LETTERS TO THE EDITOR

The risks of changing the rules for previously validated biomarkers and using the same patients several times. Response letter to Calès et al. Gastroenterol Clin Biol 2008;32:1050–60: ‘’Evaluation and improvement of a reliable diagnosis of cirrhosis by blood tests.’’


We read the work of Calès et al. [1] to identify a better strategy to improve the accuracy of the diagnosis of cirrhosis using non-invasive methods with interest. They suggest improving the patented regression algorithm called the standard Fibrometer (FM), which has been previously validated for the diagnosis of advanced liver fibrosis [2]. For this purpose, the authors have created a new formula combining the same parameters as the FM, called the 'specific Fibrometer' (sFM) for the diagnosis of cirrhosis [3].

However, we would like to note several debatable points in the principles and methodology used by Calès et al., which may not respect reference standard criteria used to check the reliability of a biomarker [4,5].

First, any change in the algorithm of a patented biomarker will give different results and so the new biomarker must first be validated in relation to the change in intention for use in the diagnosis and prognosis of liver fibrosis [2]. For this purpose, the authors have created a new formula combining the same parameters as the FM, called the 'specific Fibrometer' (sFM) for the diagnosis of cirrhosis [3].

The means ± SD for cirrhosis are different between FM and sFM because algorithms and diagnostic cut-offs have changed (0.50 ± 0.30 versus 0.11 ± 0.21, p < 0.0001). This is similar to changing the formula or the dose of a drug which may change the risk-benefit ratio.

Second, the authors’ source of data included the same patient populations used in previously published studies about FM and sFM [2,3,6] and there was no new validation population to check the accuracy of the recently constructed sFM score for the diagnosis of cirrhosis. The quality standards for a diagnostic test should be followed as described in the Standards for Reporting of Diagnostic Accuracy (STARD) criteria and the Cochrane Database of Systematic Reviews (CDSR) methods [5]. Key STARD criteria include determining whether the study population is relevant to the clinical question being addressed. The difference between advanced and non-advanced fibrosis prevalences (DANA) of the population used to validate sFM was only 1.79 for a normal rate of 2.50, suggesting that there was a spectrum bias which could have a potential impact on the diagnostic values of the biomarkers especially the FibroTest [7].

The prevalence of F4 stage in this study was 11.2%, with almost all patients in the intermediate stages of fibrosis F1 and F2 (43 and 27%, respectively). New studies on biomarkers should systematically discuss the results according to the spectrum bias adapted at each biomarker profile, such as Cacoub et al. did recently to compare biomarkers in an HIV/HCV population [8].

Third, contrary to the statement by Calès et al. in the introduction that French authorities released recommendations [9] for the use of Fibroscan along with blood tests despite the lower accuracy for non-extreme values, the diagnostic values of the FibroTest for the consecutive stages of fibrosis have been shown to be the same for both moderate and extreme stages [10,11]. Poynard et al. have shown that between two contiguous stages (one stage difference), the FibroTest's AUROCs were not significantly different; the same is true between patients with two-stage and three-stage differences, and even between four-stage differences like blood donors versus F3 or F4, and F0 versus F4 [10].

In conclusion, similar to drugs, any change in the algorithm defining an updated biomarker should be validated in
terms of the changed risk–benefit ratio and validated in newly included populations.

Disclosure

T. Poynard is the inventor and has a capital interest in Biopredictive, the company marketing FibroTest. M. Munteanu and Y. Ngo are employees of Biopredictive.

References


M. Munteanu, Y. Ngo, V. Ratziu, T. Poynard

Biopredictive, Paris, France
Service d’hépatogastroentérologie, groupe hospitalier Pitié-Salpêtrière, 47–83, boulevard de l’Hôpital, 75651 Paris cedex 13, France

Available online 15 April 2009

Disclosure

T. Poynard is the inventor and has a capital interest in Biopredictive, the company marketing FibroTest. M. Munteanu and Y. Ngo are employees of Biopredictive.

References


M. Munteanu, Y. Ngo, V. Ratziu, T. Poynard

Biopredictive, Paris, France
Service d’hépatogastroentérologie, groupe hospitalier Pitié-Salpêtrière, 47–83, boulevard de l’Hôpital, 75651 Paris cedex 13, France

Available online 15 April 2009

Which would you prefer for a liver fibrosis test: A limited fixed menu or a gourmet buffet?

Que préféreriez-vous comme test de fibrose hépatique: un menu du jour ou un buffet dégustation?

We were honoured by and delighted to read the comments of Munteanu et al. concerning our specific FibroMeter for cirrhosis [1]. They began their discussion with a debate about a so-called change in the algorithm. Our philosophy is that each of our tests is adapted to the clinical setting. Thus, we first used a panel of blood tests adapted to the aetiology of chronic liver disease. Using a test that was initially designed for significant fibrosis (Metavir F ≥ 2) to diagnose cirrhosis is not logical, therefore we also developed a test that was adapted to this diagnostic target. In fact, the trick was to provide a new test for cirrhosis based on the variables included in a test designed for another diagnostic target. The interest is two-fold: diagnostic accuracy is increased and, even more importantly, so are predictive values, with no additional cost for the user or the healthcare provider; you have two blood tests for the price of one. To continue the metaphor used by our colleagues, in the same way that you can adapt a drug dose to a target; (adjusting ribavirin doses to body mass for example), the weights of the blood markers in the algorithm can be adjusted to the target diagnosis. It would appear that the authors prefer a fixed menu to an “à la carte” prescription, although this seems to be at odds with their previous choice [2]. It is also somewhat amusing to note that the authors who first obtained their valuable expertise in blood tests with cirrhosis (PGA score) [3] as a diagnostic target, then switched to a test for significant fibrosis (Fibrotest), refuse to accept that the authors who first described a blood test for significant fibrosis change directions themselves [4]. Besides this general comment, we think that changing diagnostic cut-offs between different scores is logical, just as diagnostic cut-offs differ between diagnostic targets even in fixed menu tests such as the Fibrotest. Finally, our own metaphor is the following: why settle for a fixed menu if, at the same cost, you can choose from an à la carte buffet with many more gourmet dishes?

Munteanu et al.’s second argument brought up several points concerning the reliability of our data. Regarding the Standards for Reporting of Diagnostic Accuracy (STARD) recommendations for diagnostic tests, all of our papers incorporate these recommendations. Indeed, this was recently confirmed in an editorial by an author who is associated with Pr Poynard’s team [5]. Our study included a large population of 1,056 patients with chronic hepatitis C. This is, according to a recent review of Pr Poynard’s team in this journal, the best quality factor of a study [6]. In addition, our proportion of cirrhosis was 11.2% versus 12% in a systematic review including 33,121 HCV patients [7], which further confirms the reliability of our predictive values. Including different populations would be questionable according to Munteanu et al. This is similar to a meta-analysis with individual data [8]. In addition, this allowed us to show that the FibroMeter had the highest inter-centre diagnostic reproducibility and robustness [9].