

Biochemical scores for liver fibrosis in HIV/HBV co-infected patients: accuracy in detecting severe fibrosis / cirrhosis but not mild / moderate fibrosis

K Lacombe^{1,2,3}, V Massari¹, J Guéchet⁴, D Wendum⁵, Michelle Chevallier⁶, P Callard⁷, L Serfaty⁸, G Pialoux⁹ JL Molina¹⁰, P Miallhes¹¹, PM Girard^{2,3}

¹Inserm, UMR-S707, Paris, France; ²Université Pierre et Marie Curie, Paris, France; ³AP-HP, Hôpital Saint-Antoine, Service de maladies infectieuses et tropicales, Paris, France; ⁴AP-HP, Hôpital Saint-Antoine, Service de biochimie, Paris, France; ⁵AP-HP, Hôpital Saint-Antoine, Service d'anatomo-pathologie, Paris, France; ⁶Hospices Civils de Lyon, service d'anatomo-pathologie, Lyon, France; ⁷AP-HP, Hôpital Tenon, Service d'anatomo-pathologie, Paris, France; ⁸AP-HP, Hôpital Saint-Antoine, Service d'hépatologie, Paris, France; ⁹AP-HP, Service de maladies infectieuses et tropicales, Hôpital Tenon, Paris, France; ¹⁰AP-HP, Service de maladies infectieuses et tropicales, Hôpital Saint-Louis, Paris, France; ¹¹Hospices Civils de Lyon, service d'hépatologie, Lyon, France

1. Abstract

Background: Surrogate markers to assess liver fibrosis, such as biochemical scores, might be useful in patients with chronic hepatitis. However, the accuracy of such tools has not been evaluated in HIV-HBV co-infected patients.

Methods: A cross-sectional analysis on a panel of biochemical markers, measured at the time of liver biopsy, was performed in HIV-HBV co-infected patients recruited in an HIV-HBV French cohort-study. Patients with hepatitis C co-infection were excluded. Ten published scores validated in HBV and/or HCV mono-infected patients or HIV-HCV co-infected patients were calculated in this study population (Fibrotest, SHASTA, Hepascore, Zeng, Forns, APRI, hyaluronic acid, AST/ALT, FIB4, Fibrometer). For each biochemical score and liver biopsy, the level of fibrosis was dichotomized as follows: 1) no/very mild fibrosis (Metavir F0-F1 vs mild/bridging fibrosis/cirrhosis (Metavir F2-F3-F4) and 2) no/mild/bridging fibrosis (F0-F1-F2-F3) vs cirrhosis (F4). The Area Under the Curve (AUC) was calculated for each test and the corresponding confidence intervals were calculated by a bootstrap procedure. AUCs were compared using non-parametric tests.

Results: Fifty-five patients with a mean age of 40.5 years were included in the study, of which 23 were classified F0-F1 vs 32 with F2-F3-F4, and 43 were classified with F0-F1-F2-F3 vs 12 with F4. Cirrhosis was accurately diagnosed with, by increasing performance, Forns (AUC=0.80), hyaluronic acid (AUC=0.82), Zeng (AUC=0.83), Hepascore (AUC=0.83), SHASTA (AUC=0.88) and Fibrometer (AUC=0.88). All other tests had an AUC under 0.80 (i.e. Fibrotest, AUC = 0.75). However, no test could accurately differentiate F0-F1 from F2-F3-F4 (all AUC < 0.75).

Conclusions: In HIV-HBV co-infected patients, six biochemical scores accurately diagnosed cirrhosis. However, no score had an AUC significantly higher than that of hyaluronic acid - an easy-to-measure, single marker. No score had enough power to differentiate the F1 from the F2 stage, which is an indicator for treatment. Liver biopsy may still be the gold standard to assess fibrosis in HIV-HBV co-infected patients.

2. Background

- Evaluation of liver fibrosis is essential in patients with chronic liver disease in order to guide therapeutical management.
- Liver biopsy is still the gold standard for fibrosis assessment but presents many drawbacks (invasive procedures, sample variability, etc).
- Simple non invasive tests have been recently developed using serum biochemical markers.
- Most of them have been validated only in HCV and HBV mono-infections
- Few of them have also been validated in HIV-HCV co-infected patients.
- However, none specifically addressed the issue of HIV-HBV co-infection.
- Roughly 7-9% of HIV infected patients are also infected with chronic hepatitis B.
- The complex drug management of HIV-HBV co-infection involves an accurate evaluation of liver fibrosis before starting a treatment.
- It is therefore important to determine if liver biopsy can be efficiently replaced by non invasive procedures such as biochemical markers.

3. Objective

The objective of this study was to determine the accuracy of a panel of biochemical scores in detecting bridging fibrosis and cirrhosis in a cohort of HIV-HBV co-infected patients.

4. Patients and methods

- Patients included in the French HIV-HBV Cohort Study were proposed a liver biopsy at study entry.
- Inclusion criteria in this study were: HBsAg positivity in serum, HIV confirmed, no HCV co-infection (HCV-RNA negative), liver biopsy blindly scored by two pathologists, availability of serum markers at the time of biopsy.
- The cross sectional analysis of 10 biochemical scores published in the scientific literature was performed at the time of liver biopsy, i.e. Fibrotest, SHASTA, Hepascore, Zeng, APRI, FIB-4, AST/ALT, Forns, hyaluronic acid, Fibrometer.
- The level of fibrosis was dichotomized as follows: 1) no/mild fibrosis (Metavir F0-F1) vs bridging fibrosis/cirrhosis (Metavir F2-F3-F4) 2) no/mild/bridging fibrosis with few septa (Metavir F0-F1-F2) vs bridging fibrosis with many septa/cirrhosis (Metavir F3-F4) and 3) no/mild/bridging fibrosis (F0-F1-F2-F3) vs cirrhosis (F4).
- The Area Under the Curve (AUC) was calculated for each test and the corresponding confidence intervals were calculated by a bootstrap procedure. AUCs were compared using non-parametric tests.

5. Results (1)

- 55 patients with biochemical scoring performed within 3 months of the liver biopsy were included in the study.
- Median length of liver biopsy : 18 mm (25 – 75 % IQR = 12 – 23)

Table 1: Patients characteristics

Main characteristics of patients	Patients (n = 55)
Age (mean, SD)	40.5 (7,6)
Sex ratio (M/F)	52/3
Estimated HIV duration (median, IQR)	10.9 (8.1 – 15.4)
Estimated HBV duration (median, IQR)	8.1 (3.0 – 12.4)
CD4 cells count (mean, SD)	442 (244)
F metavir (n, %)	
F0	2 (3.6%)
F1	21 (38.2%)
F2	13 (23.6%)
F3	7 (12.7%)
F4	12 (21.8%)

Aknowledgements

This work was supported by grants from SIDACTION, ANRS (Agence Nationale de Recherche sur le Sida), Gilead Sciences, and promoted by IMEA (Institut de Médecine et d'Epidémiologie Appliquée).

The authors are grateful to the patients and the clinical teams for their commitment to the French HIV-HBV Cohort Study.

6. Results (2)

Figure 1 : Box plots of fibrosis scores according to Metavir F stages

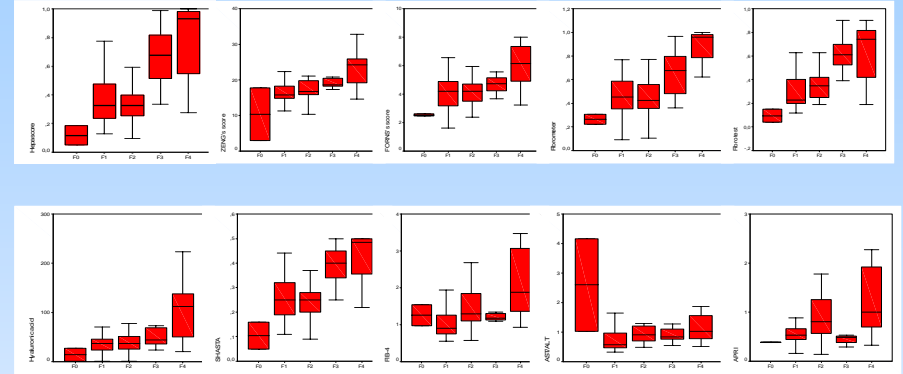


Table 2 : Comparison of AUROCs for discriminating fibrosis stages

Scores	F0-F1 vs F2-F3-F4	F0-F1-F2 vs F3-F4	F0-F1-F2-F3 vs F4
Fibrometer	0.71 (0.57 – 0.85)	0.85 (0.73 – 0.97)*	0.88 (0.73 – 0.99)*
Hepascore	0.74 (0.61 – 0.87)	0.87 (0.76 – 0.97)*	0.83 (0.68 – 0.98)
Zeng's score	0.74 (0.61 – 0.87)	0.83 (0.72 – 0.95)	0.83 (0.67 – 0.99)
Forns's score	0.70 (0.56 – 0.84)	0.75 (0.62 – 0.88)	0.80 (0.65 – 0.94)
Shasta	0.67 (0.54 – 0.81)	0.69 (0.54 – 0.84)	0.78 (0.62 – 0.93)
Hyaluronic a.	0.70 (0.56 – 0.84)	0.78 (0.64 – 0.91)	0.82 (0.66 – 0.97)
Fibrotest	0.75 (0.62 – 0.89)	0.81 (0.68 – 0.93)	0.75 (0.58 – 0.92)
Fib-IV	0.74 (0.60 – 0.87)	0.70 (0.55 – 0.84)	0.79 (0.66 – 0.93)
APRI	0.67 (0.53 – 0.82)	0.60 (0.43 – 0.77)	0.75 (0.58 – 0.92)
AST/ALT	0.65 (0.49 – 0.81)	0.61 (0.46 – 0.76)	0.64 (0.46 – 0.81)

* Significantly different from the other AUROCs (p<0.05)

5. Results (3)

- No test could accurately differentiate F0-F1 from F2-F3-F4 (all AUC < 0.75).
- Five tests could accurately discriminate patients with cirrhosis :
 - ➔ Fibrometer, Hepascore, Zeng's score, Forns's score, Hyaluronic acid.
 - ➔ Fibrometer was the only test with a significantly higher AUROC.
- Four tests could accurately discriminate F0-F1-F2 from F3-F4
 - ➔ Fibrometer, Hepascore, Zeng's score, Fibrotest
 - ➔ Fibrometer and Hepascore were the two tests with significantly higher AUROCs.

7. Conclusion

- In HIV-HBV patients, Fibrometer and Hepascore were the two tests with the highest diagnostic performance for distinguishing bridging fibrosis with many septa and cirrhosis.
- More simple tests such as APRI or AST/ALT failed to differentiate fibrosis stages in general.
- The influence of HIV infection and antiretroviral therapy on some biochemical markers such as haptoglobine, bilirubine, AST or ALT might explain the failure of simple tests to accurately evaluate the level of fibrosis.
- The use of scores including markers reflecting the matrix degradation (hyaluronic acid, metalloprotease inhibitor) increased the diagnostic performance.
- The performance of a simple and costless marker such as the hyaluronic acid was good in detecting cirrhosis.
- Those results need to be confirmed on a validation sample.