An elevated FIB-4 score predicts liver cancer development: A longitudinal analysis from 29,999 patients with NAFLD

To the Editor:

Just recently, the EASL updated their “Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis”, emphasizing the high predictive value and clinical relevance of simple non-invasive tests (NITs), such as the fibrosis-4 (FIB-4) score (calculated on the basis of age, AST/ALT levels and platelet count) to rule out advanced fibrosis and stratify the risk of liver-related outcomes in patients with non-alcoholic fatty liver disease (NAFLD). A higher FIB-4 score should trigger referral to a specialized hepatologist and justify initiation of further hepatological and metabolic work-up as well as potentially therapeutic interventions and regular surveillance. However, the predictive value of the FIB-4 score for the development of hepatocellular carcinoma (HCC) in patients with NAFLD is only poorly defined.

In a retrospective cohort study, we used the Disease Analyzer database (IQVIA) to calculate the FIB-4 score in a cohort of 29,999 patients with NAFLD (ICD-10: K76.0, K75.8) followed in 1,284 outpatient practices in Germany between 2005 and 2019 and evaluated its relevance as a potential indicator for the development of liver cancer among patients with NAFLD. Patients with other liver diseases (including cirrhosis and liver diseases other than NAFLD) or cancer diagnoses 12 months prior to the index date (initial ambulant NAFLD diagnosis) were excluded. Patients with NAFLD were stratified into a low risk (FIB-4 <1.30, n = 17,967) and an intermediate-high risk group (FIB-4 >1.30, n = 12,032), based on the EASL recommendation on NITs in patients observed in primary care or outside the liver clinic. Basic characteristics of study patients are displayed in Table S1.

Within 10 years from the index date, the cumulative incidence of liver cancer (ICD-10: C22) was significantly higher among intermediate-high risk patients with a FIB-4 index >1.3 compared to the low-risk group (0.47% vs. 0.04%, p <0.001, Fig. 1). In a multivariate Cox-regression model adjusted for age, sex, and relevant co-morbidities (diabetes, obesity, hypertension, lipid metabolism disorders), a FIB-4 index >1.3 turned out to be a strong and highly significant predictor of liver cancer development within the 10-year follow-up period (hazard ratio [HR] 12.85; 95% CI 3.58-46.16; p <0.001, Table S2).

We subsequently performed multivariable Cox-regression models to test potential associations between the individual FIB-4 score and incidence of malignancies other than liver cancer. Bonferroni correction was performed to counteract the problem of multiple comparisons. A p value of <0.005 was considered statistically significant. In contrast to liver cancer, patients with NAFLD and FIB-4 score of >1.3 showed no significantly increased incidence of head and neck cancers (HR 1.83; 95% CI 0.82-4.05, p = 0.138), gastrointestinal cancers of digestive organs other than the liver (HR 1.12; 95% CI 0.89-1.41; p = 0.342), respiratory organs (HR 0.65; 95% CI 0.46-1.02; p = 0.061), skin (HR 1.29; 95% CI 10.5-1.59; p = 0.015), breast (HR 1.34; 95% CI 1.01-1.78; p = 0.041), female genital organs (HR 0.90; 95% CI 0.57-1.44; p = 0.663), male genital organs (HR 0.95; 95% CI 0.71-1.26; p = 0.700), urinary tract (HR 1.30; 95% CI 0.90-1.87; p = 0.163), and lymphoid and hematopoietic tissue (HR 1.28; 95% CI 0.99-1.68; p = 0.064, Table S2).

In summary, we show in a large outpatient population that an elevated FIB-4 score >1.3 represents an important predictor for the development of liver cancer within a 10-year follow-up period, but not for other malignancies among patients with NAFLD. Our data strongly support the recommendations from the updated “Clinical Practice Guidelines on non-invasive tests for evaluation of liver disease severity and prognosis” by providing additional evidence for the use of the FIB-4 tool for risk stratification of patients with NAFLD. The over 12-fold increased risk for primary liver cancer in patients with FIB-4 index >1.3 confirms the specific liver cancer risk in patients with NAFLD (even without overt cirrhosis at baseline) and supports the clinical relevance of the specific cut-off value put forward in clinical guidelines to stratify patients for further evaluation and surveillance. Moreover, our data gained in a large European population are supported by a recent observation showing a 15-fold increased HCC incidence in Asian patients with NAFLD and an elevated FIB-4 score. Similarly, a much smaller study from tertiary referral centers with 1,173 European patients also indicated that FIB-4 was a useful predictor of long-term outcomes. Interestingly, our analysis revealed that within the group of patients with a high FIB-4 index – diabetes, dyslipidemia and arterial hypertension were significantly enriched, whereas unexpectedly, obesity was less prevalent in this group (Table S1). Of note, both diabetes mellitus and obesity are known independent risk factors for liver cancer.

Keywords: NASH; steatohepatitis; cancer; hepatocellular carcinoma; HCC risk; outcome; non-invasive test; NIT; FIB-4.

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Fig. 1. Kaplan-Meier curves for time to liver cancer diagnosis in patients with NAFLD in association with a baseline FIB-4 score assessment. Log-rank test, p <0.001. FIB-4, fibrosis-4; NAFLD, non-alcoholic fatty liver disease.
development. Based on the tremendous medical and socio-economic impact of NAFLD, our results from a large real-world cohort of patients with NAFLD managed in an outpatient setting corroborate the high relevance of NITs, such as the FIB-4 score, as an integral part of risk stratification for liver cancer development in NAFLD.

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

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Authors’ contribution
SHL, CR, KK, VK, NQ and TL designed the study, KK performed statistical analyses and generated figures and tables, SHL, CR, TL, FT and KK wrote the manuscript. All authors agreed to the final version of the manuscript.

Ethics approval
The “Disease Analyzer” database, used for analysis, contains anonymized electronic patient records. Patient data was analyzed in aggregated form without individual data being available. An individual consent form was not obtained following national and European legislation.

Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.08.030.

References