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Methodological aspects of the interpretation of non-invasive biomarkers of liver fibrosis: a 2008 update

Aspects méthodologiques pour l'interprétation des marqueurs non-invasifs de fibrose hépatique : mise à jour en 2008

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FibroTest;
FibroMeters

Summary

This review summarizes the methodological aspects of the interpretation of non-invasive biomarkers in liver fibrosis. A scoring system has been updated to better compare the quality of fibrosis biomarkers. Several methodological issues are related to the classical methodology using biopsy, as this is considered the gold standard. However, from evidence-based data, it appears that the methodology needs to change to prevent flawed conclusions among key opinion leaders as well as in obsolete guidelines. As waiting for the perfect biomarker for the diagnosis of advanced fibrosis to come along is probably a waste of time, in the meantime, methods can be improved. The main proposals for improving the methodology are, to take into account the spectrum bias, to assess accuracy between adjacent stages, to compare biomarkers in the same patient, to assess the cause of failure among discordant cases and to use specific statistical methods adapted for imperfect gold standards.
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Résumé

Cette revue résume les aspects méthodologiques de l'interprétation des marqueurs non-invasifs de fibrose. Un score de qualité a été mis a jour pour mieux estimer et comparer la qualité méthodologique des marqueurs. Plusieurs erreurs méthodologiques sont la conséquence de l'utilisation de la biopsie hépatique, comme s'il s'agissait d'un « gold

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standard » parfait. Au regard des nombreuses publications récentes la méthodologie doit évoluer pour éviter des conclusions erronées de la part des leaders d'opinion et pour mettre a jour des recommandations officielles obsolètes. Attendre un marqueur non-invasif parfait est une actuellement une illusion, mais les méthodes peuvent être rapidement améliorées. Les principales propositions d'amélioration sont, de tenir compte du «spectrum bias» (biais lié à l'hétérogénéité des malades), d'estimer la valeur diagnostique entre les stades adjacents de fibrose, de comparer directement les marqueurs chez les mêmes patients, d'estimer les causes d'erreur en cas de discordances y compris celles dues à la biopsie, et d'utiliser les méthodes spécifiques adaptées aux «gold standards» imparfaits.
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Abbreviations

QUALIFIB: Quality items for biomarkers of liver fibrosis
APRI: Aspartate aminotransferase/platelet ratio index
FT: FibroTest™ ,
AT: ActiTest™ ,
ST: SteatoTest (from BioPredictive, Paris, France; HCV-FibroSURE™, HBV-FibroSURE™, ALD-FibroSURE™, ASH-FibroSURE™ in the US, from LabCorp, Burlington, NC)
FM: FibroMeters
FSP: FIBROSpect II
ELF: Enhanced liver fibrosis
HS: Hepascore
FS: FibroScan

Introduction

Numerous studies strongly suggest that, due to its limitations and risks as well as the improvement in the diagnostic accuracy of new, non-invasive biomarkers, liver biopsy should no longer be considered mandatory as a first-line estimate of fibrosis in the most frequent chronic liver diseases [1-9].

In France, a nationwide survey found that, among 546 hepatologists, 81% used non-invasive biomarkers (FibroTest™-ActiTest™) and 32% used elastography (FibroScan™), with a dramatic decrease in the use of liver biopsy to only slightly more than half of patients with chronic hepatitis C, with a subsequent increase in the number of patients treated [10]. Furthermore, an overview by the French health authorities has officially approved the non-invasive FibroTest and FibroScan biomarker panels for first-line estimation of fibrosis in patients with chronic hepatitis C, with recommended reimbursement from the government, and has approved liver biopsy only as a second-line estimate in cases of discordance or non-interpretability with the non-invasive markers [11]. An updated overview is scheduled for other chronic liver diseases at the end of 2008.

There have been regular updates of previous overviews and meta-analyses of biomarkers of advanced liver fibrosis [12-17]. The specific aim of the present review is to update the methodological aspects involved in the interpretation of non-invasive biomarkers of liver fibrosis.

History of the methodology for evaluating liver fibrosis

Since the time of the landmark article by Ransohoff and Feinstein 30 years ago [18], the methodology for evaluating the efficacy of diagnostic tests has improved [19], often with input from clinicians [20]. For example, on reviewing the evaluation of biomarkers of liver injury, three major issues were observed by clinicians and pathologists [8, 9, 12, 15, 21–23].

First, liver biopsies-even those 25 mm in length-are not a perfect gold standard, given the 25% rate of discordance for fibrosis staging *vs* the true gold standard-essentially, the whole of the liver [2]. In addition to such sampling error variability, there is also intra- and interpathologist variability [24]. This means that discordance between a biomarker and a biopsy may also be due to biopsy failure, even in cirrhosis, and that the classical methodology, which uses biopsy as a perfect gold standard, has not been properly adapted.

Second, the accuracy of liver biopsy is related to the size (length) and fragmentation of the obtained sample [21].

Finally, the accuracy of a biomarker for the diagnosis of advanced fibrosis is highly sensitive to variability in the prevalence of stages that define advanced and non-advanced fibrosis (spectrum bias) [22].

Despite these methodological issues, almost all of the editorials and reviews published in the last six years have focused on methods using biopsy as the ideal gold standard

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