Non-invasive detection of liver fibrosis with transient elastography and serum markers

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Key messages:

1. Currently available methods for the non invasive assessment of liver fibrosis include transient elastography and serum markers.
2. Two aims are clinically relevant: 1) detection of significant fibrosis (indication for antiviral treatment in chronic viral hepatitis); 2) detection of cirrhosis (indication for screening of oesophageal varices and hepatocellular carcinoma).
3. Transient elastography and serum markers of fibrosis have been mostly studied and validated in chronic hepatitis C with similar performance for the diagnosis of significant fibrosis but remain to be validated in other chronic liver diseases.
4. The combination of two unrelated methods such as transient elastography and serum markers could increase the diagnostic accuracy, particularly for the diagnosis of significant fibrosis in hepatitis C but deserves to be evaluated in other chronic liver diseases.
5. Transient elastography currently appears as the most accurate tool for early detection of cirrhosis and may have prognostic value in this setting. However, it cannot replace so far upper GI endoscopy for screening of oesophageal varices in patients with cirrhosis.

Introduction

Prognosis and management of chronic liver disease greatly depend on the amount and progression of liver fibrosis. Two aims are clinically relevant: detection of significant fibrosis (i.e. Metavir F2 or greater) and detection of cirrhosis (Metavir F4). Indeed, presence of significant fibrosis is an indication for antiviral treatment in chronic viral hepatitis and presence of cirrhosis is an indication for specific monitoring of complications related to portal hypertension and to the increased risk of developing hepatocellular carcinoma.

Non invasive assessment of liver fibrosis relies on two different approaches: the measurement of liver stiffness by means of transient elastography and the use of serum fibrosis markers (summarized in Table 1) (1). The standard expression of the effectiveness of non invasive methods is to look at the area under the receiver operator characteristic curve (AUROC), which plots the sensitivity over 1 – specificity, taking liver biopsy as a reference. The development of non invasive methods is however complicated by the fact that liver biopsy is an imperfect “gold standard”, subject to sampling error and inter-observer variability. Thus, even a perfect surrogate will never score 1.0.
Transient elastography

Transient elastography (TE) (FibroScan, Echosens, Paris, France) is a novel technique that allows measuring liver stiffness. TE is rapid (less than 5 min) and can easily be performed at the bedside or in the outpatient clinic, with results immediately available. They are expressed in kilopascals (kPa), corresponding to the median value of 10 validated measurements and range from 2.5 to 75 kPa, with normal values around 5.5 kPa (2). The clinical interpretation of TE results should be always in the hands of an expert clinician taking into account two important parameters for results to be considered reliable: 1) the interquartile range (IQR), which reflects the variability of the validated measures and that should not exceed 30% of the median value; 2) the success rate the ratio of the number of successful measurements to the total number of acquisitions that should be at least 60%. Indeed, in our experience in more than 13000 examinations, liver stiffness could not be measured in 3.1% of cases and was uninterpretable (IQR >30% median or success rate <60%) in 15.8% (3). Limited operator experience and obesity were the main determinants of TE failure or unreliable results. TE results may also be influenced by acute liver injury (as reflected by ALT flares) with the risk of overestimating liver stiffness values (4).

Since the initial reports of its performance in patients with chronic hepatitis C showing a strong correlation of liver stiffness values with Metavir fibrosis stages, TE has been assessed in a variety of chronic liver diseases including chronic hepatitis B, HIV-HCV co-infection, alcoholic liver disease and non alcoholic liver disease (NAFLD). In a recent meta-analysis (5), the mean AUROC for the diagnosis of significant fibrosis, and cirrhosis were 0.84 (95% CI, 0.82-0.86), and 0.94 (95% CI, 0.93-0.95), respectively. TE thus appears as a reliable method for the diagnosis of cirrhosis in patients with chronic liver diseases, better at excluding than at predicting cirrhosis. When compared with currently available serum markers and routine blood tests, TE emerges as the most accurate non invasive method for early detection of cirrhosis (6).

Another advantage of TE is that the wide range of liver stiffness values observed in patients with cirrhosis (13-75 kPa) may be of prognostic value as suggested by several lines of evidence: the correlation of liver stiffness values with disease severity, portal hypertension (assessed either by the presence of oesophageal varices on upper GI endoscopy or by the measurement of hepatic venous pressure gradient), and recently the risk of hepatocellular carcinoma (7). Hence, TE could be used in the next future for allocating cirrhotic patients to different risk categories. However, TE cannot yet confidently predict the presence of esophageal varices in clinical practice and thus avoid the need for upper GI endoscopic screening of cirrhotic patients.

Serum markers of fibrosis

Among serum markers, there are “direct” serum markers, reflecting either the deposition or the removal of extra-cellular matrix in the liver, such as glycoproteins, the collagens family and collagenases and their inhibitors for which hyaluronate has been the most studied (1). There are “indirect” serum markers of fibrosis or simple routine blood tests such as prothrombin index, platelet count, and AST/ALT ratio. Apart from hyaluronate, “direct” and “indirect” markers, when used individually, are useful for the diagnosis or the exclusion of cirrhosis but have limited accuracy for the diagnosis of significant fibrosis. More sophisticated indices combining panels of “indirect” and “direct” markers, for which the pionniers have been the Fibrotest® (Biopredictive, Paris, France) and the AST to Platelet Ratio Index (APRI), have been proposed. Five indices are protected by patents and are currently commercially available: the Fibrotest® in Europe (Biopredictive, Paris, France) or Fibrosure® in the USA (LabCorp, Burlington, NC, USA), the Fibrometers® (BioLiveScale, Angers, France), the FibroSpect II® (Promotheus Laboratory Inc. San Diego, Ca, USA), the ELF® (Enhanced Liver Fibrosis Test, iQur Ltd, Southampton, UK) and the Hepascore® (PathWest, University of Western Australia, Australia). To date, FibroTest® and APRI have been the most extensively studied (mainly in hepatitis C).
In a recent meta-analysis (8) which pooled 6,378 subjects (with analysis of Individual data in 3,282) with both FibroTest® and biopsy, the mean standardized AUROC for diagnosing significant fibrosis was 0.84 (95% CI, 0.83-0.86), without differences between the different etiologies. In another meta-analysis (9), which pooled 4266 HCV patients, the mean AUROCs of APRI for diagnosing significant fibrosis and cirrhosis were 0.76 (0.74-0.79) and 0.82 (0.79-0.86), respectively.

When compared and validated externally, the different patented indices have similar performances for the diagnosis of significant fibrosis saving liver biopsies in around 50% of cases (1). Although non patented indices such as the Forns index, FIB-4 and APRI may have slightly lower performance, they are cost-free, easy to calculate and available almost everywhere. Finally, apart from hepatitis C, serum markers are still poorly validated in chronic hepatitis B, alcoholic liver disease and NAFLD.

Combining approaches

When TE was compared with serum fibrosis markers (Fibrotest® and APRI) in patients with chronic hepatitis C, with liver biopsy taken as reference, its diagnostic performance was similar to that of Fibrotest® and APRI (10). However, the combination of TE and Fibrotest® offered the best diagnostic performance avoiding the need for liver biopsy for the diagnosis of significant fibrosis in more than 75% of the patients.

Other approaches using stepwise algorithms combining sequentially different indices have been proposed. For instance, in a large multicenter study (11), significant fibrosis could be identified with high diagnostic performance (>94% diagnostic accuracy) using APRI as screening test, followed by Fibrotest® in APRI non-classified cases and restricting liver biopsy to patients classified F0-F1 by non invasive tests. Overall, liver biopsy could have been avoided in around 50% and 80% of cases for the diagnosis of significant fibrosis and cirrhosis, respectively. In a recent study where these two algorithms were compared in the same population of patients with chronic hepatitis C, the number of saved liver biopsies was significantly higher using combination of TE and Fibrotest® than SAFE Biopsy for detecting significant fibrosis (72% vs. 48%, respectively; p<0.0001)(12). Algorithms need to be evaluated in other chronic liver diseases.

Conclusions and propositions for a rationale use in clinical practice

Significant progress has been made in the non invasive diagnosis of hepatic fibrosis. An increasing number of reliable non invasive methods are now available, mainly validated so far in chronic hepatitis C. Although it can be anticipated that these non invasive methods will become an important tool in clinical practice, it is likely that they will reduce but not completely abolish the need for liver biopsy. While guidelines are awaited, the following recommendations can be made for rationale use of non invasive methods in clinical practice:

• Results of non invasive methods should always be interpreted by an expert clinician according to clinical context taking demographics, disease etiology and laboratory parameters into account;
• Interpretation of non invasive methods results should be done critically, taking into account quality criteria for TE (IQR and success rate) and causes of false positives for serum markers;
• Combination of two unrelated methods (TE and serum markers) should be used rather than individual methods;
• Non invasive methods should be repeated when results are discordant with clinical context or between markers, and a liver biopsy (>15 mm and read by an experienced pathologist) should be performed when discordance is unexplained.
References