Reply to: “Starting the journey: Understanding the roles of complement proteins in liver diseases through mendelian randomization”

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Dear Editor,

We sincerely appreciate the insightful comments from Dr. Rezaee-Zavareh regarding our recently published paper titled "Protein-centric omics analysis reveals circulating complements linked to non-viral liver diseases as potential therapeutic targets". These comments not only highlight the strengths of our study but also offer valuable suggestions for future research directions in this field.

As noted in the editorial, the rising prevalence and burden of chronic liver diseases (CLDs) and their related complications, including cirrhosis and hepatocellular carcinoma (HCC), highlight the necessity of identifying risk factors and potential therapeutic targets. Our study aimed to contribute to this understanding by investigating the causal role of circulating complement proteins in the risk of non-viral liver diseases using Mendelian randomization (MR) analysis.

Dr. Rezaee-Zavareh's overview of the existing literature on the crucial roles of complement proteins in liver diseases, including their dual nature in promoting both hepatocyte regeneration and inflammation, provides an excellent context for understanding the significance of our findings. The complex involvement of the complement system in liver disease pathogenesis, particularly in the progression of metabolic dysfunction-associated steatotic liver disease (MASLD) to more advanced stages, as well as in HCC tumorigenesis, metastasis, and immune suppression, highlights the potential of complement-targeted therapies for CLDs. The comments highlight the importance of Mendelian randomization (MR) as a valuable tool for investigating causal relationships, particularly when randomized controlled trials (RCTs) are not practical or ethically feasible. The examples of previous MR studies reporting causal associations between complement components and various diseases further demonstrate the growing application of this approach in understanding disease causality.

We agree with Dr. Rezaee-Zavareh's recommendation that future studies should aim to confirm these associations using genome-wide association study (GWAS) data from diverse ancestries to assess their generalizability across different ethnic backgrounds. The heterogeneity observed between the inverse-variance weighted (IVW) and weighted median (WM) methods for some associations highlight the need for additional studies to validate these findings. Furthermore, to gain a more comprehensive understanding of the underlying mechanisms and true nature of the relationships between the studied variables, it is crucial for future research in this field to investigate potential mediators, such as oxidative stress, cytokines, and chemokines.

Regarding our drug repositioning approach, we acknowledge that while we provided some experimental and clinical evidence supporting the identified drugs, further validation using...
hospital cohort data or clinical trials specifically designed to test these findings is necessary. Our study should be considered an exploratory analysis, and extensive preclinical and clinical studies are required to assess the potential of these drugs for clinical trials.

Reference


