Authors' contributions

RK drafted the letter, RJ did the critical review

Supplementary data

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Polygenic risk score: A promising predictor for hepatocellular carcinoma in the population with non-alcoholic fatty liver disease

To the Editor:

We were impressed by the promising results reported by Bianco and colleagues, who indicated that the polygenic risk score (PRS), which is based on *PNPLA3-TM6SF2-GCKR-MBOAT7* variants, may be useful for predicting the risk of hepatocellular carcinoma (HCC) in patients with non-alcoholic fatty liver disease (NAFLD) and dysmetabolism. In particular, positive PRS can be used to identify a subset of patients with dysmetabolism who are at high genetic risk of HCC.[1] Considering that all the variants included in the PRS can be assessed easily and non-invasively, the novelty of this result and its significant implications for clinical practice should be emphasized. However, we still have a few concerns regarding this study.

First, the AUC for HCC was 0.64 for hepatic fat PRS (PRS-HFC) and 0.65 for PRS-5 (PRS adjusted for HSD17B13) in the NAFLD cohort.[1] The assessment of performance for PRS is important; however, these AUC values are not stellar. In general, the traditional thresholds for AUC are defined as follows: 0.5, no discrimination; 0.5-0.7, poor discrimination; ≥0.7, acceptable discrimination; ≥ 0.8, excellent discrimination; and ≥0.9, outstanding discrimination.[2] An important question to address in future studies would be to investigate whether inherited or *de novo* genetic factors such as copy number variants, methylation marks, and rare but highly penetrant polymorphisms not captured in this analysis of common variants or other non-invasive assessments, such as ultrasound elastography,[3] can be integrated to generate a comprehensive risk score to enhance the predictive ability of PRS. In addition, this study used AUC to evaluate the predictive performance of PRS.[1] Although AUC can be used to evaluate the ability of PRS to distinguish between patients with and without HCC, it cannot quantify the contribution of PRS to the burden of HCC on a population level. Thus, the population attributable fraction (PAF) may be used to estimate the extent to which risk factors, including PRS, age, sex, body mass index, and type 2 diabetes (T2D), mostly contribute to the burden of HCC on a population level.[4]

Hepatic fat content has a strong genetic background.[5] To date, a vast amount of genome-wide association studies (GWAS) have been performed in individuals of European descent.[6] However, genetic structure differs between populations with different ethnic components.[7] Inter-ethnic differences in susceptibility to fatty liver disease have also been emphasized in multi-ethnic population studies, where for example, the susceptibility to fatty liver disease is shown to be lowest in individuals of African descent, intermediate in Europeans, and higher in Hispanics, independent of the confounders.[7] Notably, since PRS is derived from GWAS and is mostly determined in individuals of European ethnicity, it may not be meaningful for individuals of other ethnicities. Failure to include populations from different ethnicities will hinder the application of genetic discoveries (such as PRS) to multi-ethnic individuals in clinical practice. The participants included in this study, which consisted of the general population (UK Biobank [UKBB] cohort, n = 364,048; 202 individuals with HCC) and at-risk individuals (NAFLD cohort, n = 2,566; 226 individuals with HCC; and a replication cohort of 427 German patients with NAFLD), were of European descent.[1]

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Therefore, the current PRS may not be generalizable to other populations, such as African Americans, Asians, and Hispanics. To address this important issue, quantitative genetic features of ethnicity should be included as covariates in the association tests, which could help adjust the ethnicity-specific effects in the primary PRS to a certain degree. Moreover, to improve the utility and generalizability of these results for all ethnicities, future PRS research should include analyses of genetic data from different ethnic backgrounds rather than only a Eurocentric pool.

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Authors' contributions
All authors were involved in the writing of this commentary and reviewed it prior to submission.

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Reply to: "Polygenic risk score: A promising predictor for hepatocellular carcinoma in the population with non-alcoholic fatty liver disease"

To the Editor:
We thank Long *et al.* for their positive comments on the novelty and the potential clinical impact of our recent study on the use of polygenic risk scores (PRSs) to infer causality between hepatic fat and carcinogenesis, and to predict hepatocellular carcinoma (HCC) development in individuals with dysmetabolism and non-alcoholic fatty liver disease (NAFLD).[1,2]

As highlighted by Long *et al.*,[2] the PRS prediction for HCC in a large European NAFLD cohort was largely superior to that of the single genetic risk variants. However, the AUC was relatively low (<0.7) and, in fact, we refrained from proposing the clinical use of PRS as a standalone diagnostic test. Additionally, in our study, PRS and classical risk factors were independently associated with HCC and together conferred a significant improvement in diagnostic accuracy compared to each of them alone.[1]

We observed a non-linear relationship between PRS and HCC risk, and in line with previous data, a synergistic effect between PRS and severity of insulin resistance in determining liver disease.[1,3,4] Therefore, we identified the optimal thresholds to discriminate HCC risk and validated these thresholds in participants with obesity and type 2 diabetes from the UK Biobank cohort. In this population-based study, PRS alone had and AUROC of 0.70 for detecting HCC. A positive PRS test was observed in approximately 1 in 10 individuals and it was able to predict HCC with 90% specificity. We reasoned that, as part of the ability of a PRS to predict HCC is mediated by the life-long burden of genetic variants on liver damage,[1] the PRS may be

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