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ORIGINAL RESEARCH

Use of simple noninvasive biomarkers to predict liver fibrosis in HIV/HCV coinfection in routine clinical practice

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Background

Simple noninvasive tests to predict fibrosis, as an alternative to liver biopsy (LB), are needed. Of these, the aspartate aminotransferase (AST) to platelet ratio index (APRI) and the Forns index (FI) have been validated in HIV/hepatitis C virus (HCV) coinfection. However, these indexes may have lower diagnostic value in situations other than the circumscribed conditions of validation studies. We therefore examined the value of the APRI and FI in HIV/HCV-coinfected patients for the detection of significant fibrosis in real-life conditions.

Patients and methods

HIV/HCV-coinfected patients who had participated in a multicentre cross-sectional retrospective study were selected if they had undergone an LB within 24 months before the last visit. The predictive accuracy of the APRI and FI was measured using the areas under receiver-operating-characteristic curves (AUROCs). Diagnostic accuracy was determined using the positive (PPV) and negative (NPV) predictive values.

Results

A total of 519 coinfected individuals were included in the study. The AUROC [95% confidence interval (95% CI)] of the APRI was 0.67 (0.66–0.71) and that of the FI was 0.67 (0.62–0.71). The PPV of the APRI was 79% and its NPV was 66%. The PPV of the FI was 74% and its NPV was 64%. LB length was available and was ≥ 15 mm in 120 individuals. In this group, the PPV of the APRI was 85%, and that of the FI was 81%. Using these indexes, 22% of patients could be spared LB. Applying both models sequentially, 30% of patients could be spared LB.

Conclusions

In HIV/HCV-coinfected patients, the diagnostic accuracy of the APRI in real-life conditions was similar to that in the validation studies. The FI performed less well. However, combining the two indexes to make decisions on anti-HCV therapy may prevent a significant proportion of patients from having to undergo LB.

Keywords: aspartate aminotransferase to platelet ratio index (APRI), Forns index, HIV/HCV coinfection, liver biopsy, liver fibrosis

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Introduction

The evaluation and quantification of liver fibrosis in patients with HIV and hepatitis C virus (HCV) infection has multiple implications. For example, the prognosis of HCV infection is estimated from the stage of fibrosis. Given that liver disease is a leading cause of death in HIV/HCV-coinfected patients on highly active antiretroviral therapy (HAART) [1], the importance of fibrosis diagnosis cannot be understated. In addition, therapeutic decisions regarding anti-HCV treatment are usually guided by fibrosis stage. The limited efficacy of the pegylated interferon plus ribavirin combination in HIV/HCV coinfection, and its manifold adverse effects, has led to the practice of restricting this therapy to patients with higher risk of

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progressive liver disease. Thus, according to the recommendations of international guidelines and panels of experts, patients with fibrosis extending beyond the portal tracts would be candidates to receive therapy [2,3]. Finally, severe liver enzyme elevations during antiretroviral therapy are more frequent in patients with more advanced fibrosis, particularly among coinfected patients on non-nucleoside reverse transcriptase inhibitors [4–6]. Consequently, the determination of the liver fibrosis may lead us to select a safer HAART regimen for HIV/HCV-coinfected patients with advanced disease.

Liver biopsy (LB) has been the gold standard method for the diagnosis of fibrosis. However, it is invasive and limited because of variability issues [7,8]. In addition, it is costly and not easily accessible in many health care settings. Finally, expert pathologists in liver diseases are not widely available. Thus, reliable and financially viable noninvasive tests to diagnose fibrosis are needed, particularly in low-resource settings.

A high proportion of HIV/HCV-coinfected patients can be classified for fibrosis using simple blood indexes [9–17]. These tests are economical to use. However, the diagnostic value of these indexes in HIV/HCV-coinfected patients has been evaluated in specific validation studies usually carried out in tertiary care centres. It is not known whether the results obtained in the circumscribed conditions of validation studies are applicable to real-life practice. Diagnostic tests can perform less well in real-life practice, mainly because of higher variability. In a clinical setting, outside a controlled study, there are a number of sources of variability. The diagnosis of fibrosis is particularly prone to variability among observers [7]. Moreover, blood tests may also show variability among different laboratories [18]. Finally, the overall performance of tests depends on the prevalence of the diagnostic target, and thus may not be reproducible in different epidemiological settings [19]. In the light of these issues, we examined the value of the aspartate aminotransferase (AST) to platelet ratio index (APRI) and the Forns index (FI) in HIV/HCV-coinfected patients for the detection of significant fibrosis in real-life conditions.

Patients and methods

Patients

The GRAFIHCO study was a retrospective cross-sectional study that included 8829 HIV/HCV-coinfected patients seen at 95 institutions in Spain, from January 2007 to February 2008. The aim of the study was to evaluate the prevalence of liver fibrosis using simple noninvasive blood tests. Eligible patients were those coinfected with HIV and HCV who had available data recorded at their last clinical visit for calculation of the APRI and the FI [20]. Clinical, biochemical and haematological data were collected from databases or the records of the patients at each centre. For each patient, an online electronic case report form was completed.

For the present analysis, individuals who had undergone an LB were selected, provided that they fulfilled the following criteria: (1) age more than 18 years; (2) positive serum HCV RNA; (3) LB performed within 24 months before the last visit. All of the patients had given their written informed consent for the LB.

Liver histology

Liver fibrosis was staged according to the METAVIR score as follows: no or mild fibrosis (no fibrosis or stellate enlargement of portal tracts without septa; F0 and F1), moderate fibrosis (enlargement of portal tracts with rare septa; F2), severe fibrosis (numerous septa with cirrhosis; F3), and cirrhosis (F4) [21]. Data on the length of LB specimens were collected.

Simple blood indexes to predict liver fibrosis

The APRI is calculated by dividing the AST level (IU/L), expressed as the number of times above the upper limit of normal (ULN), by the platelet count (10^9/L): AST (/ULN) $\times$ 100/platelet count (10^9/l). This index has been validated in HIV/HCV-coinfected patients [9–17]. If the APRI is ≥ 1.5, patients can be classified as having significant fibrosis [fibrosis stage (F) ≥ 2], with a positive predictive value (PPV) ranging from 66 to 100%, according to different validation studies [9–16]. The low cut-off of APRI < 0.5 was found to be inaccurate to exclude F ≥ 2 [9–16].

The FI is calculated by applying the following regression equation: 7.811–3.131 ln[platelet count (10^9/L)] + 0.781 ln[gamma-glutamyl transpeptidase (GGT) (UI/L)] + 3.467 ln[age (years)] − 0.014 [cholesterol (mg/dL)]. If the FI is ≥ 6.9, patients can be considered to have F ≥ 2, with a PPV of 94% according to one study [9] and 100% according to another study [13]. The low cut-off of FI < 4.2 was found to be inaccurate to exclude F ≥ 2 [9,13].

Statistical analysis

Continuous variables are expressed as median (Q1–Q3) and the categorical variables as numbers (percentage). Continuous variables were compared using the Student's *t*-test or the Mann–Whitney *U*-test when appropriate. Categorical

variables were compared using the χ^2 test with Yates correction or Fisher's test when appropriate.

The predictive accuracy of the APRI and Forns index was tested by measuring the areas under the receiver-operating-characteristic curves (AUROCs). The diagnostic accuracy was calculated on the basis of sensitivity (S), specificity (Sp), PPV and negative predictive value (NPV). $F \geq 2$ was considered as the disease. The predictive and diagnostic accuracy of the indexes was also tested in the group of patients with larger liver biopsies.

The statistical analysis was carried out using the SPSS 15 statistical software package (SPSS, Chicago, IL, USA).

Ethical aspects

The study was performed according to the Helsinki declaration and was approved by the Ethics committee of Hospital Germans Trias i Pujol.

Results

Characteristics of the patients

The GRAFIHCO study recruited 8829 patients. An LB was performed in 1701 (19%) of them. Five hundred and nineteen (31%) of the patients with LB fulfilled the inclusion criteria for the present study. The main characteristics of the patients included in this subanalysis compared with the patients included in the GRAFIHCO study are summarized in Table 1.

Regarding the 519 individuals selected as the study group, HCV genotype was one in 300 patients (58%), two in four (1%), three in 105 (20%), four in 101 (20%) and not available in nine (1.7%). Two hundred and sixty-four patients (51%) were staged as $F \geq 2$ in the LB (Table 2). Sixty-three patients (12%) were not receiving antiretroviral therapy at their last clinical visit.

Prediction of fibrosis using the APRI and the FI

The AUROC (95% confidence interval) of the APRI was 0.67 (0.66–0.71) and that of the FI was 0.67 (0.62–0.71). The LB length was recorded in the case report form in 193 patients (37%). One hundred and twenty (62.2%) of them had biopsy specimens ≥ 15 mm. The characteristics of these patients are displayed in Table 2. The two indexes had similar predictive accuracy in the subgroup of patients with recorded biopsy length ≥ 15 mm and in the global study group. The AUROC (95% confidence interval) of the APRI was 0.66 (0.56–0.76) and that of the FI was 0.66 (0.56–0.77) for patients with biopsy size ≥ 15 mm (Fig. 1).

Applying the APRI, 111 (44%) of 255 individuals with F0 or F1 in the biopsy were correctly classified using the cut-off value <0.5 (Table 3). Among the 168 patients

Table 1 Characteristics of the patients selected for the study and excluded from the analysis

Variable	Excluded patients ($n = 8310$)	Study patients ($n = 519$)	*P*
Age (years)*	43 (39–46)	43 (39–46)	0.7
Male gender [*n* (%)]	6500 (78)	410 (79)	0.8
IDU or transfusion [*n* (%)]	6979 (84)	434 (84)	0.4
Alcohol intake >50 g/day [*n* (%)]†	1722 (23)	94 (18)	0.03
Age at HCV infection (years)*,[1]	30 (24–36)	27 (21–33)	<0.001
AST (UI/L)*	46 (32–70)	48 (34–74)	0.6
ALT (UI/L)*	52 (34–81)	61 (36–105)	0.7
GGT (UI/L)*	80 (43–151)	86 (44–163)	0.2
Cholesterol (mg/dL)*	164 (139–192)	167 (141–193)	0.4
Platelets (10^9/L)*	182 (136–230)	187 (142–234)	0.4
APRI*	0.69 (0.42–1.3)	0.67 (0.44–1.12)	0.8
Forns index*	5.6 (4.3–6.9)	5.5 (4.4–6.7)	0.4
Genotype 1 [*n* (%)]*,[2]	3778 (46)	300 (58)	<0.001
HCV viral load ($\log_{10}$ UI/mL)*,[3]	5.9 (5.4–6.5)	5.9 (5.1–6.7)	0.9
HBsAg positive [*n* (%)]	431 (5)	9 (2)	0.002
Antiretroviral therapy [*n* (%)]	7218 (87)	456 (88)	0.3
Undetectable HIV RNA [*n* (%)]	5843 (70)	402 (78)	<0.001
CD4 cell count (cells/μL)*	456 (290–674)	489 (360–670)	0.03
Nadir CD4 count (cells/μL)*,[4]	180 (80–297)	195 (96–300)	0.9

*Median (Q1–Q3).
†Alcohol intake >50 g/day during the last 5 years.
Data were available for the following numbers of patients: excluded patients: [1]7586, [2]6534, [3]6367 and [4]8202 patients; study patients: [1]438, [2]510 and [3]452 patients.
APRI, aspartate aminotransferase to platelet ratio index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IDU, injecting drug use.

with APRI < 0.5, 57 (34%) showed F ≥ 2. Thirty-nine of these misclassified subjects showed F2, 14 patients showed F3 and four patients showed F4 in the LB. Among patients with APRI ≥ 1.5, 75 (28%) of 264 with F ≥ 2 were correctly classified (Table 3). A total of 20 (21%) of 95 patients with score > 1.5 showed F < 2. Nineteen of these errors of classification showed F1 and one showed F0 in the LB.

Using the FI, 66 (26%) of 255 patients without F ≥ 2 were correctly identified (Table 3). Among patients with FI < 4.2, 38 (37%) of 104 individuals had F ≥ 2 in the LB. Thirty of them had F2, seven F3 and one F4 in the LB. For patients with FI ≥ 6.9, 84 (32%) of 264 patients with F ≥ 2 were correctly identified (Table 3). Thirty (26%) of 114 patients with FI ≥ 6.9 showed F < 2. Two of the misclassified patients showed F0 and 28 showed F1 stage in the LB.

The diagnostic accuracy of both indexes was influenced by the length of the biopsy used as reference for

Table 2 Characteristics of the study patients by length of liver biopsy

Variable	Liver biopsy length	
	All patients ($n = 519$)	Biopsy ≥ 15 mm ($n = 120$)
Age (years)*	43 (39–46)	43 (38–47)
Male sex [*n* (%)]	410 (79)	90 (75)
IDU or transfusion [*n* (%)]	434 (84)	98 (82)
Alcohol intake > 50 g/day [*n* (%)]†	94 (18)	25 (21)
Age at HCV infection (years)*,[1]	27 (21–33)	26 (20–32)
AST (UI/L)*	48 (34–74)	52 (34–88)
ALT (UI/L)*	61 (36–105)	80 (54–133)
GGT (UI/L)*	86 (44–163)	98 (47–179)
Cholesterol (mg/dL)*	167 (141–193)	169 (141–204)
Platelets (10^9/L)*	187 (142–234)	196 (143–232)
Genotype 1 [*n* (%)][2]	300 (58)	74 (62)
HCV viral load ($\log_{10}$ UI/mL)*,[3]	5.9 (5.1–6.7)	6.2 (5.7–6.8)
HBsAg positive [*n* (%)]	9 (2)	2 (2)
Liver fibrosis [*n* (%)]		
F0	68 (13)	13 (11)
F1	187 (36)	32 (27)
F2	130 (25)	37 (31)
F3	74 (14)	22 (18)
F4	60 (12)	16 (13)
Length of liver biopsy (mm)*,[4]	15 (12–20)	20 (15–25)
Time from liver biopsy to last visit (months)*	11 (5–17)	11 (5–16)

*Median (Q1–Q3).
†Alcohol intake > 50 g/day during the last 5 years.
Data were available for the following numbers of patients: all patients: [1]438, [2]510, [3]452 and [4]193 patients; biopsy length ≥ 15 mm: [1]93, [2]118 and [3]112 patients.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase; HBsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IDU, injecting drug use.

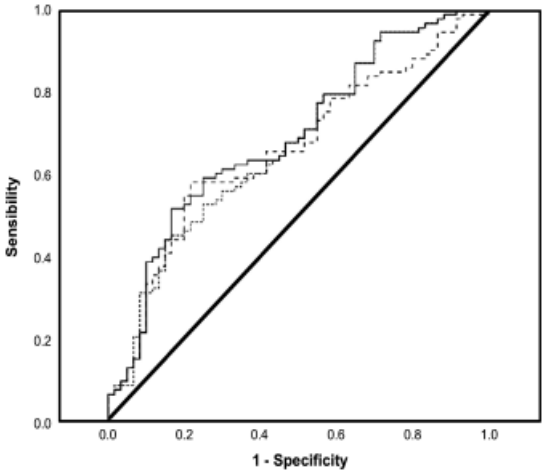

Fig. 1 Receiver-operating-characteristic curve of the aspartate aminotransferase to platelet ratio index (APRI) (dotted line), the Forns index (dashed line) and the sequential application of both indexes (solid line) for the prediction of significant fibrosis (liver biopsy length ≥ 15 mm; $n = 120$).

Table 3 Diagnostic accuracy of the aspartate aminotransferase to platelet ratio index (APRI) and the Forns index to predict significant fibrosis ($n = 519$)

Cut-off point	All patients ($n = 519$) [*n* (%)]	Fibrosis stage		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		F0–F1 ($n = 255$) [*n* (%)]	F2–F4 ($n = 264$) [*n* (%)]				
APRI							
< 0.5	168 (32)	111 (44)	57 (22)	78	44	59	66
> 0.5	351 (68)	144 (57)	207 (78)				
< 1.5	424 (82)	235 (92)	189 (72)				
> 1.5	95 (18)	20 (8)	75 (28)	28	92	79	55
Forns index							
< 4.2	104 (20)	66 (26)	38 (14)	86	26	55	64
> 4.2	415 (80)	189 (74)	226 (86)				
< 6.9	405 (78)	225 (88)	180 (68)				
> 6.9	114 (22)	30 (12)	84 (32)	32	88	74	56

PPV, positive predictive value; NPV, negative predictive value.

Table 4 Diagnostic accuracy of the aspartate aminotransferase to platelet ratio index (APRI) and the Forns index to predict significant fibrosis among patients with liver biopsy length ≥ 15 mm ($n = 120$)

		Fibrosis stage					
Cut-off point	All patients ($n = 120$) [n (%)]	F0–F1 ($n = 45$) [n (%)]	F2–F4 ($n = 75$) [n (%)]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
APRI							
<0.5	37 (31)	20 (44)	17 (21)	77	44	70	54
>0.5	83 (69)	25 (56)	58 (77)				
<1.5	94 (78)	41 (91)	53 (71)				
>1.5	26 (22)	4 (9)	22 (29)	29	91	85	44
Forns index							
<4.2	22 (18)	12 (27)	10 (13)	87	27	66	55
>4.2	98 (82)	33 (73)	65 (87)				
<6.9	94 (78)	40 (89)	54 (72)				
>6.9	26 (22)	5 (11)	21 (28)	28	89	81	43

PPV, positive predictive value; NPV, negative predictive value.

the stage of liver fibrosis. An analysis restricted to those individuals with LB size ≥ 15 mm showed improved predictive values (Table 4). Thus, the PPV to diagnose $F \geq 2$ for the APRI was 85% and for the FI it was 81%. The rates of misclassification for the detection of $F \geq 2$ were four (15%) individuals for the APRI and five (19%) for the FI. All these errors of classification of both indexes showed F1 in the LB; none of them was staged as absent fibrosis.

For patients with LB size ≥ 15 mm, 94 patients had an APRI value < 1.5. The FI was applied to these patients with indeterminate results for the diagnosis of $F \geq 2$. Ten (11%) of them showed an FI ≥ 6.9. Thus, 36 patients (30%) were classified as having $F \geq 2$ (Fig. 2). Six (17%) of them were misclassified. All of these diagnostic errors were staged as F1 in the biopsy. Thirty (40%) of 75 patients with $F \geq 2$ in the LB were correctly identified. The sequential application of the APRI and the FI yielded an S of 40%, an Sp of 87%, a PPV of 83% and an NPV of 46%. The AUROC (95% confidence interval) of both indexes to predict $F \geq 2$ was 0.69 (0.60–0.78) (Fig. 1).

A similar diagnostic yield of the APRI and the FI was found among patients with a liver biopsy performed within 12 months of their last visit. A total of 283 patients had an LB within that period of time, 64 of whom had an available biopsy size with a length of ≥ 15 mm. In the whole group of 283 individuals, an APRI ≥ 1.5 had an S of 21%, an Sp of 91%, a PPV of 79% and an NPV of 50%. An FI ≥ 6.9 showed an S of 28%, an Sp of 86%, a PPV of 72% and an NPV of 50% in those patients. In the group of 64 individuals with larger biopsy size, an APRI ≥ 1.5 yielded an S of 10%, an Sp of 95%, a PPV of 91% and an NPV of 38%, and an FI ≥ 6.9 showed an S of 18%, an Sp of 90%, a PPV of 82% and an NPV of 36% in those patients.

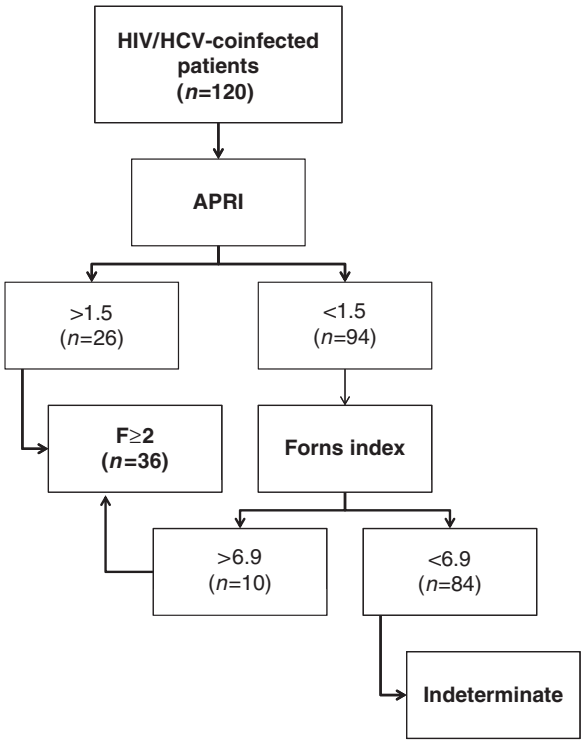

Fig. 2 Sequential application of the aspartate aminotransferase to platelet ratio index (APRI) and the Forns index to predict significant fibrosis among HIV/hepatitis C virus (HCV)-coinfected patients (liver biopsy length ≥ 15 mm; $n = 120$).

The diagnostic accuracy of the APRI and the FI according to alcohol use and HIV-related factors (such as CD4 cell count and HIV RNA suppression) is shown in Table 5.

Table 5 Diagnostic accuracy of the aspartate aminotransferase to platelet ratio index (APRI) and the Forns index to predict significant fibrosis according to alcohol use and HIV-related characteristics (liver biopsy length ≥ 15 mm; $n = 120$)

		APRI				Forns index			
Characteristic	***N***	**S (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**	**S (%)**	**Sp (%)**	**PPV (%)**	**NPV (%)**
Alcohol intake									
> 50 g/day	25	30	80	86	22	20	80	80	20
< 50 g/day	95	29	93	84	49	31	90	81	47
CD4 cell count									
< 450 cells/μL	52	38	90	86	47	31	85	77	44
> 450 cells/μL	68	23	92	83	41	26	92	85	42
Plasma HIV RNA									
Detectable	30	26	86	86	26	26	86	86	26
Undetectable	90	31	92	84	49	29	90	79	48

S, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

Discussion

In HIV/HCV-coinfected patients, the diagnostic accuracy of the APRI to predict $F \geq 2$ was similar in real-life conditions to that found in the validation studies. However, the FI performed less well. The combined use of the two indexes to diagnose $F \geq 2$ may prevent a significant proportion of patients having to undergo LB, which can be very useful in low-resource, nonreferral centres, where accessibility to biopsy or transient elastography is limited.

In the present study, the APRI and the FI predicted the presence of $F \geq 2$ with acceptable reliability. Thus, the APRI predicted the presence of $F \geq 2$ with 91% certainty, and misclassified 15% of the patients with scores ≥ 1.5, who showed only portal fibrosis in the LB. The FI predicted the presence of $F \geq 2$ with 89% certainty, and 19% of the patients with scores ≥ 6.9 showed F1. These errors of classification are not relevant as all misclassified patients had fibrosis in the LB. Therefore, 22% of the patients would benefit from not undergoing an LB, if the indexes were used as an aid for making decisions regarding anti-HCV therapy. Screening patients with indeterminate results for the APRI, i.e. those with APRI < 1.5, with the FI can increase the proportion of correctly classified patients to 30%. Hence, the percentage of patients with fibrosis $\geq$ F2 correctly identified in this study was 10% lower than in the validation studies in HIV/HCV-coinfected patients, where one-third or more of the patients were correctly classified using each index [9–16] and 40% by applying a sequential combination of the APRI and the FI [9].

In previous studies on the APRI and the FI in patients with HIV and HCV coinfection, the AUROC of the APRI to predict $F \geq 2$ has ranged from 0.66 to 0.85 [9–17]. The PPV of APRI > 1.5 to diagnose $F \geq 2$ has lain between 82% and 97% [9,13,15], after excluding extreme values [14,16]. For the FI, the AUROC values to predict $F \geq 2$ were between 0.59 and 0.77 [9–13], and the PPV of FI > 6.9 to detect $F \geq 2$ was > 90% [9,13]. Thus, the diagnostic yield of the APRI and the FI was lower in the present study than in previous validation studies in HIV/HCV-coinfected patients. The better results obtained in previous studies can be explained by the design of those studies. All of them were carried out in tertiary care centres [9–17]. One of the validation studies was a subanalysis of a randomized clinical trial [12]. It is probable that the study populations were highly selected in those studies. LB was used as a reference for the diagnosis of fibrosis in those reports, as in the present study. However, liver biopsies were reviewed at each participating centre and/or centrally by expert pathologists in the validation studies [9–17]. In contrast, we collected the information that was available on liver fibrosis classification at each centre, provided that liver fibrosis was staged following the METAVIR score. Thus, the quality of the reference for liver fibrosis was poorer in the present study compared with the validation studies.

Liver fibrosis staging in biopsies can be inaccurate because of sampling variability. This is an issue that is difficult to control. The performance of the APRI and the FI in the study population was relatively low, with a PPV for $F \geq 2$ lower than 80%. The diagnostic yield improved in the subgroup with LB lengths > 15 mm. This result is in agreement with that of a previous validation study in HIV/HCV-coinfected patients [9]. Analyses of discordant results between LB and noninvasive techniques for diagnosing fibrosis have also shown a reduction in discordance for larger biopsy samples [22].

The patients included in LB studies are usually regarded as not representative of the general HIV/HCV-infected population. The selection of patients takes into consideration factors such as adherence to HAART, number of

clinical visits missed, control of HIV disease, and abstinence from drug or alcohol abuse. Thus, the indexes evaluated in validation studies may perform less well in unselected patients. The GRAFIHCO study included a large group of patients with HIV/HCV coinfection and availability of current simple blood tests from a wide variety of health care facilities in Spain, including nonreferral centres and prisons. We compared the subgroup of patients selected for the present analysis with the whole study group. We found some expected differences between the two groups. Alcohol use was less frequent in the patients selected for this subanalysis. HIV disease control was better in the study patients, as reflected by a higher CD4 cell count and more frequent undetectable HIV RNA, in spite of similar rates of antiretroviral therapy prescription in the two groups. All of these characteristics are consistent with the profile of a typical candidate to undergo LB, i.e. a patient who is abstinent from alcohol, does not miss clinical visits and is adherent to antiretroviral therapy. However, the magnitude of the differences between groups in alcohol intake, HIV RNA and CD4 cell counts was small. In addition, these variables did not significantly affect the performance of the indexes. These suggest that the degree of selection in this population was not high. Finally, the APRI and the FI showed similar values in both the GRAFIHCO population and the patients selected for this analysis. To our knowledge, this is the first study that attempts to validate simple indexes for the prediction of liver fibrosis in patients that could be regarded as fairly representative of a large population with HIV/HCV coinfection in a Western country.

In conclusion, the APRI and the FI can be used to predict clinically relevant liver fibrosis in HIV/HCV-coinfected patients in nonreferral health care facilities. The simplicity and wide availability of the tests involved in the calculation of these indexes, coupled with their low cost, makes them attractive as elective techniques for the diagnosis of fibrosis in low-resource settings.

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Appendix

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