Complement Proteins and Liver Diseases: A Response to the Correspondence

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We greatly appreciate the response from Shi Y et al. (1) to our editorial (2). Studying diseases via newer research methods may reveal new mechanisms and identify novel therapeutic approaches. A recent research work by Shi Y et al. exemplifies this by leveraging Mendelian randomization (MR) and drug repositioning approach in identifying potential roles of the complement protein system for non-viral liver diseases (3).

As the authors pointed out, MR studies can initially establish and confirm the causal link between complement proteins and liver diseases, but this association must be further confirmed in a broader population. For example, a study of Chinese Han men used a bidirectional MR method, and it has been determined that MASLD has a significant causal relationship with serum C3 levels; however neither C3 nor C4 serum levels have a significant causal relationship with MASLD (4). In the study by Shi and colleagues (3), among the 28 circulating complement components that they evaluated, only a significant causal association between the C8 gamma chain and MASLD via the inverse-variance weighted MR method has been reported, and that association was not significant by the weighted median method. This again underscores the importance of using different MR methods and/or genome-wide association study data from other ancestries, which may significantly impact study outcomes.

Comprehensive evaluation via the MR method in diverse populations and clinical validation will enable us to bridge the gap between understanding the mechanisms involving complement proteins in liver diseases and offering new treatment options or diagnostic and prognostic biomarkers.
References: