Independent Assessment and Cost–Performance Analysis of Noninvasive Liver Fibrosis Biomarkers in HIV-HCV Coinfected Patients: The Fibrovic Study—ANRS HC02

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Abstract

Background: Many non-invasive liver fibrosis scores have been proposed as alternatives to liver biopsy (LB) in HCV infected patients. Fibrotest (FT), SHASTA, and Fib-4 scores have been tested by their promoters in small cohorts of HIV-HCV co-infected patients.

Aim: To independently compare the diagnostic accuracy and cost-performance of the FT, APRI, Forns, Hepascore (HS), Fibrometer (FM), SHASTA, and Fib-4 scores in a large cohort of HIV-HCV co-infected patients in order to differentiate between those with mild to moderate fibrosis and those with advanced liver disease.

Patients & Methods: 272 HIV-HCV co-infected patients, naïve for HCV treatment, had had a LB before inclusion in the prospective ANRS HC02 Ribavic trial: 197 (72%) men, age 39.9 years, LB length 18.6 mm, fibrosis stage (Metavir) F1 in 68 (25%) patients, F2 in 109 (40%), F3 in 67 (25%), and F4 in 28 (10%). The diagnostic accuracy of each score was determined by the area under the ROC curve (AUROC), and the accuracy (rate of well-classified patient) compared to LB. The cost-effectiveness of each score was calculated as the ratio of the incremental cost/incremental AUC performance.

Results: FT, HS, and FM could be applied to all patients and were more accurate than other scores, with AUROCs of 0.64, 0.69, and 0.70 for the diagnosis of significant fibrosis (≥F2), respectively. The AUROC values for the diagnosis of F3F4 were 0.72, 0.76, and 0.78, respectively. The correlation coefficient indexes were 0.372, 0.456 and 0.484, respectively. For a global analysis, FT, HS, and FM showed an accuracy of 62%, 68% and 71%, respectively. The Fib-4, APRI, and Forns index could be applied to 37-61% of patients and showed lower accuracies. Attempts to find a better test by using a combination of FT, HS and FM did not significantly increase the diagnostic performance of each test. The cost-performance ratio was better for HS than for FT or FM.

Conclusion: Among non-invasive liver fibrosis biomarkers in HIV-HCV co-infected patients, Fibrometer, Hepascore and Fibrotest can be applied to all patients and can correctly classify patients with severe fibrosis. Hepascore showed a better cost-performance ratio.

Background

- Many noninvasive liver fibrosis scoring systems, such as Fibrotest (FT), APRI, Forns, Hepascore (HS), and Fibrometer (FM), have been proposed as alternatives to liver biopsy in patients infected with the hepatitis C virus (HCV).
- Scant information exists about the applicability of these models in coinfected patients; only FT, SHASTA, and Fib-4 scores have been tested in small cohorts of HIV-HCV coinfected patients.

Aim

- To compare, independently from the promoters of the scores, diagnostic accuracies and cost-effectiveness of FT, SHASTA, Fib-4, HS, FM, APRI, and Forns scores in a large cohort of HIV-HCV coinfected patients to differentiate those with mild to moderate fibrosis from those with advanced disease.

Methods

Patients

- This study included 272 serum samples from HIV-HCV coinfected patients who were HCV treatment naive and who underwent percutaneous liver biopsy before inclusion in the prospective multicenter ANRS HC02 Ribavic trial.

Noninvasive Biomarkers

- FT, SHASTA, Fib-4, HS, FM, APRI, and Forns scores were determined for all patients using fasting serum samples that were obtained at the time of entry in the Ribavic trial and stored at –80°C until analysis.
- α_2-Macroglobulin (α2M), apolipoprotein A_1 (Apo A_1), and haptoglobin were measured using a modular analyzer (BNII; Dade Behring, Marburg, Germany).
- Total bilirubin, gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using a Hitachi 917 Analyzer and Roche Diagnostics reagents (both Mannheim, Germany).
- Hyaluronic acid, urea, total cholesterol, albumin levels, and platelet counts were determined using validated methods.
- All biochemical parameter and score determinations were made without knowledge of liver biopsy results.

Statistical Analysis

- Area under the receiving operating curve (AUROC) was compared with the Hanley-McNeil test, and accuracies were compared with the McNemar or chi-square test.
- Statistical analysis was performed using SAS V8.2 statistical software (SAS Institute Inc., Cary, NC).

Cost–Performance Analysis

- We compared the costs of noninvasive biological scores and their related performances.
- The area under the curve (AUC) was used as the measure of performance, and it was scaled as the difference from 0.5 (ie, the AUC of a test with no apparent accuracy).
- Incremental cost–performance ratios between scores were calculated when 1 score performed better but was more expensive than another; this was presented as the ratio of the cost difference between the 2 scores to the AUC difference. They were expressed in euros (2006) per percentage of AUC.
- Incremental ratios represent the price to be paid, in addition to the cost of a score that performed less, and the use of a better score to increase the chance by 1% of correctly ranking results of 2 liver histology tests in patients with and without fibrosis.

Results

General Characteristics

- Baseline demographic and disease characteristics are listed in **Table 1**.
- The mean length of the liver biopsy specimens was 18.6 ± 7.9 mm (range, 6-44 mm).
- According to METAVIR fibrosis staging, 204 (75%) of 272 patients had significant fibrosis (≥F2), 95 (35%) of 272 had severe fibrosis (≥F3), and 28 (10%) of 274 had cirrhosis (F4).

Table 1. Main Demographic, Laboratory, and Liver Histologic Features of 272 HIV-HCV Coinfected Patients

Characteristic	Mean Value ± SD	Minimum	Maximum
Male/Female, n	197/75	—	—
Age, y	39.9 ± 5.4	21.0	57.0
α2M, g/L	3.6 ± 1.3	1.2	7.4
Apo A_1, g/L	1.5 ± 0.4	0.4	2.5
Bilirubin, µmol/L	10.2 ± 7.5	0.0	54.7
GGT, IU/L	124.0 ± 116.8	12.0	869.0
Haptoglobin, g/L	0.9 ± 0.5	0.1	2.5
Hyaluronic acid, µg/L	85.4 ± 117.3	10.0	1412.0
AST, IU/L	87.6 ± 64.3	5.0	371.0
ALT, IU/L	67.8 ± 53.2	5.0	325.0
Urea, g/L	0.3 ± 0.1	0.1	0.7
Cholesterol, g/L	1.6 ± 0.5	0.5	3.9
Platelet count, 10^9/L	196.4 ± 65.5	60.0	434.0
Albumin, g/L	42.3 ± 4.7	27.2	63.5
Liver fibrosis stage, n (%)			
F0	0 (0)	—	—
F1	68 (25)	—	—
F2	109 (40)	—	—
F3	67 (25)	—	—
F4	28 (10)	—	—

α2M = α_2-macroglobulin; Apo A_1 = apolipoprotein A_1; GGT = gamma-glutamyl transferase; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Liver fibrosis stage by METAVIR scoring system.

Score Accuracies

- **Table 2** shows the AUCs of the noninvasive fibrosis scores for the diagnoses of ≥F2, ≥F3, and F4.
  - For the ≥F2 diagnosis, the AUCs of FM and HS were significantly higher than the AUC of the Forns index ($P < .05$).
  - For the ≥F3 diagnosis, 3 scores (FM, HS, and FT) had higher AUCs than the others.
  - All scores increased significantly (Kruskal-Wallis test $P < .0001$) as fibrosis stage increased (data not shown).

Table 2. Accuracies of Noninvasive Biological Markers, as Measured by the AUC, for the Diagnosis of Liver Fibrosis in 272 HIV-HCV Coinfected Patients

	AUC (95% CI)			R Index With LB
Liver Fibrosis Stage	≥F2	≥F3	F4	
Fibrometer	0.70 (0.64, 0.76)*	0.78 (0.73, 0.83)	0.84 (0.78, 0.88)	0.484
Hepascore	0.69 (0.63, 0.74)*	0.76 (0.71, 0.81)	0.83 (0.78, 0.88)	0.456
Fibrotest	0.64 (0.58, 0.70)	0.72 (0.66, 0.77)	0.81 (0.76, 0.85)	0.372
Fib-4	0.65 (0.59, 0.71)	0.69 (0.63, 0.75)	0.72 (0.67, 0.78)	0.337
SHASTA	0.64 (0.58, 0.70)	0.68 (0.62, 0.73)	0.72 (0.67, 0.78)	0.321
APRI	0.65 (0.59, 0.71)	0.67 (0.61, 0.72)	0.70 (0.64, 0.75)	0.308
Forns index	0.59 (0.53, 0.65)	0.66 (0.60, 0.72)	0.79 (0.74, 0.84)	0.278

*$P < .05$ versus Forns index.
AUC = area under the curve; HCV = hepatitis C virus; R index = correlation coefficient using the Spearman rank correlation; LB = liver biopsy.
Liver fibrosis stage by METAVIR scoring system.

- **Table 3** shows the diagnostic performances of noninvasive biomarkers for the diagnosis of significant liver fibrosis (≥F2).
  - Fib-4, APRI, and Forns scores could be applied to 37%, 53%, and 60% of cases, respectively, whereas FM, HS, and FT could be applied to all cases.
  - FM, HS, and FT had significantly higher accuracy (62%-71%) than other scores (22%-43%) ($P < .05$).

Table 3. Performance of Noninvasive Biological Surrogate Markers for the Diagnosis of Significant Liver Fibrosis (≥F2 by METAVIR Scoring System) in 272 HIV-HCV Coinfected Patients

	Fibrometer	Hepascore	Fibrotest	Fib-4	APRI	Forns
Cutoff value	0.5	0.5	0.5	≤0.6/≥1.0	<0.5/≥1.5	<4.2/≥6.9
Undetermined cases, %	0	0	0	37	53	60
Accuracy, %	71*	68*	62*	43	33	22
PPV, %	80	81	83	88	86	82
NPV, %	40	38	35	34	44	32
Sensitivity, %	82	75	63	71	73	52
Specificity, %	37	47	60	62	63	67

*$P < 0.5$ versus Fib-4, APRI, and Forns.
Undetermined cases = test unsuitable; Accuracy = rate of well-classified patients (patient for whom results of noninvasive makers differed by less than 2 stages of fibrosis in the METAVIR scoring system).
HCV = hepatitis C virus; PPV = positive predictive value; NPV = negative predictive value.

Cost–Performance Analysis

- A cost–performance analysis was performed on the 3 scores with higher accuracies for significant liver fibrosis (FM, HS, and FT) (**Table 4**).
- The least expensive score was HS (50 per serum sample compared with 88 for FT and 111 for FM).
  - The HS showed a cost–performance ratio of 2.6 per percentage of AUC.
  - The incremental cost–performance analysis showed that HS was better than FT (ie, less expensive and with greater efficacy), whereas the incremental ratio was 61.0 per percentage of AUC when comparing HS and FM.

Table 4. Cost–Performance Ratios of the 3 Main Noninvasive Biological Markers Suitable for the Diagnosis of Significant Fibrosis (≥F2) in HIV-HCV Coinfected Patients

	Cost per Sample	Performance % AUC	Incremental Cost (A)	Incremental Performance % AUC (B)	Incremental Cost/ Incremental Performance Ratio /% AUC (A)/(B)
No screening	0	50	—	—	—
Hepascore	50	69	50*	19†	2.6
Fibrotest	88	64	—	—	Dominated‡
Fibrometer	111	70	61	1	61§

In a cost-efficiency analysis, the scores are presented in order of increasing cost. The incremental values are then calculated between 2 successive lines each time a more efficient (but more expensive) score was observed (eg, *50-0;†69-50). ‡When the most expensive score between 2 successive lines is also the least efficient, it is "dominated" by the least expensive score, and the incremental values are not calculated. §The interpretation of the incremental cost–performance ratio is the following: the gain of 1% in the area under the receiving operating curve (AUROC) when using Hepascore rather than the absence of score (the hazard) is associated with a cost of 2.6; the 1% gain in the AUROC when using Fibrometer rather than Hepascore is associated with a cost of 61.

Conclusions

- Among noninvasive liver fibrosis biomarkers in HIV-HCV coinfected patients, HS, FM, and FT can always be applied and can accurately classify patients with severe fibrosis.
- HS showed the best cost–performance ratio.

Acknowledgment

The authors acknowledge all the participating members in the Ribavic ANRS HC02 Trial and the French National Agency for AIDS and Viral Hepatitis (ANRS).

Presented at the 57th Annual Meeting of the American Association for the Study of Liver Diseases; October 27 – 31, 2006; John B. Hynes Convention Center, Boston, Massachusetts