Non-invasive tests and advanced chronic liver disease in NAFLD: Two steps forward and one step back?

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We read with great interest the study by Dr Mozes and the LITMUS investigators on non-invasive tests (NITs) in NAFLD[1] and commend the authors on their comprehensive individual patient data meta-analysis. The authors have confirmed that a sequential algorithm of FIB-4 and liver stiffness measurement with vibration controlled transient elastography (LSM-VCTE) has superior diagnostic performance for both ruling in and ruling out advanced fibrosis and/or cirrhosis. Indeed, this concept has been demonstrated by several studies, including our own work[2-4]. However, we would like to highlight a few key points for clarification.

Firstly, the authors suggest that there is a reduction in liver biopsies from 33% to as low as 19% when using the proposed rule-in cut-offs for cirrhosis as summarised in Sankey diagrams. In our opinion, this comparative reduction in biopsies is not justified as the first diagnostic algorithm is examining the endpoint of advanced fibrosis, whereas the others are optimised for cirrhosis. Furthermore, this comparison appears misleading as the initial assumption is that all patients who are not classified as low-risk for advanced fibrosis require a liver biopsy in the first algorithm. This is not reflective of real-world clinical practice, even in tertiary care where the prevalence of advanced fibrosis is high. Indeed, the biopsy rate quoted in this algorithm is higher than the 30% prevalence of advanced fibrosis in the study cohort. Moreover, the algorithm does not account for the proportion of patients who have overt clinical, laboratory or radiological signs of cirrhosis with or without portal hypertension, where liver biopsy is not clinically indicated. Our group has demonstrated that only subjecting those classified as indeterminate risk of advanced fibrosis (using a higher LSM-VCTE cut-off) to liver biopsy in similar algorithms can be an acceptable and cost-effective strategy[2, 4, 5].

Similarly, the LSM-VCTE cut-offs selected by the authors do not take into account the paradigm of compensated advanced chronic liver disease (cACLD) that was established in the Baveno VI consensus[6]. A LSM-VCTE cut-off of ≥15kPa is highly suggestive of cACLD and identifies those at risk of decompensation and hepatocellular carcinoma. Indeed, our group has recently showed that lower cut-offs

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of ≥12kPa can in fact rule-in cACLD with 92% specificity[7]. Likewise, the cut-offs to rule in cirrhosis proposed by the authors are the same or higher than the well-established and validated cut-off of ≥20kPa for clinically significant portal hypertension (CSPH). This cut-off forms the basis of the Baveno VI variceal screening criteria, which have been validated in NAFLD[8]. This suggests that the patients ruled in as cirrhotic in this study are likely to have CSPH and that the proposed cirrhosis cut-offs have no additional value in terms of patient management.

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Finally, the clinical utility of the authors' findings should be appropriately framed. In the diagnostic algorithms presented, the false negative rate is 10%. This is suboptimal in terms of missed diagnoses of cirrhosis at a prevalence of 11%. Furthermore, there is a high rate of indeterminate results in the proposed algorithms. The real goal in terms of clinical utility of NITs is to accurately identify those at risk of liver-related complications, while reconciling an acceptable number of false negative diagnoses with false positives and indeterminate results. This may require additional clinical data to be analysed with histology. Furthermore, decision curve analysis may aid in this process, as we have previously demonstrated[2, 3, 9].

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In summary, although the study by Dr Mozes and colleagues reaffirms that two-step algorithms are better than one, there has been limited progress forward in terms using NITs for clinical diagnosis or prognostication in NAFLD in the current paradigm of cACLD. We believe that the two-step algorithm is optimal for patients in primary care where the prevalence of advanced fibrosis is relatively low. In populations with a higher prevalence of advanced fibrosis/cirrhosis encountered in secondary care, FIB4/NFS most likely have lower utility, and the dual cut-off LSM/VCTE for cACLD should be used. The authors have a unique opportunity to test this using their data.

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