Editorial Commentary

Validation of the European Association for the Study of the Liver algorithm for the noninvasive diagnosis of advanced fibrosis in metabolic-dysfunction associated steatotic liver disease

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Metabolic-dysfunction associated steatotic liver disease (MASLD), formerly known as non-alcoholic fatty liver disease (NAFLD) (1), is characterized by the accumulation of fat in the liver cells, independent of excessive alcohol consumption and has emerged as the most prevalent chronic liver condition in Western countries, underscoring a significant public health concern (2). The progression of MASLD to advanced fibrosis, marked by excessive extracellular matrix deposition and scar tissue formation, is a critical stage in MASLD natural history that significantly increases the risk of liver-related complications mortality (3). Non-invasive tests (NITs), such as liver stiffness measurement (LSM) with transient elastography (TE) and serum biomarkers, have gained prominence for assessing liver fibrosis in patients with suspected/confirmed NAFLD, offering a safer and less invasive alternative to liver biopsy (4). These NITs could play a crucial role in early detection and management, potentially reducing the need for biopsy. In 2021, the European Association for the Study of the Liver (EASL) released their clinical guideline paper on NITs for the evaluation of liver disease severity and prognosis (5).

In their recent study, published in *Hepatology*, Canivet *et al.* aimed to validate the EASL algorithm for diagnosing advanced liver fibrosis in patients with NAFLD (6). The researchers aimed to evaluate the performance of the EASL algorithm using two distinct patient cohorts. First, they conducted a retrospective analysis on 1,051 patients with NAFLD, available liver biopsies, and noninvasive tests from three French University Hospitals. This analysis included four NITs: fibrosis-4 (FIB-4), vibration controlled transient elastography (VCTE), FibroMeter, and Fibrotest—with the enhanced liver fibrosis (ELF) score available for 396 patients. Second, they evaluated an additional cohort from primary care and diabetes (PCD) clinics comprised of 230 patients assessed with FIB-4, VCTE, and ELF. In the PCD cohort, liver biopsy was offered to patients exhibiting a suspicion of significant fibrosis based on VCTE reading, inconsistent cirrhosis investigation results, or willingness to join a clinical trial. As per EASL algorithm, there was a three-tiered approach for diagnosis of advanced fibrosis, which included FIB-4 ≥1.30, followed by VCTE ≥8.0 kPa, and one of three patented serum tests. Per EASL algorithm, liver biopsy was considered only if the third-line test result was discordant from the VCTE result.

The biopsy cohort included 1,051 patients with a median age of 58.1 years, with 60% being males and 50% having diabetes. The distribution of liver fibrosis stages was as follows: F0 (11.3%), F1 (22.6%), F2 (26.5%), F3 (25.2%), and cirrhosis (14.3%). The area under the receiver operating characteristic (AUROC) curves for advanced fibrosis using FIB-4, VCTE, FibroMeter virus second generation (FMV2G), and Fibrotest were 0.773,

0.841, 0.806, and 0.753, respectively. As a standalone test, VCTE outperformed the blood fibrosis tests, with FMV2G being the most accurate blood test. The sensitivity of these tests ranged from 62% to 88%, with specificities being lower for FIB-4 and VCTE. The EASL stepwise algorithmic approach improved specificity and positive predictive value (PPV) at each step. For instance, agreement between FIB-4 ≥1.30 and VCTE ≥8.0 kPa raised specificity and PPV by about 25% compared to FIB-4 alone. Additionally, an agreement between VCTE and a patented serum test increased specificity by 25% and PPV by 20–30% compared with VCTE alone. The EASL algorithm with Fibrotest or FMV2G as the third-line test showed an overall diagnostic accuracy of 81.4–82.8%, requiring liver biopsy in only 7–13% of patients. This algorithm demonstrated a specificity of 90% for advanced fibrosis but moderate sensitivity at 71.3%. Regarding the diabetes clinics/primary care cohort, 230 patients were assessed using the EASL algorithm, with 68 having FIB-4 ≥1.30, 34 showing VCTE ≥8.0 kPa, and 27 with ELF ≥9.8. While 30% required a second-line VCTE and 15% a third-line ELF, liver biopsy was necessary in only 3% of cases. Finally, the authors showed that the EASL algorithm's predictive values for diagnosing advanced fibrosis varied with fibrosis prevalence, showing increased PPVs in higher prevalence settings. In primary care, where prevalence is lower, about 40% of patients needed a second-line VCTE and 15% a third-line test, with liver biopsy requirements remaining stable across prevalence rates.

The study by Canivet *et al.* is the first to assess the validity of the EASL proposed algorithm and showed promising results (6). The inclusion of two distinct cohorts is a significant aspect of the study, and the approach to simulate the algorithm's accuracy across different prevalence rates is innovative, providing insights into its applicability in diverse clinical settings. The patients from the biopsy cohort represent a population selected to undergo biopsy mainly for NAFLD with suspected fibrosis, based on the presence of abnormal liver blood tests, hyperferritinemia, and/or increased values in non-invasive fibrosis tests (7). Thus, they were more likely to have advanced fibrosis compared to patients from the general population. Despite this, the algorithm performed well keeping a satisfactory negative predictive value, consistently above 80%, while the PPV incrementally increased with the addition of more concordant NITs. However, the sensitivity was somewhat lower, around 70%, mostly due to initially low FIB-4 results. As the authors suggest, this could be improved by the periodical repeat of FIB-4 in cases of higher suspicion, such as the population of the biopsy cohort (8). One could also argue that the use of the FIB-4 is not appropriate in secondary care settings, where the prevalence of advanced fibrosis is higher than 10%, which would have a significant impact on the negative predictive value of a low result (9). Moreover, the evaluated NITs were most likely part of the decision-making process to proceed to a liver biopsy, therefore their diagnostic accuracy is most likely artificially increased.

On the other hand, the PCD cohort mirrored a real-world scenario in primary care and diabetes clinic setting, where NAFLD is often undiagnosed or presents in earlier stages. As per 2021 EASL guidelines, simple fibrosis scores such as FIB-4 play mostly a role of gatekeeper in the primary care setting where the prevalence of severe fibrosis is lower and a negative predictive value (NPV) of a score <1.30 would be higher. They assessed the performance of the EASL algorithm in relation to the estimated prevalence of fibrosis, finding that NPVs remained above 90% for a suspected fibrosis prevalence of up to 25%. This comparison is critical in understanding the algorithm's utility across varying clinical landscapes. Notably the need for liver biopsy was significantly reduced, with only 3% in the primary care diabetology clinic cohort requiring this. This validates our previous modelling data which suggested that concordant non-invasive fibrosis tests are equivalent to a liver biopsy in low prevalence settings (10).

Considering the current landscape of MASLD management, identifying patients with advanced fibrosis is crucial to reduce adverse liver outcomes. While acknowledging the limitations of FIB-4 and other NITs, the study by Canivet *et al.* highlights the reliability of the EASL-recommended pathway for screening for advanced fibrosis. However, clinicians should consider the patient population being tested, as the prevalence of advanced fibrosis significantly influences the interpretation of these results. FIB-4 is a useful first-line test in primary care settings, however its use is not advisable in secondary care, where more accurate tests should be preferentially used.

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