Reply to: FIB4 cut off of 1.3 may be inappropriate in a primary care referral pathway for patients with non-alcoholic fatty liver disease.

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We would like to thank Dr Shah and co-authors for their interest and appreciation of our study (1). They argue that for a primary care pathway for patients with NAFLD, selecting patients with earlier stages of fibrosis might be more appropriate given the increased mortality that patients with F2 have. To achieve this, they propose lowering the cut-off of FIB-4 to 1.0 in order to capture such patients and they present some data from their cohort to support this argument.

FIB-4 consists of ALT, AST, age and platelet count and has been specifically developed for advanced fibrosis (F3 stage). Studies that looked at FIB4 for F2 fibrosis did not report satisfactory diagnostic accuracies, probably because platelet counts start to drop from F3 onwards (2). Therefore, lowering the FIB-4 cut-off to 1.0 would result in an increase in the number of indeterminate results without necessarily an increase in the number of patients with F2 diagnosed. Moreover, the ELF test which was used as the second step test in our algorithm, has a superior diagnostic accuracy for F3 compared to F2 fibrosis (3), and this is true for all other available serum or imaging modalities for fibrosis in NAFLD (2). Therefore, even if desirable, currently the tools to diagnose F2 fibrosis (rather than F3) are suboptimal.

There are three important considerations in our pathway that in our opinion mitigate such concerns. Firstly, we advocate that all patients who have NAFLD but not advanced fibrosis are actively managed in primary care with a focus on metabolic comorbidities. In that way, the cardiovascular risk**, which is the main cause of death in patients with NAFLD,** is reduced (4). **Moreover, tight management of comorbidities such as obesity, diabetes and hypertension could potentially reduce the risk of liver disease progression**. Secondly, we propose that all patients who do not have advanced fibrosis are re-tested after 3 years, in order to capture those who do progress. Thirdly, the proposed algorithm has a negative predictive value for the diagnosis of advanced fibrosis of over 95%, which greatly increases the effectiveness and efficiency of the current standard of care (5).

Although the authors are enthusiastic about data from their cohort, we would argue that the excellent AUROCs reported are due to a significant spectrum bias in the cohort, that includes 86 healthy donors and 22 patients with NAFLD, of which only few have fibrosis. The performance in the validation cohort is much lower, which makes the applicability of such findings questionable.

In summary, and until better diagnostic tests for F2 fibrosis in NAFLD are available, a pragmatic approach aiming at testing patients with NAFLD for advanced fibrosis in primary care could reduce unnecessary referrals and increase case-finding of patients at risk of complications of liver disease (1).

1. Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, Suri D, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. J Hepatol 2019;71:371-378.
2. Crossan C, Tsochatzis EA, Longworth L, Gurusamy K, Davidson B, Rodriguez-Peralvarez M, Mantzoukis K, et al. Cost-effectiveness of non-invasive methods for assessment and monitoring of liver fibrosis and cirrhosis in patients with chronic liver disease: systematic review and economic evaluation. Health Technol Assess 2015;19:1-409, v-vi.
3. Guha IN, Parkes J, Roderick P, Chattopadhyay D, Cross R, Harris S, Kaye P, et al. Noninvasive markers of fibrosis in nonalcoholic fatty liver disease: Validating the European Liver Fibrosis Panel and exploring simple markers. Hepatology 2008;47:455-460.
4. Tsochatzis EA, Newsome PN. Non-alcoholic fatty liver disease and the interface between primary and secondary care. Lancet Gastroenterol Hepatol 2018;3:509-517.
5. Crossan C, Majumdar A, Srivastava A, Thorburn D, Rosenberg W, Pinzani M, Longworth L, et al. Referral pathways for patients with NAFLD based on non-invasive fibrosis tests: Diagnostic accuracy and cost analysis. Liver Int 2019;39:2052-2060.