Reply to "An elevated FIB-4 score predicts liver cancer development: a longitudinal analysis from 29,999 NAFLD patients" and to "Poor performance of FIB-4 in elderly individuals at risk for chronic liver disease – implications for the clinical utility of the EASL NIT guideline"

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Dear Editor,

We thank Loosen et al. [1] and van Kleef et al. [2] for their interest in our work [3]. The observation of Loosen et al. that FIB4 ≥ 1.3 is associated with an over 12-fold increase in the risk of hepatocellular carcinoma in a large cohort of 29,999 NAFLD patients in Germany followed-up between 2005 and 2019 is very important, and confirms previous observations in the Asian population with NAFLD [4]. This data underlines that patients with FIB4 over 1.3 should be referred for further evaluation and surveillance, as suggested by our CPGs.

On the other hand, van Kleef et al. suggest that FIB4 is not a reliable first-line test for liver fibrosis assessment in subjects ≥ 65 years old participating in the Rotterdam study, taking liver stiffness measurement (LSM) using vibration controlled transient elastography (VCTE) as a reference standard. In their study, FIB4 had poor discriminative performance (AUROC 0.635) and missed 40/159 (25.2%) individuals above the age of 65 with LSM ≥8 kPa. The Rotterdam study is a large cohort sampled from a general, unselected population, with available data on liver biochemistry, metabolic syndrome, alcohol consumption, and LSM, and included 3.891 participants of whom 6.0% had LSM ≥ 8 kPa. The study has however several drawbacks that we would like to underline. First,

and most important, a LSM ≥ 8 kPa does not necessarily imply the presence of significant liver fibrosis, especially in a random population sample. LSM has suboptimal specificity and positive predictive value (PPV), even more in a context of low prevalence of significant fibrosis (please see our considerations on the dependency of sensitivity, specificity, PPV and NPV on prevalence of a given endpoint of interest in the general population in our CPGs [3]). Several patients with FIB4 <1.30 and VCTE >8.0 kPa would likely not have advanced fibrosis, which leads to an underestimation of the sensitivity of FIB-4 for advanced fibrosis in this work. Since it is not possible to assess the number of patients with advanced fibrosis who would have been missed using FIB4 in the Rotterdam study (no liver biopsy available), robust endpoints such as the development of liver-related events should be used instead. Longitudinal studies performed in the general population, similar to the Rotterdam cohort, have shown that prognosis of patients with FIB4 <1.30 is excellent and, even more, that repeating FIB4 allows to refine the prognosis during the follow-up and therefore probably to retrieve later at-risk patients for VCTE examination [5,6]. The letter by Loosen et al. [1] further adds to this body of evidence supporting favorable outcomes in subjects with FIB4 < 1.30. Second, performing a FIB4 examination is indicated in any patient who has risk factors for advanced fibrosis in the context of non-alcoholic fatty liver disease or alcohol related liver disease. Hence, performing FIB4 in individuals ≥65 yrs is somehow an artificial exercise - if the at-risk period only begins at age 65, then investigations are of little need because of the long period of fibrosis development.

Irrespective of these considerations, in an ideal world, patients with risk factors for chronic liver disease should be evaluated using the best available non-invasive methods for liver fibrosis assessment. We acknowledge that FIB4 is limited by false negatives and false positives. Future referral pathways and screening programmes will have to evolve, for instance taking advantage of the increased availability of point- and 2D-shear wave ultrasound elastography embedded in most high-end ultrasound devices, or of the broader availability of patented serum tests of fibrosis with high accuracy. Until then, we maintain that FIB4 is the recommended first-line test in current referral pathways due to a good balance between simplicity, availability, price, and a diagnostic accuracy that beats individual routine blood test and doctor's clinical acumen alone [7].

Finally, beyond diagnostic accuracy and rate of referral, the clinical benefit and utility of algorithms for liver fibrosis screening in subjects over 65 should be ultimately demonstrated through cost effectiveness studies.

References

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