Letter to the Editor

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FIB-4 cut-off of 1.3 may be inappropriate in a primary care referral pathway for patients with non-alcoholic fatty liver disease

To the Editor:

We would like to compliment Ankur Srivastav *et al.* for developing a primary care referral pathway for patients with non-alcoholic fatty liver disease (NAFLD), to stratify patients and reduce unnecessary referrals.[1] The use of the fibrosis-4 (FIB-4) index to detect patients with advanced fibrosis has been looked at in several studies[2,3] and a lower cut-off of 1.3 to rule out advanced fibrosis has been proposed in an algorithm.[4] Amongst all histological features, liver fibrosis is associated with adverse long-term outcomes in patients with NAFLD.[5] The time duration leading to the development of advanced liver disease was 22–26 years in F0-1, 9.3 years in F2, 2.3 years in F3 and 0.9 years in decompensated F4.[6] Advanced stages of fibrosis F3-F4 have a hazard ratio of 2.54 and 5.19, respectively, in comparison with a hazard ratio of 0.87 and 0.88 in lower stages of fibrosis F0-F1. There is a progressive increase in mortality with the increasing stages of fibrosis, with stage F2 having an intermediate hazard ratio of 1.36 between F0-F1 and F3 and F4. Thus, the FIB-4 cut-off of 1.3 may be appropriate to distinguish F0-F2 *vs.* F3-F4 in the setting of patient enrolment in drug trials where advanced fibrosis needs to be identified. However, in the setting of a primary care referral pathway it would be inappropriate to use 1.3 as a lower cut-off as it would include F2 fibrosis, which also confers an increased risk of mortality. It would be thus be appropriate to have a cut-off to differentiate F0 *vs.* F1-F4 which would confidently rule out all patients with fibrosis. The patients with fatty liver disease without any fibrosis can then be successfully managed by primary care physicians, where lifestyle modification and control of risk factors alone would be the required management.

We looked at our cohort of 108 individuals (86 healthy donors and 22 patients with NAFLD) in whom we compared FIB-4 and magnetic resonance elastography (MRE) *vs.* liver biopsy to assess fibrosis stage F0 *vs.* F1-F4.

FIB-4 performed well *vs.* biopsy with an AUROC of 0.963 (Fig. 1) MRE performed even better than FIB-4 with an AUROC of 0.997. A FIB-4 cut-off of 1.0, showed 100% sensitivity and 94.3% specificity to rule out any fibrosis (F0 *vs.* F1-F4). This cut-off was

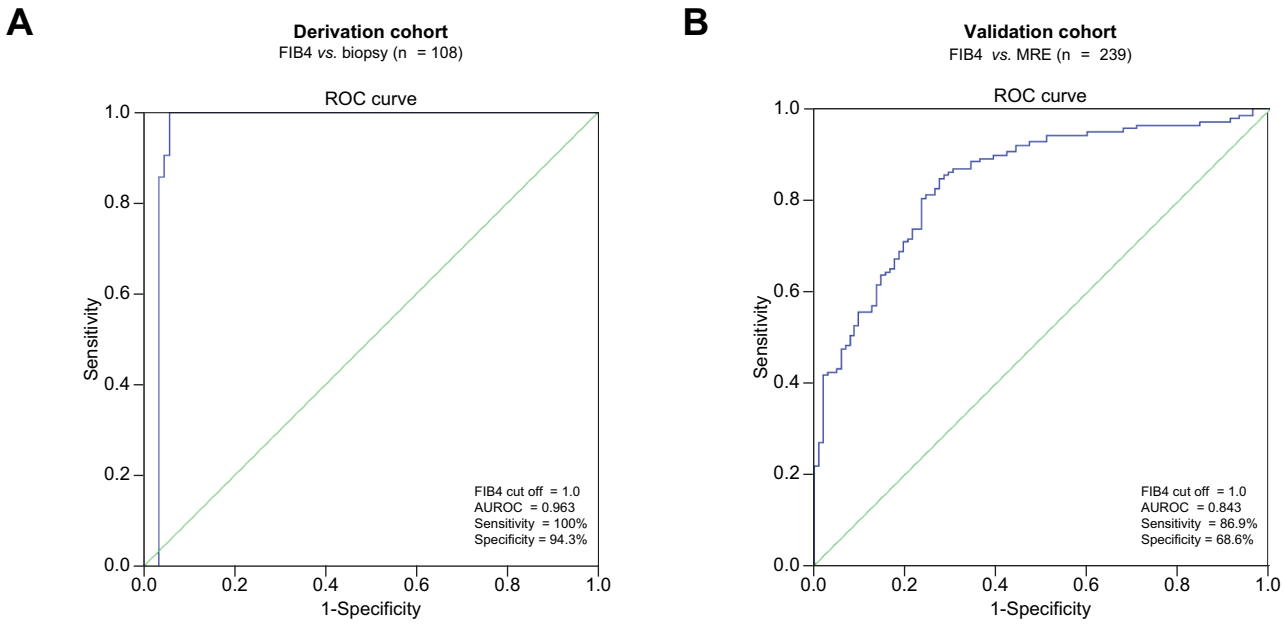

Fig. 1. Comparison of FIB4 versus liver biopsy and MRE in derivation and validation cohort. (A) Derivation cohort, FIB4 versus biopsy (B) Validation cohort, FIB4 versus MRE Area under the receiver operating characteristic curve (AUROC) for fibrosis4 index (FIB4) versus liver biopsy in derivation cohort and FIB4 versus Magnetic resonance elastography (MRE) in validation cohort was calculated. Sensitivity, specificity was calculated from FIB4 cutoff 1.0 obtained from the derivation cohort which was applied to the validation cohort.

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validated *vs.* MRE in a cohort of 239 patients with NAFLD. In this validation cohort, FIB-4 with a cut-off of 1.0 was slightly inferior, with an AUROC of 0.843 (86.9% sensitivity 68.6% specificity).

Our cut-off of 1.0 performed well in the derivation cohort however this cohort comprised of young healthy living donors who underwent a liver biopsy during living donor liver transplant. This cut-off needs to be validated in a larger cohort of NAFLD. However, we do strongly feel that a cut-off of 1.3 is inappropriate, as it would include patients with F2 fibrosis in a primary care referral pathway.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Authors' contributions

Conceptualization, Samir Shah; Acquisition of data, Swati Kamble; Interpretation of data, Akash Shukla, Drafting of the manuscript, Hiteshi Dhami-Shah; Critical revision of the manuscript for important intellectual content, Samir Shah, Akash Shukla; Study supervision, Samir Shah.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.12.025.

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