EDITORIAL

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Combination of Non-Invasive Fibrosis Tests: a Solution for the Prediction of Advanced Fibrosis in Non-Alcoholic Fatty Liver Disease?

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An increasingly common cause of chronic liver disease in adults and children is non-alcoholic fatty liver disease (NAFLD) [1]. According to the EASL–EASD–EASO Clinical Practice Guidelines [2], NAFLD is characterized by excessive hepatic fat accumulation, associated with insulin resistance, and is defined by the presence of steatosis in > 5% of the hepatocytes. This proportion is quantified by histological analysis, or by a proton density fat fraction > 5.6%, assessed with proton magnetic resonance spectroscopy (1HMRS) or quantitative fat/water selective magnetic resonance imaging (MRI) [2].

Non-alcoholic fatty liver disease may present in various ways: as simple steatosis, non-alcoholic steatohepatitis, liver cirrhosis, or even hepatocellular carcinoma (HCC) [3-6]. Of all the pathologic changes found in NAFLD, it appears that fibrosis alone is independently associated with long-term overall mortality, liver transplantation, and liver-related events (i.e. cirrhosis, liver failure and portal hypertension) [7], which makes the quantification of this parameter even more important.

For the moment, the gold standard in the assessment of fibrosis is biopsy. This is an invasive method, with potential adverse effects and great inter- and intra-observer variability [8-10]. In addition, we must not forget that in NASH patients, the histopathologic assessment may be flawed due to the inhomogeneous distribution of fibrosis. Ratziu et al. [10] analyzed two samples of the right liver lobe in all patients and found agreement regarding fibrosis stage in only 47% of patients, while differences of at least 1 or 2 stages were found in 41% and 12% of cases, respectively [10]. As a result, research is increasingly focused on finding alternative, non-invasive techniques for the assessment of fibrosis. As mentioned in EASL-ALEH Clinical Practice Guidelines, the non-invasive tests for evaluation of liver disease severity and prognosis are based on two approaches: a "physical" one (the measurement of liver stiffness) and a "biological" one, relying on the quantification of serum markers. Although these approaches are complementary, they are based on different rationales [11].

As far as the physical approach is concerned, liver stiffness, measured using elastographic techniques, is a physical property, intrinsic to the hepatic parenchyma. Various studies, using mainly transient elastography (TE), have showed that liver stiffness is strongly correlated with fibrosis stage, but – when compared with other categories of patients (such as those with chronic viral hepatitis) – the correlation is somewhat weaker in NASH patients [12]. This can be partly explained by the different distribution pattern in the two conditions. The accumulation of dense stellate portal fibrosis (present in viral hepatitis) will increase liver stiffness in direct proportion, while the perisinusoidal fibrosis distributed especially in the centrolobular areas (typical for NASH) will not induce a similar increase rate, as proven by morphometric studies [13]. According to the EFSUMB and EASL Guidelines and Recommendations on the Clinical Use of Liver Ultrasound Elastography [11, 14], TE can be used to confidently exclude severe fibrosis and especially cirrhosis in NAFLD patients, with a high negative predictive value (around 90%). The main shortcoming of TE is that it provides unreliable results in patients with a high BMI and/or thoracic fold thickness [2]. Some of these situations may be prevented using the XL probe, thus decreasing the failure rate, which however remains significant in patients with a distance between the skin and liver capsule above 3.4 cm and in extremely obese patients (BMI > 40 kg/m^2) [15, 16].

In what concerns the biological approach, a large number of biochemical markers related to inflammation, apoptosis and oxidative stress have also been reported to diagnose liver fibrosis

in NAFLD patients [17-19], but these are insufficiently accurate when used alone [20, 21]. Therefore, the models elaborated for the non-invasive diagnosis of fibrosis, including related clinical and biochemical indicators have become the focus of research in NAFLD, as well. Several clinical scoring systems have indeed been applied in diagnosing fibrosis, such as the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), FIB-4, Forns' Index, the BARD score, FibroMeter NAFLD, the Hui model, the non-invasive Koeln-Essen-index (NIKEI), the S Index and the NAFLD fibrosis score (NFS) [22-29].

In this issue of the *J Gastrointestin Liver Dis*, Yang et al. [30] have assessed in 453 consecutive patients with biopsy-proven NAFLD, the diagnostic performance of nine clinical non-invasive fibrosis models for advanced fibrosis prediction: APRI, FiB-4, Forns' Index, BARD, FibroMeter NAFLD, the Hui model, NIKEI, the S Index and the NAFLD fibrosis score (NFS). All the nine fibrotic models were correlated with the fibrosis stage in patients with NAFLD. Despite the high negative predictive value and specificity for diagnosing fibrosis of all these models, the positive predictive value and sensitivity were low. These results suggest that these models are more useful in excluding significant and advanced fibrosis in NAFLD, than in predicting their presence.

Although the highest area under the ROC curve and negative predictive value were found for APRI, BARD, FibroMeter NAFLD and NIKEI, the use of only one non-invasive model was not accurate enough to diagnose severe fibrosis in NAFLD. Conversely, the authors have proven that, using a step layered combination of APRI, BARD, FibroMeter NAFLD and NIKEI leads to an increased diagnostic performance for the prediction of advanced fibrosis in NAFLD, with 89.13% specificity, 72.50% sensitivity, 74.36% negative predictive value and 88.17% positive predictive value.

Undoubtedly, studies are still necessary before prediction models and blood-based biomarkers become available for routine clinical care in patients with NAFLD [31]. The future may bring more complex models, including clinical, routine blood-based variables, markers that reflect the dynamic nature of the fibrogenesis, alongside with molecular markers, quantitative proteomic technology, and physical parameters, such as liver stiffness assessed by elastographic techniques.

Conflicts of interest: None to declare.

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