RNA copies/mL): <400 (n = 10), <200 (n = 38), <80 (n = 19), <50 (n = 648), <40 (n = 38), and <20 (n = 130).

[d] HCV genotype was determined in 880 patients.

* $P < .05$ with the "no events" group.

Statistical Analysis

Differences between the groups were analyzed using the χ^2 test, *t* test, or Mann–Whitney test, as appropriate. Normality was assessed using the Kolmogorov–Smirnov test. The primary endpoint was the composite variable of overall death (OD) or LRE, whichever occurred first. We used receiver operating characteristic (ROC) curves to determine the ability of liver biopsy and FIB-4 to predict clinical outcomes. We compared the ROC curves following the method of Hanley and McNeil [19]. The Kaplan–Meier estimator was used to estimate the cumulative probability of LRE and OD/LRE; the cumulative probability of LRE was calculated taking into account OD as a competitive risk.

We used multivariate Cox regression analysis to test the association between liver biopsy and FIB-4 and OD/LRE. Proportionality of hazards was assessed graphically using log–log plots for categorical covariates and Schoenfeld residuals for categorical and numerical covariates. All values were adjusted for baseline covariates that were significantly different between patients with and without OD/LRE and for baseline covariates considered of clinical relevance by the investigators.

As several patients underwent retreatment with interferon plus ribavirin, those who achieved SVR after retreatment were included in the SVR group and thus contributed time and data only to the SVR group. For patients who had >1 event, only the first was included in the analysis of the association between category of response and "any event." The statistical analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp, Armonk, New York).

Table 2. Frequency of Events During Follow-up in HIV/Hepatitis C Virus–Coinfected Patients, Stratified According to Response to Interferon Plus Ribavirin[a]

Event	No SVR (n = 575)	SVR (n = 328)	Total (N = 903)	*P* Value
Overall death, No. (%)	43 (7.5)	3 (0.9)	46 (5.1)[b]	<.001
Liver decompensation, No. (%)	61 (10.6)	3 (0.9)	64 (7.1)	<.001
Hepatocellular carcinoma, No. (%)	11 (1.9)	2 (0.6)	13 (1.4)	.114
LREs, No. (%)	67 (11.7)	4 (1.2)	71 (7.9)	<.001
Overall death/LREs, No. (%)	83 (14.5)	7 (2.1)	90 (10)	<.001

Abbreviations: HIV, human immunodeficiency virus; LRE, liver-related event; SVR, sustained virologic response.

[a] Median (interquartile range) follow-up in months for no SVR and SVR was 62.9 (42.7–81.1) and 59.7 (42.1–79.7), respectively.

[b] Liver-related deaths, 24; AIDS-related deaths, 2; non-liver-related/non-AIDS-related deaths, 20 (non-AIDS defining cancer, 6; non-AIDS-related infections, 5; suicide, 2; acute myocardial infarction, 1; stroke, 1; acute renal failure, 1; bleeding duodenal ulcer, 1; trauma, 1; drowning, 1; and unknown cause, 1).

RESULTS

Patient Characteristics and Treatment Response

From the 1574 patients who started treatment between January 2000 and January 2008 included in the database, we selected the 903 patients with a baseline assessment of liver fibrosis by both liver biopsy and FIB-4. The median interval between liver biopsy and FIB-4 was 4.5 months (interquartile range [IQR], 2.2–12.0 months). The baseline characteristics of the patients are shown in Table 1. In brief, 75.3% were male, the median age was 40 years, 23.2% had prior AIDS-defining conditions, the median baseline CD4 count was 529 cells/μL, 66.0% had an undetectable HIV RNA load, 64.1% were infected by HCV genotype 1 or 4, and 68.8% had an HCV RNA level ≥500 000 IU/mL.

A total of 413 patients (45.7%) were treated with pegylated interferon alfa-2a plus ribavirin, 389 (43.1%) were treated with pegylated interferon alfa-2b plus ribavirin, and 101 (11.2%) were treated with standard interferon alfa 3 times weekly plus ribavirin. During treatment of hepatitis C, 753 patients (83.3%) were on combination antiretroviral therapy. A total of 328 patients (36.3%) achieved an SVR, including 24 of 108 patients who received a second course of interferon plus ribavirin.

Clinical Outcomes

After a median follow-up of 62 months (IQR, 42.5–80.3 months) since the date interferon plus ribavirin was stopped, 46 patients had died, 64 had had liver decompensation, and 13 had had episodes of HCC; most events occurred among patients without SVR (Table 2).

The ability of liver biopsy and FIB-4 to predict clinical outcomes in the entire cohort and in patients without SVR is shown in Figure 1. The values for the AUROCs were significantly higher for FIB-4 than for liver biopsy for prediction of

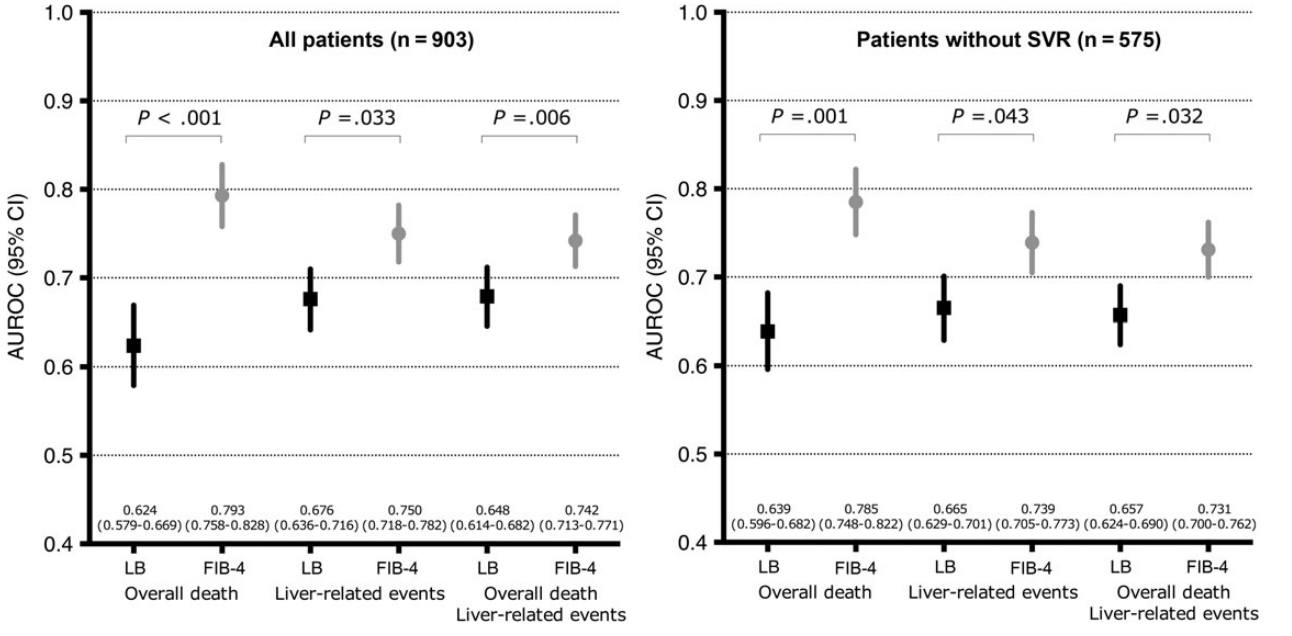

Figure 1. Accuracy of liver biopsy (LB) and FIB-4 index for the prediction of overall death (OD), liver-related events (LREs), and OD/LREs, whichever occurred first, in all patients and in patients without sustained virologic response (SVR). Abbreviations: AUROC, area under the receiver operating characteristic curve; CI, confidence interval.

Table 3. Predictive Values of Different Categories of Fibrosis Assessed by Liver Biopsy and FIB-4 Index for the Prediction of Clinical Outcomes

Method and Cutoff Value	Event, No.		Total No.	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
	Yes	No							
Overall death or LRE									
Liver biopsy ≥F3	54	300	354	60.0 (49.3–70.7)	63.1 (59.7–66.5)	15.2 (11.4–19.1)	93.4 (91.3–95.6)	1.63 (1.34–1.97)	0.63 (.49–.82)
Liver biopsy <F3	36	513	9						
Total	90	813	903						
FIB-4 ≥ 3.25	40	118	158	44.4 (33.6–55.3)	85.5 (83.0–88.0)	25.3 (18.2–32.4)	93.3 (91.4–95.1)	3.06 (2.30–4.07)	0.65 (.54–.78)
FIB-4 < 3.25	50	695	745						
Total	90	813	903						
Biopsy ≥F2	71	519	590	78.9 (69.9–87.9)	36.2 (32.8–39.5)	12.0 (9.3–14.7)	93.9 (91.1–6.7)	1.24 (1.10–1.39)	0.58 (.39–.88)
Biopsy F0–F1	19	294	313						
Total	90	813	903						
FIB-4 ≥ 1	85	670	755	94.4 (89.2–99.7)	17.6 (14.9–20.3)	11.3 (8.9–13.6)	96.6 (93.4–9.9)	1.15 (1.08–1.22)	0.32 (.13–.75)
FIB-4 < 1	5	143	148						
Total	90	813	903						
LREs									
Biopsy ≥F3	45	309	354	63.4 (51.5–75.3)	62.9 (59.5–66.2)	12.7 (9.1–16.3)	95.3 (93.4–97.1)	1.71 (1.40–2.08)	0.58 (.43–.79)
Biopsy <F3	26	523	549						
Total	71	832	903						
FIB-4 ≥ 3.25	34	124	158	47.9 (35.6–60.2)	85.1 (82.6–87.6)	21.5 (14.8–28.2)	95.0 (93.4–6.7)	3.21 (2.40–4.30)	0.61 (.49–.77)
FIB-4 < 3.25	37	708	745						
Total	71	832	903						
Biopsy ≥ F2	59	531	590	83.1 (73.7–92.5)	36.2 (32.8–39.5)	10.0 (7.5–12.5)	96.2 (93.9–8.4)	1.30 (1.16–1.46)	0.47 (.28–.79)
Biopsy F0–F1	12	301	313						
Total	71	832	903						
FIB-4 ≥ 1	68	687	755	95.8 (90.4–100)	17.3 (14.7–20.1)	9.0 (6.9–11.1)	98.0 (95.4–100)	1.16 (1.09–1.23)	0.24 (.08–.74)
FIB-4 < 1	3	145	148						
Total	71	832	903						

Abbreviations: CI, confidence interval; LRE, liver-related event; NPV, negative predictive value; PPV, positive predictive value.

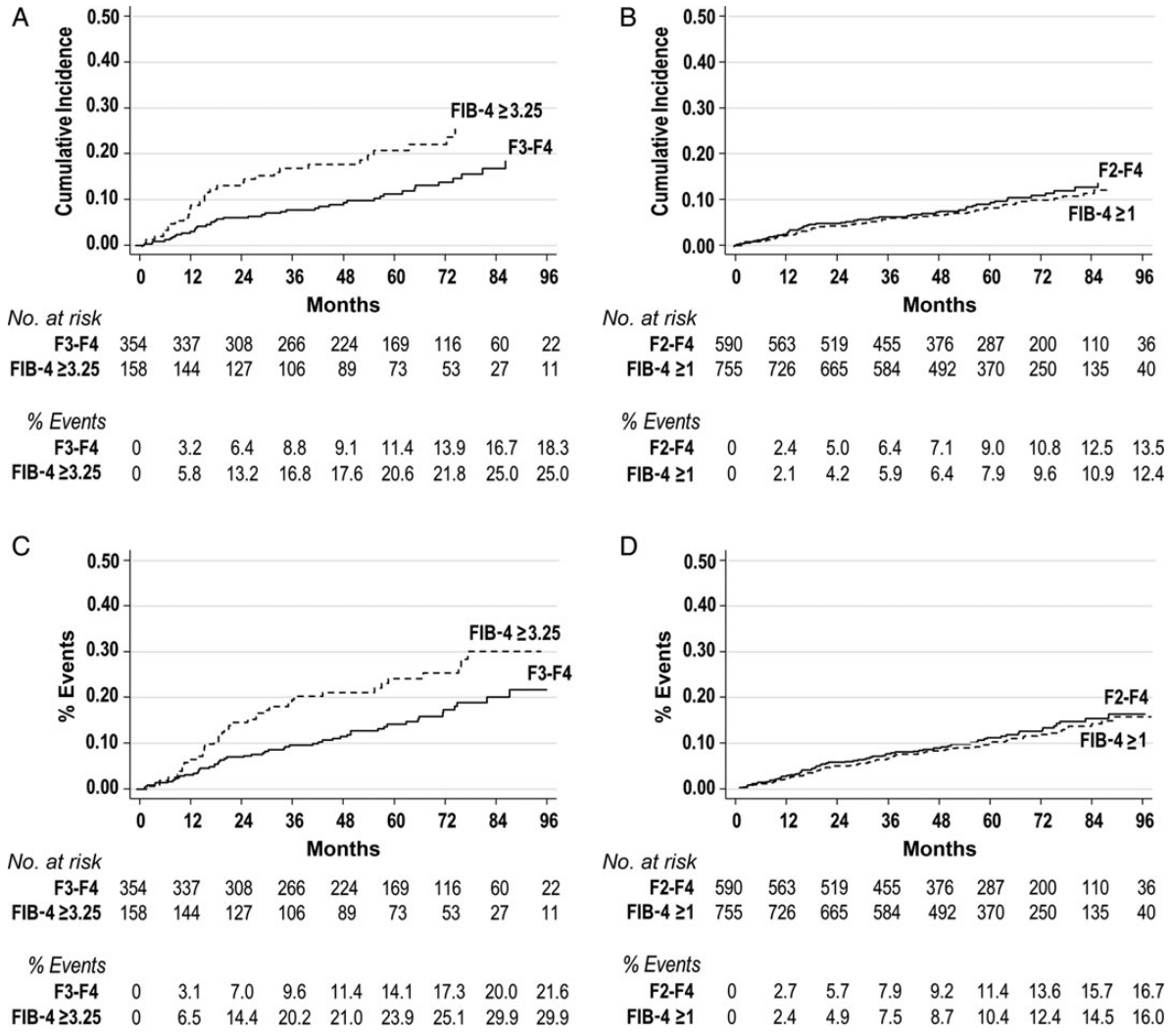

Figure 2. Kaplan–Meier plots of liver related events (LREs) (*A,B*) and overall death (OD)/LREs (*C,D*) according to liver biopsy and FIB-4 index. The cumulative probability of LREs was calculated taking into account OD as a competitive risk.

clinical outcomes (OD, LRE, and the composite endpoint OD/LRE), considering all patients and patients without SVR. We also compared the performance of the APRI index [5] and liver biopsy, and found that the former performed better than the latter for OD, LRE, and OD/LRE, although the AUROCs for the APRI index for all those clinical outcomes were lower than the AUROCs for the FIB-4 index (data not shown).

The predictive value of the different categories of fibrosis assessed by liver biopsy and FIB-4 for the prediction of clinical outcomes is shown in Table 3. When we assessed cutoffs for advanced fibrosis, the specificity, positive predictive values, and positive likelihood ratios of FIB-4 were higher than those of liver biopsy for both OD/LRE and LRE. In addition, the number of patients who were well classified was significantly higher with FIB-4 than with liver biopsy for both OD/LRE (735/903 [81%] vs 567/903 [63%]; $P < .001$) and LRE (742/903 [82%] vs 568/903 [63%]; $P < .001$). When we assessed cutoffs for significant fibrosis, the sensitivity and negative predictive values of FIB-4 were higher than those of liver biopsy. In addition, for these same cutoff values, the negative likelihood ratio was lower for FIB-4 than for liver biopsy for both OD/LRE and LRE.

The probability of events according to liver biopsy and FIB-4 is shown in Figure 2. The probability of events increased during follow-up for the 2 categories of fibrosis assessed by both liver biopsy and FIB-4. Of note, FIB-4 enabled better risk stratification than liver biopsy for LRE and for the composite endpoint of OD/LRE in the category of advanced fibrosis. For example, the 5-year probability of LRE according to FIB-4 values ≥3.25 and liver biopsy stages F3–F4 were 20.6% and 11.4%, respectively. Likewise, the 5-year probability of OD/LRE according to

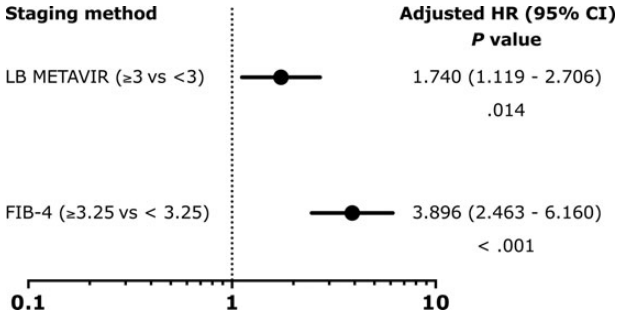

Figure 3. Adjusted hazard ratios (HR) (95% confidence intervals [CIs]) of overall death/liver-related events, whichever occurred first, for patients with advanced fibrosis assessed by liver biopsy (LB) and FIB-4. The Cox proportional models were adjusted for age, sex, human immunodeficiency virus (HIV) transmission category, Centers for Disease Control and Prevention HIV clinical category, $CD4^+$ cell nadir, hepatitis C virus (HCV) genotype, HCV RNA, alcohol intake, methadone use, and achievement of sustained virologic response.

FIB-4 values ≥3.25 and liver biopsy stages F3–F4 were 23.9% and 14.1%, respectively.

Cox proportional models adjusted for age, sex, HIV transmission category, Centers for Disease Control and Prevention (CDC) HIV clinical category, $CD4^+$ cell nadir, HCV genotype, HCV RNA, alcohol intake, methadone use, and achievement of SVR showed that, in comparison with nonadvanced fibrosis, advanced fibrosis by both liver biopsy and FIB-4 significantly increased the hazard of OD/LRE (Figure 3). Of note, the adjusted hazard ratio was 2.24 times higher for FIB-4 than for liver biopsy.

Finally, we analyzed the prognostic value of FIB-4 in the subgroup of 118 patients with biopsy-confirmed cirrhosis (Metavir stage F4). The frequency of OD/LRE was 12 of 69 (17.4%) for those with a FIB-4 <3.25, and 19 of 49 (38.8%) for those with FIB-4 ≥3.25 ($P = .011$). In a Cox model performed in the subgroup of patients with Metavir F4 (adjusted for age, sex, HIV transmission category, CDC clinical category, $CD4^+$ cell nadir, HCV genotype, HCV RNA, alcohol intake, methadone use, and achievement of SVR), the adjusted hazard ratio of OD/LRE for patients with FIB-4 ≥3.25 vs FIB-4 <3.25 was 4.695 (95% confidence interval, 1.864–11.825; $P = .001$).

DISCUSSION

We studied 903 HIV/HCV–coinfected patients in whom fibrosis was evaluated at baseline using both liver biopsy and FIB-4; 328 achieved SVR with interferon and ribavirin. After a median follow-up of 5 years, we found that FIB-4 was more accurate than liver biopsy for the prediction of clinical outcomes in the whole cohort and in the subgroup of patients who did not achieve SVR. We also found that well-defined FIB-4 cutoffs enabled a better prognostic classification and risk stratification of patients than Metavir fibrosis staging. To our knowledge, this is the first study to show that FIB-4 has a higher prognostic value than liver biopsy in HIV/HCV–coinfected patients.

Liver biopsy has traditionally been the preferred method for staging liver fibrosis and assessing the risk of disease progression and mortality in patients with compensated chronic hepatitis C, whether with or without HIV coinfection [20–22]. However, over the last few years, various studies have shown that noninvasive methods, including serum markers and measurement of liver stiffness, are equal to or better than liver biopsy, not only for staging liver fibrosis, but also for assessing prognosis in patients with chronic hepatitis C. In a prospective study with >500 patients with chronic hepatitis C, it was found that over a 5-year period, FibroTest was a better predictor than liver biopsy for both decompensation and liver-related mortality [11]. In another prospective study, the authors assessed the 5-year prognostic value of liver biopsy, liver stiffness, FibroTest, APRI, and FIB-4 in a group of 1457 patients with chronic hepatitis C (140 coinfected with HIV) and showed that these methods were all able to predict survival, although liver stiffness and FibroTest had a better prognostic value than liver biopsy, FIB-4, and APRI [12]. In a third study that evaluated the prognostic value of liver biopsy, Hepascore, APRI, and FIB-4 in a group of 406 patients with chronic hepatitis C over a 10-year period, it was found that Hepascore was as accurate as liver biopsy for the prediction of liver-related outcomes [13]. Of note, APRI and FIB-4 were not predictive of outcomes; however, because the last 2 indices were calculated in only 37% of the study subjects, the possibility that a type 2 error prevented the demonstration of an association between APRI or FIB-4 and liver-related outcomes could not be excluded [13]. A recent study comparing the prognostic value of liver biopsy and liver stiffness in 297 HIV/HCV–coinfected patients followed up for a median of 5 years found that both methods performed similarly in predicting OD; however, liver stiffness performed better than liver biopsy in predicting LRE [14].

The differences we found in the prognostic value of FIB-4 and fibrosis staging by liver biopsy can be explained by the different ability of both methods to reflect changes in portal hypertension, the most accurate predictor of outcome in compensated liver disease [23]. Most of the histological staging systems for fibrosis, such as Metavir, group all types of cirrhosis into a single category. Such an approach significantly reduces interobserver variability between histopathologists but does not take account of the different clinical stages of cirrhosis [24]. However, FIB-4 is calculated with laboratory parameters that may reflect changes proportional to liver function derangement, such as platelet count, which has been used as a marker of advanced portal hypertension for many years [25]. In addition, AST and

alanine aminotransferase concentrations correlate with liver inflammation [26], which in turn correlates independently with progression of fibrosis in HIV/HCV–coinfected patients [27]. The prognostic ability of FIB-4 is further supported by the analysis carried out in patients with biopsy-confirmed cirrhosis, which showed that hazard of OD/LRE was significantly higher for those patients with FIB-4 ≥3.25 than for those with FIB-4 <3.25.

Our study has several limitations. First, the population was not a random, community-based population of HIV/HCV–coinfected patients. Second, our study design was not entirely prospective. However, we believe that its characteristics make it unlikely that the results differ considerably from those that would have been obtained in an entirely prospective study. This is because the patients were followed by the same infectious diseases physicians in the same reference hospitals throughout the course of the disease, with standard clinical and laboratory parameters assessed at least every 6 months. Third, interpretation of biopsy specimens was not centralized and lacked quality control in terms of percentage of biopsy cylinders that were ≥2.5 cm in length. However, this limitation is typical of liver biopsy in usual clinical practice, and pathologists at each institution had extensive experience in scoring samples from patients with viral hepatitis and staged liver biopsy samples following the criteria established by the Metavir Cooperative Study Group.

The strengths of our study include the high number of patients studied, the long follow-up period, and the fact that all the information in the database was monitored to verify that it was consistent with each patient's medical records.

In conclusion, we found that FIB-4, a noncommercial index that is easily applied using routinely collected data, was better than liver biopsy when assessing the prognosis of HIV/HCV–coinfected patients. We believe that this finding is of relevance in both clinical practice and research. In clinical practice, FIB-4 can be used to estimate the short- and long-term risk of LRE and OD in HIV/HCV–coinfected patients and inform medical decisions on anti-HCV therapy and frequency of follow-up visits. In research, FIB-4 enables easy stratification of the risk of OD and LRE in HIV/HCV–coinfected patients in both observational studies and clinical trials.

Notes

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Potential conflicts of interest. All authors: No reported conflicts.

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APPENDIX

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