Editorial

Can we precisely classify liver fibrosis without biopsy in hepatitis C?

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"...the noninvasive diagnosis of liver fibrosis has become more sophisticated ... from simple scores to multivariate algorithms, then simple combinations of fibrosis tests and finally the mathematical combination of results provided by a blood test and device."

The prognosis of patients with chronic hepatitis C (CHC) is closely linked to the progression of liver fibrosis [1]. Indications for antiviral therapy, achievement of sustained viral response under treatment and the need for screening for hepatocellular carcinoma or large esophageal varices are also related to the amount of liver fibrosis. Thus, a precise evaluation of liver fibrosis is mandatory for the management of CHC patients.

Classically, liver fibrosis is evaluated on a liver biopsy and categorized in histological fibrosis stages according to semiquantitative scores. According to Metavir fibrosis (F) staging, which depicts liver fibrosis according to five stages (F0–4), significant fibrosis is defined as F ≥ 2, severe fibrosis as F ≥ 3 and cirrhosis as F4. However, the pathological evaluation of liver fibrosis has several limitations: liver biopsy is an invasive procedure feared by patients and with potential severe complications [2,3], the heterogeneous distribution of fibrosis in the liver induces sampling variability [4] and reproducibility of fibrosis staging using semiquantitative histological staging is limited [5]. Consequently, during the past decade, noninvasive tests for the diagnosis of liver fibrosis have been developed.

The popular fibrosis tests are simple scores combining blood fibrosis markers according to a formula easy to perform at the bedside, such as the aspartate aminotransferase:alanine aminotransferase ratio, the aspartate aminotransferase:platelets ratio or the FIB-4 index. Beyond their simplicity, validation studies in large cohorts of patients and meta-analyses showed that simple scores have only moderate accuracy for the diagnosis of significant fibrosis, severe fibrosis or cirrhosis [6–8]. In fact, the diagnostic accuracy of simple scores is good at their extreme values but only fair in a large 'gray zone'

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corresponding to intermediate results where liver biopsy is still required [9,10].

A second category of blood fibrosis tests was developed by using multivariate algorithms, usually provided by binary logistic regression: FibroTest™, HepaScore®, FibroMeter® or ELF Test™. Multivariate algorithms, usually constructed for the binary diagnosis of significant fibrosis, are more complex and need computerization for their calculation. They are significantly more accurate than simple scores [6,8]. Similar to simple scores, multivariate algorithms show high diagnostic accuracy at their extreme values for the diagnosis of significant fibrosis or cirrhosis, but they also allow for a significant reduction of the gray zone and thus for a reliable diagnosis in a significantly higher number of patients [9,10]. Because results of multivariate algorithms are well correlated with fibrosis stages determined on liver biopsy, some authors have proposed fibrosis classifications that give an estimation of the histological fibrosis stage derived from the result of the multivariate algorithm, without any liver biopsy requirement [10,11]. However, the diagnostic accuracy of these fibrosis classifications remains poorly evaluated and seems only fair-to-moderate except when a specific methodology is used [12,13].

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A significant advancement in the noninvasive diagnosis of liver fibrosis has been the development of liver stiffness measurement by transient elastography. FibroScan® is a device that measures in the liver the velocity of a shear wave induced by a mechanical impulse on the skin, and then calculates the liver stiffness [14]. Liver stiffness measurement by FibroScan is easy to perform, noninvasive, well accepted by patients, rapid (it only takes a few minutes) and gives an immediate result. In CHC patients, the accuracy of FibroScan is good for the binary diagnosis of significant fibrosis and excellent for cirrhosis [6,8]. FibroScan results are well correlated with histological fibrosis stages determined upon liver biopsy, but they are also influenced by several other conditions: inflammation, steatosis, cholestasis, central venous pressure or even food intake. Moreover, current fibrosis classifications derived from FibroScan results are only moderately accurate, also due to methodological flaws [12,13].

More recently, combinations of blood (e.g., simple scores and multivariate algorithms) and physical (e.g., FibroScan) fibrosis tests have been developed to improve diagnostic accuracy and reduce the gray zone where liver biopsy is required. The Sequential Algorithm for Fibrosis Evaluation (SAFE) sequentially combines two blood tests: a simple score (aspartate aminotransferase:platelets ratio index) as first-line test, then a multivariate algorithm (FibroTest) as second-line test and finally a liver biopsy if the diagnosis remains undetermined [15]. The Bordeaux algorithm uses simultaneously a blood test (FibroTest) and a device (FibroScan), with a liver biopsy as a requirement in case of a discrepancy between them [16]. Despite the fact that they combine single fibrosis tests with simple rules, these fibrosis test combinations appear complex for use in clinical practice: the SAFE implies several diagnostic steps, and the Bordeaux algorithm requires a multivariate algorithm and a liver stiffness measurement that is only available in specialized centers. This complexity may seem offset by the excellent diagnostic accuracy with 90–95% of patients well classified [13,15,16]. However, a major limitation of the SAFE and the Bordeaux algorithm is that they provide only a binary diagnosis of fibrosis: significant fibrosis versus no/mild fibrosis, or cirrhosis versus no cirrhosis. Consequently, in clinical practice, physicians first have to apply the algorithm for the diagnosis of significant fibrosis and then, if the noninvasive diagnosis is significant fibrosis, apply the algorithm for the diagnosis of cirrhosis to discriminate F2/3 patients from cirrhotic (F4) patients. We showed that this successive use for precise diagnosis leads to a significant decrease in diagnostic accuracy and, in addition, a significant increase in liver biopsy requirement (70% with the SAFE and 50% with the Bordeaux algorithm) compared with their use restricted to the single binary diagnosis [13].

We have developed several statistical techniques to improve the noninvasive diagnosis of liver fibrosis. These include blood tests adapted to a diagnostic target [17], synchronous combinations of fibrosis tests to improve diagnostic accuracy [18] and reliable diagnosis intervals for fibrosis tests in order to improve diagnostic precision [9,10]. Finally, by using all these methods, the synchronous combination of a blood test (FibroMeter) with a device (FibroScan) resulted in a new accurate noninvasive classification of fibrosis [19]. This classification provides a precise diagnosis (six diagnostic classes), with robust and high diagnostic accuracy, and discards the need for liver biopsy [19]. Compared with the SAFE and Bordeaux algorithms, this new classification of fibrosis has the same diagnostic accuracy but offers a

more precise diagnostic without any liver biopsy requirement [13]. Our new noninvasive classification of fibrosis may appear to be very complex for use in clinical practice because it requires the user to first perform a multivariate algorithm of blood markers and liver stiffness measurement, and then several calculations to produce a diagnosis. Nevertheless, all calculation steps are computerized and, finally, the user has only to provide the results of blood sampling and liver stiffness on a website to obtain an accurate estimation of the histological fibrosis stage.

In conclusion, the noninvasive diagnosis of liver fibrosis has become more sophisticated over time: from simple scores to multivariate algorithms, then simple combinations of fibrosis tests and finally the mathematical combination of results provided by a blood test and device. This increasing refinement has run parallel with an improvement in diagnostic accuracy and it now seems possible to offer a fully noninvasive management of patients with CHC. The improvement in performance and precision of the diagnosis of liver alterations should result in increased care quality. Methodological complexity should not scare clinicians. Indeed, numeric technology offers simplified result sheets that are easy to use, such as the Model for End-Stage Liver Disease score or the Lille score for severe alcoholic hepatitis. However, the use of these diagnostic tests has to be recommended by recognized guidelines [20].

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