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Letter to the Editor

Implementing non-invasive markers for liver fibrosis in clinical practice

To the Editor:

We read with interest the article by Leroy et al. regarding a prospective, independent validation of six non-invasive markers for liver fibrosis in chronic hepatitis C [1]. The overall performance of the markers tested, which included Fibrotest, Fibrometer, Hepascore, MP3, Forns' index and APRI, was very similar to those originally reported, the area under the ROC curve (AUROC) ranging between 0.78 and 0.86 for diagnosis of significant fibrosis ($\geqslant$F2 by METAVIR). The authors tested the statistical independence of the non-invasive scores in order to propose a logical algorithm to be used in clinical practice and they found that some combinations of non-invasive markers gave a better performance than the single scores. Indeed, a combination of APRI and Fibrotest allows to predict presence of significant fibrosis with more than 90% accuracy. In their article, Leroy and colleagues also referred to the sequential algorithm that we had previously proposed to diagnose liver fibrosis in chronic hepatitis C [2]. In our algorithm, APRI is used 100% as first-line test, followed by Fibrotest and then by liver biopsy in misclassified cases. The application of this algorithm has resulted in a 50% reduction of liver biopsies to diagnose F2 fibrosis with a diagnostic accuracy of 94%.

We sought to compare the performance of Leroy's algorithm and our algorithm for the diagnosis of significant fibrosis in chronic hepatitis C. We investigated a consecutive series of 188 monoinfected HCV patients (mean age 48.6 ± 12.4, 51.6% males) who underwent a percutaneous liver biopsy. For all patients APRI and Fibrotest were calculated using fasting serum samples obtained on the same day of liver biopsy. Patients with comorbidities were excluded. METAVIR staging was: F0–F1 = 30.5%, F2 = 45.5%, F3 = 12.5%, F4 = 11.5%. The performance of the non-invasive methods was measured as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and AUROC. The mean length of liver specimens was 17 ± 3 mm. The AUROCs for significant fibrosis were 0.75 and 0.79 for APRI and Fibrotest, respectively. Table 1 shows the performance and the main features

Table 1
Performance of two algorithms combining non-invasive markers for liver fibrosis to diagnose significant fibrosis ($\geqslant$F2 by METAVIR) in 188 HCV patients

	Sebastiani's algorithm	Leroy's algorithm
APRI Patients in whom APRI was performed (%)	100	100
Fibrotest Patients in whom Fibrotest was performed[a] (%)	60	100
Patients in whom Liver biopsies was avoided (%)	54	19
Sensitivity (%)	100	91.2
Specificity (%)	69.3	97.3
PPV (%)	83.1	98.1
NPV (%)	100	87.9
Accuracy (%)	87.8	93.6
AUROC (95% CI)	0.89 (0.72–0.97)	0.94 (0.86–0.99)
+ LR	3.2	3.0
− LR	0	0.09

APRI, AST-to-platelet-ratio; PPV, positive predictive value; NPV, negative predictive value; AUROC, area under the ROC curve; CI, confidenc interval.

[a] Sebastiani's algorithm: cutoff = 0.49 for significant fibrosis; Leroy's algorithm: cutoff = 0.59 for significant fibrosis, 0.22 for no-mild fibrosis.

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of our algorithm and those of Leroy's algorithm. Both algorithms employed APRI 100% at baseline. The main difference between the two algorithms was that Fibrotest is again required for all cases according to Leroy's algorithm, while our algorithm uses Fibrotest only in 60% of cases. Our algorithm presents with 100% NPV for the exclusion of significant fibrosis while Leroy's algorithm showed 98% PPV for the prediction of significant fibrosis. Though the overall accuracy of both algorithms was excellent, with a slightly better performance of Leroy's, the application of our algorithm resulted in a much greater reduction of liver biopsies (54% vs. 19%, $p < 0.0001$).

Reducing the need for liver biopsies and Fibrotest implies a clear advantage in terms of risks, costs and better patient-compliance.

Leroy's study confirms that most non-invasive markers do not overcome 75–85% accuracy in patients with chronic hepatitis C. Non-invasive markers, should be used sequentially while liver biopsy should be limited to the subset of patients with inaccurate response to non-invasive markers. Liver biopsy and non-invasive markers should be considered as agonists and not as antagonists towards the goal of correctly classifying the stage of liver fibrosis in patients with chronic hepatitis C.

References

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[2] Sebastiani G, Vario A, Guido M, Noventa F, Plebani M, Pistis R, et al. Stepwise combination algorithms of non-invasive markers to diagnose significant fibrosis in chronic hepatitis C. J Hepatol 2006;44:686–693.

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