CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

cfDNA ULP-WGS for prognosis in HCC

Linvencorvir phase 2 trial for HBV
Signature gene set for discrimination of MASLD progression
Incidence of adverse events associated with NAFLD
JCAD in cholestatic fibrosis
Prognosis of MASLD

KASL

Editorial

Starting the journey: Understanding the roles of complement proteins in liver diseases through mendelian randomization

Mohammad Saeid Rezaee-Zavareh[1], Naomy Kim[2], and Ju Dong Yang[2,3,4]

[1]Middle East Liver Diseases Center, Tehran, Iran; [2]Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [3]Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [4]Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

See Article on https://doi.org/10.3350/cmh.2023.0343

With the increasing prevalence and burden of metabolic dysfunction-associated steatotic liver disease (MASLD) and alcohol-associated liver disease (ALD), the burden of chronic liver diseases (CLDs) and their associated complications, including cirrhosis and liver cancer, is increasing.[1] Global MASLD prevalence is estimated to be about 30%, with more than 50% increase from 1990–2006 (25.26%) to 2016–2019 (38%).[2] ALDs are also widely prevalent types of CLDs, and about half of the deaths related to CLDs are thought to be caused by heavy alcohol consumption.[3] Hepatocellular carcinoma (HCC), as one of the important complications of CLDs, is considered the main type of primary liver cancer and is ranked the third leading cause of cancer death worldwide.[4] A deeper understanding of CLDs in various aspects, including their risk factors and new pharmacological targets for their treatment, can help to decrease their burden.

Previous studies have highlighted the critical roles of complement proteins in hepatic regeneration, liver injuries, and diseases such as ALD, MASLD, and autoimmune hepatitis (AIH).[5-8] These proteins, essential in the innate immune system, function through tightly regulated enzymatic cascades and are primarily produced by the liver.[6,8] The liver is susceptible to complement-mediated injury, as alterations in complement levels from liver disease itself can contribute to the exacerbation of liver disease pathogenesis. While complement proteins can be protective, promoting hepatocyte regeneration and liver cell proliferation and survival,[8] their activation can also lead to increased inflammation and liver injury, amplifying local inflammation and potentially leading to fibrosis and cirrhosis.[7] In HCC, complement proteins have been implicated in tumorigenesis, metastasis, and immune suppression, suggesting that targeting these pathways could probably offer new therapeutic avenues.[9] The presence of

Corresponding author : Ju Dong Yang
Karsh Division of Gastroenterology and Hepatology, Cedars-Sinai Medical Center, Comprehensive Transplant Center, Cedars-Sinai Medical Center, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, 8900 Beverly Blvd, Los Angeles 90048, CA, USA
Tel: +1-310-423-1971, Fax: +1-310-423-2356, E-mail: judong.yang@cshs.org
https://orcid.org/0000-0001-7834-9825

complement proteins in various cell types, such as platelets and neutrophils, underscores their importance in the immune response to injury and pathogens, but also highlights how their rapid mobilization can exacerbate liver disease progression.[10] Given their important role in liver diseases, research into complement-targeted therapies holds promise for developing more effective treatments targeting CLD and HCC.

Although randomized controlled trials are considered the gold standard for establishing causal relationships between outcomes and exposures, performing such studies is not always possible due to various reasons. Therefore, Mendelian randomization (MR) serves as a method for causal inference using observational data and single nucleotide polymorphisms as instrumental variables to infer causal relationships. Although MR cannot replace RCTs, it can provide complementary information.[11,12] There are several MR studies that have reported the causal association between different complement components and certain diseases such as deep vein thrombosis,[13] ischemic stroke,[14] periodontitis,[15] multiple myeloma,[16] chronic prostatitis,[17] and Alzheimer's disease.[18] As establishing a causal relationship for the effect of complement components in causing liver diseases can be challenging due to the aforementioned reasons (e.g., inverse causality), MR studies can be useful in this regard. So far, no MR studies have assessed the relationship between complement components and CLDs.

Shi et al.[19] in a recently published paper assessed the causal association between 28 circulating complement components and CLDs, including alcohol-related cirrhosis (ALC), MASLD, and three major autoimmune liver diseases, namely AIH, primary sclerosing cholangitis (PSC), primary biliary cholangitis (PBC), and HCC, through two-sample MR. In this study, the authors found a significant association between genetically predicted complement component levels of C1q C chain (C1QC) with AIH, C8 gamma chain (C8G) and complement factor H-related protein 5 (CFHR5) with PSC, CFHR1, CFHR2, and C1QC with ALC, C8G with MASLD, and finally CFHR2, C7, and C15 with HCC using the inverse-variance weighted (IVW)

method. No significant association was reported between any of the 28 evaluated complement components and PBC. Additionally, when evaluating causal association with the weighted median (WM) method, only a significant association for ALC with CFHR1 and CFHR2, and for HCC with C7 and C15, was reported. Next, using identified complement proteins associated with each liver disease, the authors investigated to identify liver disease-associated proteins from the complement protein-protein interaction network in biological processes. They utilized network-based drug repositioning to assess whether specific complement proteins could serve as pharmacological targets for the treatment of liver diseases. They identified effective drugs for different liver diseases, supported by experimental or clinical evidence.

Taken together, the results via MR and evaluation of common biological processes between both proteins associated with liver disease and from the complement regulatory network demonstrate that certain complement components may play important roles in some non-viral liver diseases and HCC. It should be noted that genome-wide association study (GWAS) data for six liver diseases and the selection of complement components as instrument variables were from Icelanders and European ancestries retrospectively. Therefore, future studies should confirm the association using other available GWAS data from other ancestries to confirm the generalizability of the results in a wider population with different ethnic backgrounds. Furthermore, some of the associations identified between complement proteins and liver diseases through the IVW method were not confirmed via WM. This implies that the associations lack consistency across all studies, displaying significant heterogeneity. It underscores the necessity of conducting additional studies to validate these findings. There may be mediators, such as diseases or conditions like oxidative stress or cytokines and chemokines[20] affecting the association between complement proteins and liver diseases, and they need to be considered when adjusting the demonstrated associations.

With a drug repositioning approach, the study has attempted to propose that the identified association between

---

Abbreviations:

CLD, chronic liver diseases; AIH, autoimmune hepatitis; ALC, alcohol-related cirrhosis; ALD, alcohol-associated liver disease; PSC, primary sclerosing cholangitis; PBC, primary biliary cholangitis; HCC, hepatocellular carcinoma; MASLD, metabolic dysfunction-associated steatotic liver disease; CFHR, complement factor H-related protein; C8G, complement C8 gamma chain; GWAS, genome-wide association study; WM, weighted median; IVW, inverse-variance weighted; MR, mendelian randomization; OR, odds ratio; CI, confidence interval

complement proteins and some non-viral diseases can have clinical utility. Although the authors provided some experimental and clinical evidence for each identified drug, no hospital cohort data or clinical trials specifically validated the findings of this study or the utility of these identified drugs. On the other hand, although the authors provided some common biological processes that both liver disease-associated proteins and proteins from the complement regulatory network are involved in, information specifically related to complement deregulation from immunological mechanisms is still limited, and more studies are needed to shed light on the mechanisms involved for possible different effects of the complement system on non-viral diseases. While this study hypothetically provides an opportunity for a better understanding of the direction in identifying novel therapeutics, it could be considered an exploratory analysis, and there is certainly a need for extensive preclinical and clinical studies to assess the potential of a drug for an earlier phase clinical trial.

Authors' contribution

Concept and Design: JDY, MSR-Z. Data Acquisition or Interpretation: MSR-Z, NK, JDY. Drafting the Manuscript: MSR-Z. Critical Revision: NK, JDY. Final Approval and Agreement: All Authors.

Conflicts of Interest

J.D.Y. provides a consulting service for AstraZeneca, Eisai, Exact Sciences, Exelixis, Fujifilm Medical Sciences, and Gilead Sciences. M.S.R-Z. and N.K. declare no conflict of interest.

REFERENCES

1. Younossi ZM, Wong G, Anstee QM, Henry L. The global burden of liver disease. Clin Gastroenterol Hepatol 2023;21:1978-1991.

2. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology 2023;77:1335-1347.

3. Rehm J, Shield KD. Global burden of alcohol use disorders and alcohol liver disease. Biomedicines 2019;7:99.

4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209-249.

5. Shin E, Schwarz KB, Jones-Brando LV, Florea LD, Sabunciyan S, Wood LD, et al. Expression of HLA and autoimmune pathway genes in liver biopsies of young subjects with autoimmune hepatitis type 1. J Pediatr Gastroenterol Nutr 2022;75:269-275.

6. Fan X, McCullough RL, Huang E, Bellar A, Kim A, Poulsen KL, et al. Diagnostic and prognostic significance of complement in patients with alcohol-associated hepatitis. Hepatology 2021;73:983-997.

7. Lin CJ, Hu ZG, Yuan GD, Lei B, He SQ. Complements are involved in alcoholic fatty liver disease, hepatitis and fibrosis. World J Hepatol 2018;10:662-669.

8. Thorgersen EB, Barratt-Due A, Haugaa H, Harboe M, Pischke SE, Nilsson PH, et al. The role of complement in liver injury, regeneration, and transplantation. Hepatology 2019;70:725-736.

9. Xiao Z, Yeung CLS, Yam JWP, Mao X. An update on the role of complement in hepatocellular carcinoma. Front Immunol 2022;13:1007382.

10. Ricklin D, Reis ES, Lambris JD. Complement in disease: a defence system turning offensive. Nat Rev Nephrol 2016;12:383-401.

11. Ference BA, Holmes MV, Smith GD. Using mendelian randomization to improve the design of randomized trials. Cold Spring Harb Perspect Med 2021;11:a040980.

12. Song Y, Ye T, Roberts LR, Larson NB, Winham SJ. Mendelian randomization in hepatology: A review of principles, opportunities, and challenges. Hepatology 2023 Oct 24. doi: 10.1097/HEP.0000000000000649.

13. Luo P, Xu J, Xu K, Jing W, Liu L, Xu P. Exploring the genetic relationship between deep vein thrombosis and plasma protein: a new research idea. Expert Rev Hematol 2022;15:867-873.

14. Cui HK, Tang CJ, Gao Y, Li ZA, Zhang J, Li YD. An integrative analysis of single-cell and bulk transcriptome and bidirectional mendelian randomization analysis identified C1Q as a novel stimulated risk gene for Atherosclerosis. Front Immunol 2023;14:1289223.

15. Alayash Z, Baumeister SE, Holtfreter B, Kocher T, Baurecht H, Ehmke B, et al. Complement C3 as a potential drug target in periodontitis: Evidence from the cis-Mendelian randomization approach. J Clin Periodontol 2024;51:127-134.

16. Wang Q, Shi Q, Wang Z, Lu J, Hou J. Integrating plasma proteomes with genome-wide association data for causal protein identification in multiple myeloma. BMC Med 2023;21:377.

17. Zhang S, Xie X, Yu L, Jiang N, Wei X, Hu Y. Investigating causal relations between genetic-related intermediate endophenotype and risk of chronic prostatitis: mendelian randomization study. Oxid Med Cell Longev 2022;2022:4560609.

18. Rasmussen KL, Nordestgaard BG, Frikke-Schmidt R, Nielsen SF. An updated Alzheimer hypothesis: Complement C3 and risk of Alzheimer's disease-A cohort study of 95,442 individuals. Alzheimers Dement 2018;14:1589-1601.

19. Shi Y, Dong H, Sun S, Wu X, Fang J, Zhao J, et al. Protein-centric omics analysis reveals circulating complements linked to non-viral liver diseases as potential therapeutic targets. Clin Mol Hepatol 2024;30:80-97.

20. Yin Q, Yang Q, Shi W, Kahlert UD, Li Z, Lin S, et al. Mendelian randomization analyses of chronic immune-mediated diseases, circulating inflammatory biomarkers, and cytokines in relation to liver cancer. Cancers (Basel) 2023;15:2930.