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Noninvasive Tests of Liver Fibrosis and Their Combination in NAFLD: From Selected Patients to Real-Life Populations

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Abbreviations: AUROC, area under the receiver operating characteristic curve; ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; NAFLD, nonalcoholic fatty liver disease; NFS, NAFLD fibrosis score; VCTE, vibration-controlled transient elastography.

Nonalcoholic fatty liver disease (NAFLD) has become extremely common, now affecting 25% of the worldwide population.[1] All physicians, regardless of their specialty, are seeing NAFLD patients in their daily clinical practice, and all are challenged by the identification of the small subgroup having an advanced form of the disease. As with the other causes of chronic liver disease, it is now well established that liver fibrosis is the main predictor of the prognosis in NAFLD,[2] justifying the interest in diagnosing fibrosis. Because it is not conceivable to perform liver biopsy (currently the best reference, albeit imperfect, for liver fibrosis evaluation) in large populations, noninvasive testing represents an attractive option for the diagnosis and screening of NAFLD patients with advanced liver disease in need of specialized management. The noninvasive tests currently available are mainly represented by blood tests, either simple blood tests combining common indirect markers of liver fibrosis or specialized blood tests, including direct markers of liver fibrogenesis and fibrolysis, and elastography devices.

In this issue of HEPATOLOGY, Anstee et al. performed the largest study to date in terms of sample size on noninvasive tests of liver fibrosis in NAFLD.[3] They used the data from the international STELLAR-3 and STELLAR-4 phase 3 therapeutic trials to evaluate two simple blood fibrosis tests (Fibrosis-4 [FIB-4] and NAFLD fibrosis score [NFS]), a specialized patented blood test (enhanced liver fibrosis [ELF] test), and elastography measured through vibration-controlled transient elastography (VCTE) with the FibroScan device in 3,202 patients with biopsy-proven NAFLD. To ensure the best reference, liver biopsies were centrally read by an expert pathologist. Area under the receiver operating characteristic curve (AUROC) of the four noninvasive tests studied ranged from 0.74 to 0.80 for the diagnosis of advanced fibrosis. Using published cutoffs, VCTE provided a very low rate of undetermined diagnosis compared to the three blood tests (8% vs. 43%-51%) but at the expense of a lower specificity (71% vs. 89%-98%). Agreement between fibrosis tests improved sensitivity to 89%-96% and specificity to 97%-99% but with a subsequent increase in the rate of undetermined diagnosis to 64%-77% because of disagreement between tests. On the contrary, sequential algorithms (FIB-4 first, then ELF or VCTE) decreased the rate of undetermined diagnosis to 20%-24% but with a concomitant impairment in sensitivity, which decreased to 69%-77%.

This study confirms the good accuracy of blood tests and VCTE for the diagnosis of advanced fibrosis in NAFLD, especially when it is remembered that the AUROC of noninvasive tests cannot exceed 0.90 due to the limitations of liver biopsy.[4] Interestingly, the blood test FIB-4, which includes very common and simple parameters (serum transaminases, platelets, and age), showed similar accuracy as the specialized tests ELF and VCTE, with AUROC approximately 0.80. NFS provided a lower AUROC for advanced fibrosis (0.74), but this test may have been disadvantaged by the high prevalence of diabetes, a population in which NFS is not adapted, with most of the patients falling in the indeterminate or positive results because the variable hyperglycemia/diabetes is included in the formula.[5] The study of Anstee et al. confirmed in NAFLD what has been previously observed in chronic hepatitis C, namely the concept that agreement between a blood test and liver stiffness measurement improves the diagnostic accuracy of the noninvasive evaluation of liver fibrosis. However, this strategy has the disadvantage of significantly increasing the rate of undetermined diagnosis because of disagreement between both tests and requiring two tests in all patients, which induces additional costs when considering the very large population to evaluate. In this context, a more interesting approach could be the sequential use of fibrosis tests, particularly a simple blood test used as first-line evaluation, followed by a specialized test in case of a positive result. Compared to the "agreement" strategy, the "sequential" strategy increased by 2-fold the rate of negative evaluation while maintaining sensitivity for advanced fibrosis between 70% and 80%.

All the study results must, however, be taken with caution before generalization to clinical practice. Indeed, patients enrolled correspond to a very particular population selected for potential inclusion in a therapeutic trial targeting patients with advanced fibrosis (STELLAR-3) or cirrhosis (STELLAR-4). Therefore, the study population includes a very high (71%) rate of patients with advanced fibrosis and 41% with cirrhosis, which induces a strong spectrum effect. Such a population with overrepresentation of the diagnostic target artificially increases positive predictive value and decreases negative predictive value. This explains the unexpected very low (40%-60%) negative predictive value and excellent >90% positive predictive value observed for single fibrosis tests in the study, whereas they were, respectively, >90% and 66% in a recent meta-analysis.[6] Similarly, the rate of patients with undetermined diagnosis is much higher than what could be expected in less selected NAFLD

patients. On their side, sensitivity and specificity are not supposed to be affected by the prevalence of the diagnostic target. However, a linear relationship between the distribution of the fibrosis stages and the level of the AUROC has previously been demonstrated, suggesting the spectrum effect may also have some influence on these diagnostic indexes and cut-off calculations.[7] All this underlines the crucial importance of the "context of use" of fibrosis tests. Meta-analyses about diagnostic accuracy of noninvasive liver tests will therefore have to consider how patients were included in the selected studies and to stratify their analysis accordingly to avoid biased conclusions. As an example, adding the Anstee et al. study to the Xiao et al. meta-analysis would have probably significantly modified the results because of its different design and high weight (3,302 patients). Finally, the authors assessed accuracy for identifying advanced fibrosis or cirrhosis, whereas patients with F2, hence "significant" fibrosis, are considered to be part of the target population for specialized treatment. The studied biomarkers also only account for the diagnosis of fibrosis and not steatohepatitis, another important element in what is currently considered to be the population that needs treatment.[8] The granular stratification of the NAFLD disease with the noninvasive tests remains an unresolved issue.

Now that treatments for nonalcoholic steatohepatitis (NASH) will soon be available, a challenge is to identify the asymptomatic patients with unknown advanced liver disease. This will require close collaboration with the other specialties, especially general practitioners and, even more, diabetologists who manage many NAFLD patients in their daily clinical practice. Educating them in the use of the noninvasive liver tests to identify at-risk patients represents a very attractive option to organize a well-structured and cost-effective pathway between their clinics and specialized liver centers. This suggests using the noninvasive liver tests outside the liver clinics where they have been developed and validated. As acknowledged by Anstee et al., their study results do not apply to this context of use. A recent work has evaluated the use of FIB-4 and then ELF by general practitioners for NAFLD patients.[9] This pathway reduced unnecessary referrals from primary care to specialized liver centers by 81% and, importantly, detected 5 times more cases of advanced fibrosis. We need to accumulate these real-life data and evaluate noninvasive tests in this context of use to validate the screening of advanced liver disease in the large NAFLD

population. This challenge is a mandatory prerequisite to achieve a significant impact on the worldwide burden of NAFLD with the new upcoming treatments.

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