Authors' contributions

SJ: Analysis and interpretation of data; drafting of the manuscript; statistical analysis. MT: Study concept and design; obtained funding; acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. HBJ: Acquisition of data; critical revision of the manuscript for important intellectual content. TH: Study concept and design; acquisition of data; obtained funding; critical revision of the manuscript for important intellectual content. AK: Study concept and design; analysis and interpretation of data; obtained funding; study supervision; critical revision of the manuscript for important intellectual content.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.06.006.

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Reply to: "External validation of a genetic risk score that predicts development of alcohol-related cirrhosis"

To the Editor:

Thank you for the opportunity to respond to the letter from Johansen *et al.*,[1] extending our earlier findings reported in the *Journal*.[2]

By applying our 3-SNP (single nucleotide polymorphism) score, Johansen *et al.* were able to stratify alcohol-related liver disease risk in a cohort with less extreme (but still elevated-risk) alcohol intake. The AUCs and odds ratios in this Danish cohort were very similar to those which we reported.

Johansen *et al.* comment that '… the closer the patients come to clinical disease, the less powerful a genetic score is compared to other non-invasive tests.' This is true, and important, and applies to all risk stratification protocols – not only genetic risk scores. A patient with clinical symptoms needs tests which evaluate their current situation. It is patients who are at high risk of conditions which have not yet occurred, or in some cases people from the general population, who may benefit from risk stratification through genetic scores. Specifically, patients with normal results for "… non-invasive tests for advanced fibrosis like ELF (enhanced liver fibrosis) test and FIB-4 (fibrosis-4) index …" may still develop significant fibrosis, cirrhosis and hepatocellular carcinoma in the future. Genetic tests can give a predictive measure of their underlying risk, as opposed to tests for already existing liver fibrosis (*e.g.* FIB-4 and ELF) that are intermediate tests diagnosing 'early disease' usually without symptoms.

The distinction between 'trait' and 'state' markers has been explored for a number of psychiatric conditions, including alcohol dependence and alcohol-related disease. For a long time no trait markers (able to assess future risk of disease) could be confirmed but genetic risk scores now offer this possibility for many conditions. The effectiveness of such scores in improving outcomes, and the ways to integrate them with current patterns of investigation, are being explored[3–5] and although the predictive value of a genetic score will always depend on the heritability of the condition, results so far are promising.

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Conflict of interest

JBW and DS have no conflict of interests. TRM has conducted clinical research with AbbVie, Genfit, Gilead, and Merck but none of these are related to this manuscript.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JBW drafted the response and DS and TRM edited. All authors read, critically reviewed and approved the final version.

Supplementary data

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A risk prediction model for hepatocellular carcinoma after hepatitis B surface antigen seroclearance: Considerations

To the Editor:

We read with great interest the article by Yang *et al.* reporting a risk prediction model for hepatocellular carcinoma (HCC) after hepatitis B surface antigen (HBsAg) seroclearance.[1] Currently, the optimal treatment endpoint of chronic hepatitis B (CHB) is seroclearance of HBsAg, which has been well-documented to significantly decrease the risk of developing HCC in patients with CHB.[2] However, some patients who achieve HBsAg seroclearance still develop HCC.[3,4] In previous studies, several risk factors were identified, including cirrhosis or diabetes mellitus, male sex, and old age at HBsAg seroclearance. However, most of these studies were limited by insufficient population size and/or follow-up period. In this study, a total of 831 patients were enrolled, among whom 40 patients developed HCC during follow-up. Through univariate and multivariate Cox regression analyses, age at HBsAg seroclearance, cirrhosis, family history of HCC, and more-than moderate drinking were identified as independent factors associated with HCC development. Based on these independent risk factors, a prediction model for HCC development after HBsAg seroclearance was established. We appreciate that the authors provided a promising model to predict HCC after HBsAg seroclearance. Despite the strengths of this study, several important issues warrant further discussion.

In this study, the authors identified age at HBsAg seroclearance as an independent risk factor of HCC, which may be interpreted as exposure time to HBV in endemic regions as they stated. However, it should be noted that age itself is a potent factor for the development of most cancers, including HCC.[5] In spite of the different etiological characteristics, the incidence of HCC has been shown to increase with age in epidemiological studies (Fig. 1A-C).[6] Moreover, separate cohort studies have shown that despite HBV infections, most HCC cases develop in patients over 60 years old (Fig. 1D,E).[7] Given the large deviation of patients' age and long-term period of follow-up in this cohort, the onset of HCC is likely to be attributed in large part to advancing age despite the HBsAg seroclearance. Therefore, the age at HCC diagnosis or last follow-up should be categorized (*e.g.*, >60 or not) and included as another potential risk factor in the analysis, which may further justify the effect of age at HBsAg seroclearance (*i.e.*, exposure time to HBV) on HCC development.

In terms of alcohol consumption, in addition to self-reported alcohol use (two and one standard drink of alcohol per day for males and females, respectively), drinkers with serum gamma-glutamyltransferase (GGT) levels over 100 U/L and no evidence of obesity or cholestatic liver disease were also classified as having more-than-moderate alcohol consumption. Accurate estimation of alcohol consumption from questionnaires

Keywords: Chronic hepatitis B; HBsAg seroclearance; Hepatocellular carcinoma; Gamma-glutamyl transpeptidase.
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