Letter to the Editor

JOURNAL OF HEPATOLOGY

Reply to: "Accurate diagnosis of NAFLD-related hepatic fibrosis with non-invasive methods: A comment for moving forward"

To the Editor:

We thank Dr Li for his valuable comments in line with 2 important topics in the field of non-invasive liver tests: the process of developing non-invasive strategies and the context of their use.

Populations can differ between centres, but the fact that non-invasive tests are developed and evaluated in samples of patients selected for liver biopsy is probably a more important source of heterogeneity. Indeed, liver biopsy comes at the end of a multi-step process, which is influenced by awareness of liver diseases, as well as local guidelines and procedures. Such heterogeneity largely contributes to the differences in sample characteristics and diagnostic accuracy observed between the different published studies. As mentioned by Li, it is highly likely that a test or an algorithm developed and well-fitted in a single centre population may not be suitable for other centres. In our study, the patient characteristics significantly differed between the 4 participating centres.[1] We pooled data from the 4 centres with the aim of capturing the different patient profiles in a more representative sample which would provide robust results applicable to clinical practice. The randomization in derivation and validation sets allowed an internal cross-validation which is referred to in the TRIPOD guidelines as a phase IIa study.[2] We now encourage other teams to perform independent and external validation of our findings, which corresponds to phase IV in the TRIPOD guidelines.

Our algorithms were developed in a population of patients included in tertiary care centres where the prevalence of the target is high, and it is important to underline our results are relevant in this context of use. Interestingly, our results were similar to those of Shah *et al.*, who reported on a large prospective cohort from the US, also including patients from tertiary centres but with a lower prevalence of advanced fibrosis (23%).[3] As in our work, the higher cut-off for Fibrosis-4 (FIB4) was calculated at 2.67, providing 98% specificity and a positive predictive value (PPV) of 80%. Most false positive results obtained with our algorithm were in patients with some fibrosis on liver biopsy, mostly F2 stage. A recent meta-analysis has shown that liver-related prognosis in non-alcoholic fatty liver disease (NAFLD) significantly worsens beyond the F2 fibrosis stage.[4] Therefore, it is not surprising that FIB4 >2.67 identifies a subset of patients with NAFLD in tertiary care centres who have impaired liver-related prognosis.[5] We found similar prognostic significance in NAFLD for vibration-controlled transient elastography and the specialized blood test FibroMeter.[6] Taken together, all these findings suggest that, beyond imperfect PPVs, non-invasive fibrosis tests identify a subset of patients for whom specialized management and treatment of the disease is mandatory.

Considering the high prevalence of NAFLD and the low rate of patients who progress to advanced disease, non-invasive tests could be particularly useful for identifying advanced fibrosis in at-risk populations. In such a context, the prevalence of the target is much lower than in specialized tertiary care centres. As an example, the global prevalence of advanced fibrosis among patients with type 2 diabetes mellitus has been estimated at 5%.[7] As underlined by Li, PPV decreases alongside disease prevalence. However, in such contexts, it should also be underlined that negative predictive values are even better, which allows non-invasive fibrosis tests to very confidently exclude advanced fibrosis in a large majority of patients with NAFLD. Considering the expected poor PPV in the specific context of screening for advanced fibrosis, we agree that at-risk patients selected by the first-line test should undergo evaluation with specialized fibrosis tests to confirm the diagnosis. With this approach, the diagnostic accuracy of the second-line specialized test is likely to match that found in published studies. Indeed, the screening test will select an at-risk population that is likely similar to the populations in which specialized fibrosis tests were developed and validated.

Financial support

University Hospital of Angers.

Conflict of interest

Jerome Boursier reports consulting activities with Echosens.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JR and CC drafted the manuscript, JB made critical revision.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2020.04.020.

References

[1] Boursier J, Guillaume M, Leroy V, Irles M, Roux M, Lannes A, et al. New sequential combinations of non-invasive fibrosis tests provide an accurate diagnosis of advanced fibrosis in NAFLD. J Hepatol 2019;71:389–396.

[2] Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ 2015;350:g7594.

[3] Shah AG, Lydecker A, Murray K, Tetri BN, Contos MJ, Sanyal AJ. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1104–1112.

[4] Taylor RS, Taylor RJ, Bayliss S, Hagstrom H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Gastroenterology 2020;S0016-5085. 30137-2.

[5] Angulo P, Bugianesi E, Bjornsson ES, Charatcharoenwitthaya P, Mills PR, Barrera F, et al. Simple noninvasive systems predict long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2013;145:782–789.e4.

Keywords: Non-alcoholic fatty liver disease; Liver fibrosis; Blood test; VCTE.
Received 8 April 2020; accepted 9 April 2020
https://doi.org/10.1016/j.jhep.2020.04.020

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[6] Boursier J, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, et al. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. J Hepatol 2016;65:570–578.
[7] Younossi ZM, Golabi P, De Avila L, Paik JM, Srishord M, Fukui N, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 2019;71:793–801.

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