were conducted separately in each individual cohort, with Korean patients as the validation cohort, precisely as we recognized their differences. We are encouraged by the fact that despite significant differences between the two cohorts (as analyzed by Zhou[1]), the same immune targets remained robust and significant. Our multivariate analyses of these factors within each cohort also show that these clinical characteristics do not significantly confound our analyses (Table S8).[2] We hope that this will encourage other groups to expand their work beyond Asian cohorts to examine if the same immune targets can be validated in their cohorts.

Finally, the author commented on the rationale for using the word "trajectory" in our study. We used the word "trajectory" in a broad sense of the different paths the immune response can take in response or irAEs to immunotherapy, not in the narrower sense of a timepoint analysis. Response and irAEs in immunotherapy are generally understood to occur in tandem, as mentioned above. Our study uncouples these two events and shows that there are differences in the immune responses in each event. In addition, we have also conducted timepoint analysis with pre- and post-treatment samples with implications on the potential movements and modifications of these immune cells, supporting the distinct "trajectory" pathways that the cells took in response to ICB.

In conclusion, we thank the author once again for the tremendous interest and time invested in interpreting and understanding our study. We would acknowledge the limited sample sizes but remain encouraged by our data that show the potential of novel combination immunotherapy, which we are currently planning to expand to a larger scale clinical validation.

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Conflict of interest

All authors declared no conflict of interest.

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

Authors' contributions

S. Chuah and V. Chew drafted the letter and D. Tai edited and approved the final version.

Supplementary data

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An individualized cirrhosis screening strategy might be more cost-effective in the general population

To the Editor:

We read with great interest the article by Labenz, Arslanow *et al.*[1] recently published in *Journal of Hepatology*. This article showed that the structured early detection of asymptomatic liver cirrhosis (SEAL) approach, involving assessment of elevated liver enzymes and calculation of the aspartate aminotransferase (AST)-to-platelet ratio index (APRI), has the potential to increase the detection of advanced liver fibrosis and cirrhosis in the general population. This prospective study is important and timely for guiding the detection of early cirrhosis in clinical practice. After careful consideration, we put forward the following suggestions.

First, the performance of the non-invasive methods for diagnosing advanced fibrosis and cirrhosis might be affected by patient age and comorbidities. Wang *et al.* reported that the APRI showed

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poor performance in detecting significant fibrosis among patients with chronic hepatitis B (CHB) aged ≤30 years, with an area under the receiver-operating characteristic curve (AUROC) of 0.567.[2] Similarly, McPherson *et al.* demonstrated that age is a confounding factor during accurate non-invasive diagnosis of advanced fibrosis. The non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS) and fibrosis 4 (FIB-4) scores also exhibited poor performance in patients with NAFLD aged ≤35 years and showed an unacceptably poor specificity in patients aged ≥65 year.[3] Moreover, it was reported that accuracy of the APRI for diagnosing cirrhosis is markedly reduced in patients with NAFLD and diabetes compared to those without diabetes (AUROC: 0.92 *vs.* 0.73, $p = 0.002$).[4] The presence of diabetes significantly decreased the efficacy of the FIB-4 score and NFS for detecting advanced fibrosis among patients with NAFLD.[5] The unsatisfactory performance of the non-invasive fibrosis score in certain subgroups of patients may be related to the reduced utility of AST and platelet levels, both of which are affected by age and comorbidities. In the study by Labenz, Arslanow *et al.*, patients aged ≤35 years were excluded, and the median age of patients was 61.9 years. Approximately half of the patients in whom advanced fibrosis/cirrhosis was detected by the SEAL algorithm also presented with diabetes (44.4%), dyslipidemia (42.2%) or arterial hypertension (44.4%). The features of this population could reduce the efficacy of the non-invasive fibrosis score. Thus, we suggest that flexible cut-off values should be applied for nationwide cirrhosis screening in populations with diverse ages and comorbidities to further improve the detection of advanced fibrosis or cirrhosis.

Second, the aetiology of chronic liver disease (CLD) is an important factor for making decisions in selecting non-invasive fibrosis scores. Previous studies have reported that the APRI displays satisfactory results in diagnosing cirrhosis in patients with hepatitis C infection. Nevertheless, the APRI displayed unsatisfactory performance in patients with NAFLD, with lower AUROC values than the FIB-4 index for detecting both advanced fibrosis (0.75 *vs.* 0.80) and cirrhosis (0.75 *vs.* 0.85).[6] Additionally, the APRI showed worse performance than the FIB-4 index for the detection of advanced fibrosis (AUROC: 0.76 *vs.* 0.80) and cirrhosis (AUROC: 0.72 *vs.* 0.78) in patients with CHB.[6] In Labenz, Arslanow *et al.*'s study, we found that only 45 of the 245 individuals who underwent a diagnostic work-up by a liver expert were diagnosed with advanced fibrosis or cirrhosis. This rate indicates that the APRI exhibits moderate detection accuracy (18.37%, 45/245). In addition, since the population diagnosed with CLD has a much higher prevalence of advanced fibrosis (0-27.9%) and cirrhosis (2.4-4.0%) than those without CLD,[7] the rate of missed diagnosis for cirrhosis could be further reduced by using a lower cut-off value of the non-invasive fibrosis score in patients with CLD. Taken together, these findings suggest that specific strategies that target CLD populations with distinct aetiologies as well as non-CLD populations would provide a more suitable screening method for cirrhosis.

In summary, the implementation of an individualized cirrhosis screening strategy using different non-invasive methods and cut-off values according to the characteristics of the population might be more productive and cost-effective, and warrants further investigation.

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Conflicts of interest

The authors have read guidance on competing interests, and they declare no competing interests.

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Authors' contributions

Siru Zhao and Xingmei Liao contributed to the drafting of the manuscript. Rong Fan contributed to the critical revision. All authors contributed to the approval of the final manuscript prior to submission.

Supplementary data

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