LIVER FIBROSIS

Prediction of liver fibrosis in human immunodeficiency virus/hepatitis C virus coinfected patients by simple non-invasive indexes

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Background: Liver biopsy is an invasive technique with associated major complications. There is no information on the validity of five non-invasive indexes based on routinely available parameters, estimated and validated in hepatitis C virus (HCV) monoinfected patients, in human immunodeficiency virus (HIV)/HCV coinfected patients.
Aim: To validate these predictive models of liver fibrosis in HIV/HCV coinfected patients.
Patients: A total of 357 (90%) of 398 patients from five hospitals were investigated, who underwent liver biopsy and who had complete data to validate all of the models considered.
Methods: The predictive accuracy of the indexes was tested by measuring areas under the receiver operating characteristic curves. Diagnostic accuracy was calculated by estimating sensitivity, specificity, and positive (PPV) and negative (NPV) predictive values.
Results: The models performed better when liver biopsies ⩾15 mm were used as reference. In this setting, the Forns and Wai indexes, models aimed at discriminating significant fibrosis, showed PPV of 94% and 87%, respectively. Using these models, 27–34% of patients could benefit from exclusion of liver biopsy. If both models were applied sequentially, 41% of liver biopsies could be spared. The indexes aimed at predicting cirrhosis achieved NPV of up to 100%. However, they showed very low PPV.
Conclusions: The diagnostic accuracy of these models was lower in HIV/HCV coinfected patients than in the validation studies performed in HCV monoinfected patients. However, simple fibrosis tests may render liver biopsy unnecessary in deciding anti-HCV treatment in over one third of patients with HIV infection and chronic hepatitis C.

Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) dual infection is highly prevalent among intravenous drug users as a result of shared transmission routes.[1] In addition, chronic hepatitis C seems to follow an accelerated course in HIV infection.[2] Thus liver failure is increasingly affecting HIV/HCV coinfected patients, as their AIDS free survival is being prolonged.[3] For these reasons, HCV infection should be treated in this setting. However, the available treatment for HCV infection is far from optimal. Indeed, HIV/HCV coinfected patients show even worse responses to pegylated interferon plus rivabirin than HCV monoinfected patients.[4] In this regard, different strategies have been proposed and evaluated to improve the selection of patients to receive therapy. A rational screening is to perform a liver biopsy and reserve treatment for those with more advanced stages of liver fibrosis. We have shown that this approach would spare up to 40% of coinfected patients from anti-HCV therapy.[5]

Liver biopsy is an invasive technique. Although infrequent, there are major complications associated with liver biopsy.[6] Mild adverse events are more frequent, such as pain, that occurs in more than 30% of biopsied patients.[6] Moreover, the procedure is costly[7] and can be limited by sampling error as only 1/50 000 of the organ is sampled. Hence some authors have validated models to predict the severity of liver fibrosis by non-invasive means. Some rely on routine laboratory tests, easily available in clinical practice.[8–14] There are only two reported models which have focused on non-invasive diagnosis of liver fibrosis among HIV/HCV coinfected patients.[15 16] However, none of the models has been validated by independent authors in this population. In addition, the usefulness of these indexes may be curtailed because some of the predictive markers, such as α_2 macroglobulin, haptoglobin, or apolipoprotein A1[15] and hyaluronic acid[16] are not routinely used in clinical practice.

Our aim was to validate five predictive models of liver fibrosis comprising readily available laboratory data, previously constructed and validated in HCV monoinfected patients,[8–14] in HIV/HCV coinfected patients.

METHODS

Patients

This retrospective cross sectional study included 398 consecutive patients with HIV/HCV coinfection who were admitted to five hospitals in southern Spain for liver biopsy, from January 1991 to January 2005. Liver biopsies were taken mainly with the aim of establishing the prognosis and indicating therapy for chronic hepatitis C. Eligible patients were those coinfected with HIV and HCV who had undergone liver biopsy, regardless of levels of transaminases. Exclusion criteria included positive hepatitis B surface antigen, other causes of liver disease (autoimmune, tumoral, biliary, or vascular associated liver disease) and prior anti-HCV therapy.

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the receiver operating curve; AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST platelet ratio index; ULN, upper limit of normal; HAART, highly active antiretroviral therapy

Clinical, biochemical, and haematological data within one month of liver biopsy were collected from databases that abstracted patient records.

For each patient a case report form was completed. It included the main demographics, and clinical, laboratory, and virological data at the time of liver biopsy. Recorded demographics included age, sex, risk category, and history of alcohol intake. Data regarding both HIV and HCV infections were recorded, including plasma HIV-RNA, CD4+ T cell counts at the time of liver biopsy, and antiretroviral therapy. Regarding HCV infection, data recorded included genotype, viral load, both at the time of liver biopsy, and date of infection. The latter was estimated as the first year of needle exchange in intravenous drug users. The date of HCV infection was considered as unknown for subjects infected through sexual contact or an undefined source.

This study was approved by each local ethics committee. All patients gave written informed consent for liver biopsy.

Predictive indexes of fibrosis

Among the indexes based on routinely available laboratory tests, we selected those with internal[8 9] or external validation.[10–14] These indexes were elaborated with the aim of discriminating significant fibrosis, F2 to F4 stages, and/or cirrhosis in HIV seronegative patients:

Indexes aimed at discriminating significant fibrosis

Forns and colleagues[8] and Wai and colleagues[9] validated their results in a separate group of patients. The index by Forns and colleagues[8] is calculated by applying the following regression equation:

7.811−3.131 ln (platelet count (10^9/l)) + 0.781 ln (γ-glutamyl-transpeptidase (UI/l)) + 3.467 ln (age (y)) − 0.014 (cholesterol (mg/dl)).

In the estimation of the model by Forns and colleagues,[8] the authors excluded drinkers of more than 30 g/day of alcohol and the predominant HCV genotype was 1. The high prevalence of genotype 3 in HIV/HCV coinfected patients[3] and its influence on cholesterol levels[17] could have affected the accuracy of the index in our study. Because of this, we also analysed a subgroup of patients with alcohol intake <50 g/day and without genotype 3 to validate this model. The index by Wai and colleagues,[9] known as the AST platelet ratio index (APRI), is calculated by dividing the aspartate aminotransferase (AST) level (UI/l), expressed as the number of times above the upper limit of normal (ULN), by platelet count (10^9/l):

AST (/ULN) ×100/platelet count (10^9/l)

Alcohol drinkers were not excluded from elaboration of the index. The cut off points validated by these authors and positive (PPV) and negative (NPV) predictive values of the indexes are shown in table 1.

Indexes aimed at discriminating cirrhosis

APRI was also aimed at predicting cirrhosis.[9] The index by Bonacini and colleagues[10] has been recently validated by Saadeh and colleagues[13] This index was calculated by assigning arbitrary scores to three laboratory parameters and summing them with a possible value of 0 to 11. The laboratory parameters were scored as follows:

(a) platelet count (10^9/l): >340 = 0; 280–340 = 1; 220–270 = 2; 160–219 = 3; 100–159 = 4; 40–99 = 5; <40 = 6.
(b) ALT/AST ratio: >1.7 = 0; 1.2–1.7 = 1; 0.6–1.19 = 2; <0.6 = 3.
(c) international normalised ratio: <1.1 = 0; 1.1–1.4 = 1; >1.4 = 2.

Alcohol drinkers were not excluded from validation of this index. AST/ALT ratio and platelet count were assessed as indexes in numerous previous surveys.[11 12 14] Alcohol drinkers were not excluded in some of the studies that validated AST/ALT ratio[11] or platelet count.[12] The cut off points validated by these authors and PPV and NPV of the indexes are shown in table 1.

Laboratory methods

Blood determinations

HCV infection was diagnosed when serum specific antibodies were identified by enzyme immunoassay and a recombinant immunoblot assay before 1996. Since December 1996, diagnosis of HCV infection was made when a positive

Table 1 Cut off points, and positive (PPV) and negative (NPV) predictive values of the indexes evaluated, prevalence of significant fibrosis or cirrhosis in the validation studies, and proportion of liver biopsies that could be prevented

Models aimed at predicting significant fibrosis					
Model	**Score cut off point**	**PPV (%)**	**NPV (%)**	**Prevalence of significant fibrosis (%)**	**Liver biopsies prevented (%)**
Forns[8]				26	51
	<4.2	40	96		
	>6.9	66	80		
APRI[9]				47	51
	<0.5	61	86		
	>1.5	88	64		
Models aimed at predicting cirrhosis					
Model	**Cut off score**	**PPV (%)**	**NPV (%)**	**Prevalence of cirrhosis (%)**	**Liver biopsies prevented (%)**
APRI[9]				15	15
	<1	38	98		
	>2	57	93		
Saadeh[13,14]				29	29
	<3*	—	—		
	>7	100	73		
ALT/AST ratio[11,14]				23–34	Up to 34
	<1	43–100	78–88		
Platelet count [12]				13	13
	<150	93	99		

AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST platelet ratio index.
*The authors did not provide enough data to calculate PPV and NPV for this cut off point.

EIA-3 was found and serum viral RNA was detected by either qualitative or quantitative polymerase chain reaction. HCV genotype was determined by line probe assay.

Histological evaluation

Specimens were immediately placed in buffered formalin. After 24 hours of fixation they were embedded in paraffin using routine methods. Histological evaluation was made on sections stained with haematoxylin-eosin and Masson's trichrome. A single pathologist, who was not aware of the clinical data of the patients, evaluated all of the stained sections at each centre. Liver fibrosis was scored following the Knodell histological activity index modified by Scheuer.[18] A minimum liver biopsy length of 10 mm was required. Reproducibility of liver fibrosis staging was assessed by blinded re-evaluation by a single pathologist of 50% of the liver biopsies from each centre randomly selected.

Statistical methods

Continuous variables were expressed as median (Q1–Q3) and 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 where appropriate.

The predictive accuracy of the indexes was tested by measuring the areas under the receiver operating characteristic curves (AUROC). The cut off points evaluated were those previously validated for each index in HIV uninfected patients. Diagnostic accuracy was calculated by sensitivity, specificity, PPV, and NPV. Significant fibrosis (stages 2–4) or cirrhosis (stage 4) was considered as the disease depending on the index. Performance of the indexes was also assessed using ROC curves in different subpopulations of patients, classified according to the size of their liver biopsies. Agreement between pathologists from different centres and the central pathologist was assessed by the kappa test.

Statistical analysis was carried out using the SPSS 11 statistical software package (SPSS, Chicago, Illinois, USA).

RESULTS

Characteristics of the patients

A total of 357 (90%) of 398 patients had complete data for validation of all of the models. The main characteristics of the study patients by date of liver biopsy are summarised in table 2.

Liver biopsy was carried out in 321 (90%) patients after 1997. HCV genotype was 1 in 189 (53%), 3 in 87 (24%), 4 in 46 (13%), and not available in 36 (10%) patients. Median $CD4^+$ cell counts by the time of liver biopsy were 494 (336–653) cells/ml. Median nadir $CD4^+$ cell counts were 255 (136–396) cells/ml. A total of 189 (53%) patients showed undetectable HIV viral load achieved with highly active antiretroviral therapy (HAART) by the date of liver biopsy: 221 (62%) patients received protease inhibitor based HAART before liver biopsy, 57 (16%) were treated with nevirapine based antiretroviral regimens, and 71 (20%) were prescribed efavirenz based HAART. Good agreement was found between each centre's pathologist and the central pathologist in scoring significant fibrosis (kappa scores 0.76–0.80) and cirrhosis (kappa scores 0.87–0.93).

Predictive models of fibrosis applied to HIV infected patients with chronic hepatitis

Models aimed at predicting significant fibrosis

AUROC for the models of Forns and colleagues[8] and APRI[9] by biopsy length are shown in table 3. Both models performed better for biopsy size ⩾15 mm. Further increases in biopsy length did not improve AUROC. Because of this, 263 (74%) of 357 patients, in which liver biopsy length was at least 15 mm, were selected to validate these indexes. Characteristics of these patients are shown in table 2.

For the model of Forns and colleagues,[8] applying the lower cut off level (<4.2), 42 (38%) of 110 patients without significant fibrosis were correctly identified (table 4).

The presence of significant fibrosis could not be excluded with certainty, as 33 (44%) of 75 patients with a score <4.2 had significant fibrosis (NPV 56%). Applying the higher cut off level (>6.9), 66 (43%) of 153 patients with significant fibrosis were correctly identified (table 4). Sixty six (94%) of 70 patients with a score >6.9 showed significant fibrosis. Two of the four falsely classified patients showed F0 and two showed F1 stage at liver biopsy. In the study group, 106 patients reported alcohol intake <50 g/day and harboured genotype non-3. We also applied the model by Forns and colleagues[8] to these patients. AUROC was 0.77 (0.65–0.83). Diagnostic accuracy for this analysis was:

Table 2 Characteristics of human immunodeficiency virus (HIV) infected patients with chronic hepatitis C virus (HCV) at the time of liver biopsy according to sample length

Variable	Liver biopsy length: All patients, ⩾10 mm (n = 357)	Liver biopsy length: ⩾15 mm (n = 263)
Age (y)	37 (33–40)	37 (34–41)
Males (n (%))	296 (83)	220 (84)
Intravenous drug use or transfusion (n (%))	332 (93)	241 (92)
Alcohol intake >50 g/day (n (%))	89 (25)	77 (29)
Age at HCV infection* (y)	21 (18–26)	21 (17–25)
Duration of HCV infection* (y)	15 (11–19)	17 (12–19)
AST (UI/l)	65 (44–103)	5 (44–96)
ALT (UI/l)	83 (55–132)	80 (54–133)
GGT (UI/l)	105 (56–186)	106 (57–184)
Cholesterol (mg/dl)	170 (144–194)	170 (144–194)
Platelets (10^9/l)	187 (146–224)	186 (146–217)
International normalised ratio	1.1 (1–1.3)	1.1 (1–1.2)
Genotype 1† (n (%))	189 (53)	134 (51)
HCV viral load‡ $\log_{10}$ (UI/ml)	6.0 (5.7–6.4)	5.95 (5.6–6.4)
Significant fibrosis (F2–F4) (n (%))	196 (55)	153 (58)
Cirrhosis (n (%))	46 (13)	40 (15)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyl-transpeptidase.
Not available in: (a) biopsy length ⩾10 mm: *32 patients; †36 patients; ‡31 patients; (b) biopsy length ⩾15 mm: *24 patients; †26 patients; ‡24 patients.

Table 3 Area under the receiver operating characteristic curves (95% confidence interval) of the indexes validated in human immunodeficiency virus/hepatitis C virus coinfected patients by liver biopsy length

Biopsy length (mm)	n	Models aimed at discriminating significant fibrosis		Models aimed at discriminating cirrhosis			
		Forns[8]	APRI[9]	APRI[9]	Bonacini[10]	ALT/AST	Platelets
⩾10	357	0.71 (0.66–0.76)	0.73 (0.66–0.78)	0.77 (0.69–0.85)	0.69 (0.61–0.77)	0.60 (0.50–0.69)	0.79 (0.72–0.86)
⩾15	263	0.77 (0.71–0.83)	0.80 (0.75–0.86)	0.79 (0.71–0.87)	0.71 (0.63–0.79)	0.60 (0.50–0.69)	0.79 (0.72–0.86)
⩾20	146	0.76 (0.70–0.85)	0.80 (0.73–0.88)	0.80 (0.74–0.88)	0.73 (0.66–0.80)	0.62 (0.50–0.70)	0.80 (0.73–0.87)

AST, aspartate aminotransferase; ALT, alanine aminotransferase; APRI, AST platelet ratio index.

(a) low cut off (<4.2): sensitivity 79%, specificity 48%, PPV 63%, and NPV 67%;
(b) high cut off (>6.9): sensitivity 41%, specificity 98%, PPV 96%, and NPV 60%.

Twenty three (96%) of 24 patients with a score >6.9 showed significant fibrosis.

Using the APRI, for patients with a score <0.5, 36 (33%) of 110 without significant fibrosis would be correctly classified (table 4). Among the 48 patients with a score <0.5, 12 (25%) showed significant fibrosis (75% NPV). Seven showed F2, four patients showed F3, and one patient F4 stage on liver biopsy. For patients with a score >1.5, 78 (51%) of 153 with significant fibrosis were correctly classified (table 4). Seventy eight (89%) of 88 patients with a score >1.5 showed significant fibrosis. Seven of 11 misclassified patients showed F1 and three showed F0 stage on liver biopsy.

A total of 175 patients showed a score <1.5 in the APRI. These patients with indeterminate results were screened with the Forns and colleagues[8] index, and 21 (12%) showed a Forns score >6.9. Two patients were misclassified. Thus the diagnostic accuracy of the index of Forns and colleagues[8] applied to APRI indeterminate results (score <1.5) was: sensitivity 25%, specificity 98%, PPV 91%, and NPV 64%. Combining both indexes, 109 (41%) patients could be spared from liver biopsy.

The diagnostic accuracy of the indexes was not affected by HIV related variables. Patients with and without undetectable HIV RNA at the time of liver biopsy had an AUROC of 0.77 (0.70–0.82) and 0.75 (0.70–0.80) for the Forns model and 0.80 (0.75–0.84) and 0.79 (0.73–0.82) for the APRI, respectively. Patients with $CD4^+$ cell counts ⩽500 and >500 at the time of liver biopsy had an AUROC of 0.77 (0.72–0.84) and 0.76 (0.71–0.82) for the Forns model and 0.79 (0.74–0.83) and 0.79 (0.75–0.84) for the APRI, respectively.

Models aimed at predicting cirrhosis

AUROC values for these models are shown in table 3. The models performed better for biopsy size ⩾15 mm. Further increases in biopsy length did not improve AUROC. Because of this, patients with a liver biopsy length of at least 15 mm were selected to validate these indexes.

For APRI, 126 (93%) of 135 patients with a score <1 did not have cirrhosis (table 5). Nine (23%) of 40 patients with cirrhosis were classified falsely. For patients with a score >2, 21 (46%) of 46 had cirrhosis and 25 (11%) of 223 without cirrhosis were identified falsely. PPV for both cut off points was low (table 5).

For the Bonacini model,[10] all 34 patients with a score below the low cut off did not show cirrhosis (table 5). Twenty (29%) of 68 patients with score above the high cut off had cirrhosis, and 48 (16%) of 297 without cirrhosis were incorrectly identified. PPV for both cut off points was low (table 5).

The AST/ALT ratio was not accurate in predicting the absence or presence of cirrhosis (table 6). Platelet count, using a cut off of 150 10^9/l, allowed prediction of the absence of cirrhosis with 92% certainty. The presence of cirrhosis was predicted with 33% certainty (table 6).

DISCUSSION

In this study, we attempted to validate predictive models of liver fibrosis previously estimated in HCV monoinfected patients. We selected models based on data easily available, which had been subject to internal or external validation. The diagnostic accuracy of these models was lower in HIV/HCV coinfected patients than in validation studies performed in HCV monoinfected patients. However, simple fibrosis tests may render liver biopsy unnecessary for deciding therapy against HCV in over one third of patients with HIV infection and chronic hepatitis C, as significant liver fibrosis may be predicted in such patients.

Liver biopsy is an invasive technique with associated morbidity and mortality[6] and has a significant cost.[7] Because of this, others have attempted to find accurate non-invasive markers of liver fibrosis in chronic hepatitis C. However, only two studies evaluated a models to predict liver fibrosis in HIV infected patients with chronic hepatitis C, but

Table 4 Diagnostic accuracy of the models aimed at predicting significant fibrosis in the study group

Cut off point	All patients (n = 263) (n (%))	Fibrosis stage		Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
		Stage 0–1 (n = 110) (n (%))	Stage 2–4 (n = 153) (n (%))				
Forns model[8]							
<4.2	75 (29)	42 (38)	33 (22)	78	38	64	56
>4.2	188 (71)	68 (62)	120 (78)				
<6.9	193 (73)	106 (96)	87 (57)				
>6.9	70 (27)	4 (4)	66 (43)	43	96	94	55
APRI[9]							
<0.5	48 (18)	36 (33)	12 (8)	92	33	66	75
>0.5	215 (82)	74 (67)	141 (92)				
<1.5	175 (67)	100 (91)	75 (49)				
>1.5	88 (34)	10 (9)	78 (51)	51	91	87	57

APRI, AST platelet ratio index; PPV, positive predictive value; NPV, negative predictive value.

Table 5 Diagnostic accuracy of the AST platelet ratio index (APRI) and Bonacini model in predicting cirrhosis in the study group

Cut off point	All patients (n = 263) (n (%))	Fibrosis stage: Stage 0–3 (n = 223) (n (%))	Fibrosis stage: Stage 4 (n = 40) (n (%))	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
APRI							
<1	135 (51)	126 (57)	9 (22)	78	57	24	93
>1	128 (49)	97 (43)	31 (78)				
<2	217 (83)	198 (89)	19 (47)				
>2	46 (17)	25 (11)	21 (53)	53	89	46	91
Bonacini model[10]							
<3	21 (8)	21 (9)	0 (0)	100	9	17	100
>3	242 (92)	202 (91)	40 (100)				
<7	208 (79)	185 (83)	23 (57)				
>7	55 (21)	38 (17)	17 (43)	43	83	31	89

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

they were based on laboratory parameters not routinely performed which limits their clinical applicability.[15 16] In addition, a cumbersome determination, only publicly available very recently, is involved in the calculation of the Fibrotest. This model appears to identify correctly an increased number of HIV/HCV coinfected patients with and without significant hepatic fibrosis, potentially sparing half of the patients from liver biopsy.[15] This index has been subject to external validation by independent authors in only one study in patients with chronic hepatitis C without HIV infection.[19] Unfortunately, the diagnostic yield of the test was not reproduced by these authors. A novel model, also based on non-routinely used laboratory parameters, has recently been elaborated in HIV/HCV coinfected patients.[16] However, this index was not validated in a separate group of patients by the authors. In addition, the performance of the model did not improve previous simpler indexes.

In the present study, the models aimed at discerning significant from non-significant fibrosis reliably predicted the presence of substantial fibrosis. Thus the model of Forns and colleagues[8] predicted the presence of significant fibrosis with 96% certainty, and only 4% of patients with a score >6.9 showed non-significant fibrosis. Similarly, the APRI predicted the presence of significant fibrosis with 91% certainty, and misclassified 9% of patients with a score >1.5 who showed F0 to F1 stage fibrosis on liver biopsy. Hence 27–34% of patients would benefit from exclusion from liver biopsy as a tool for deciding anti-HCV therapy. This represents one third of patients potentially excluded from liver biopsy compared with half of patients prevented from liver biopsy in the original studies.[8 9] If patients with indeterminate results with the APRI are screened with the Forns model,[8] 40% of patients could be spared liver biopsy by combining both models, as treatment for HCV could be indicated in these cases.

The APRI has recently been validated in patients with chronic hepatitis C with HIV infection.[16] Among HIV coinfected patients, AUROC was 0.71. Liver biopsy size >10 mm was required by the authors in this study. This poor result is in agreement with our findings as the APRI had an AUROC value of 0.73 for liver biopsies ⩾10 mm in our study. We found that with larger liver biopsies as reference, this and other indexes performed better. In this regard, another recent study validated the APRI in patients with chronic hepatitis C without HIV infection.[20] At least six portal tracts were required and mean length of the biopsy core was 19 mm. The AUROC of the APRI was 0.80, which is in agreement with our results for larger liver biopsies. Thus the potential variability of liver biopsy, whose diagnostic performance is critically affected by sample size, probably influenced the diagnostic yield of the indexes of fibrosis found in previous studies.

The APRI, the Bonacini model,[10] and platelet count showed high levels of certainty in predicting the absence of cirrhosis. This may be reassuring for patients and physicians but is of little clinical use. Thus patients classified as not having cirrhosis still need a liver biopsy for treatment decisions. In contrast, these models did not confidently predict the presence of cirrhosis, as the PPV was low. These disappointing results are in agreement with a recent survey on patients without HIV infection.[20]

Liver biopsy was used as a reference for the diagnosis of fibrosis. However, the accuracy of liver biopsy for assessing fibrosis is limited by observer and sampling variability. Several studies have assessed interobserver variability in the evaluation of fibrosis. These surveys concluded that

Table 6 Diagnostic accuracy of the aspartate aminotransferase/alanine aminotransferase (AST/ALT) index and platelet count in predicting cirrhosis in the study group

Cut off point	All patients (n = 263) (n (%))	Fibrosis stage: Stage 0–3 (n = 223) (n (%))	Fibrosis stage: Stage 4 (n = 40) (n (%))	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
AST/ALT							
<1	197 (75)	172 (77)	25 (63)				
>1	66 (25)	51 (23)	15 (38)	38	77	23	87
Platelet count							
<150	76 (29)	51 (23)	25 (63)	63	37	33	92
>150	187 (71)	172 (77)	15 (37)				

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

reproducibility in staging fibrosis in chronic hepatitis C is good, whatever the scoring system.[21] In the present study, interobserver variability was also low. In contrast, sampling variability is more difficult to control. We evaluated the performance of the indexes evaluated in this study for different liver biopsy sizes. We observed that increasing the liver biopsy size from 10 mm to 15 mm improved the diagnostic yield but further increases did not provide better yields. This is in accordance with a previous survey that analysed discordant results between liver biopsy and markers of fibrosis.[22] In this study, patients categorised as staging errors on liver biopsy showed smaller biopsy size. However, larger biopsies, ⩾15 mm or ⩾25 mm, were similarly frequent in patients with and without discordant results.

The patients included in this study may not be fully representative of the HIV/HCV population. Only patients who adhered to clinical visits and antiretroviral therapy were selected for liver biopsy. In addition, patients were usually scheduled to undergo liver biopsy only if they had been abstinent from alcohol and other drugs, and HIV infection was stable and under control. Thus there was a possible bias towards patients with less advanced HIV infection and less concomitant alcohol related liver disease. However, the indexes evaluated in this study would probably have performed worse in patients with these associated problems.

The presence of HIV infection changes the course of chronic hepatitis C. Thus coinfected patients show accelerated evolution of chronic hepatitis C, most probably related to immunosuppression.[2] These patients are exposed to antiretroviral drugs that are associated with elevations in transaminases, bilirubin, γ-glutamyl-transpeptidase, and cholesterol, all of which can distort the results of some indexes. Moreover, antiretroviral therapy may alter the course of liver fibrosis in HCV infection.[23 24] However, analysis of the study population stratified by $CD4^+$ cell counts and undetectable HIV RNA achieved with antiretroviral therapy did not show changes in the performance of the indexes. Indeed, inclusion of HIV related variables in the validation of the Fibrotest in HIV/HCV coinfected patients did not improve the diagnostic yield of the model.[16]

In conclusion, therapy for HCV may be decided without liver biopsy evaluation of fibrosis in over one third of HIV infected patients with chronic hepatitis C using simple indexes. Absence of cirrhosis, but not its presence, and significant liver fibrosis can be predicted with certainty in most patients. However, these results clearly need improvement. Hence achieving a non-invasive tool, readily available at the bedside, to predict liver fibrosis in the setting of HIV/HCV coinfection, still requires further investigation.

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