

Dear Dr. Li,

We thank you for your encouragement and advice. We respectfully resubmit our manuscript titled “**Research progress on the roles of complement in liver injury**” (Manuscript No.: 103839), for your further consideration as a minireview for publication in *World Journal of Hepatology*. We also thank the reviewers for their valuable comments and suggestions. We have revised the manuscript according to their advice. All amendments are highlighted in yellow in the revision, and our point-by-point responses are provided below this letter. We have carefully checked every sentence in the revised manuscript to eliminate/reduce any potential syntax errors. This revised version of the manuscript has been edited and proofread by two native English biologists from *Medjaden*, a professional publication-service company.

Please feel free to contact me if you have any further questions. We look forward to hearing from you soon.

Sincerely,

Yi-Huai He

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First, we would like to express our sincere gratitude to the reviewers for their constructive and positive comments.

Peer-review report(s).

Reviewer #1:

The review article titled "Research Progress on the Roles of Complement in Liver Diseases" offers an exploration of the complement system's multifaceted roles in liver pathophysiology, addressing its impact on various liver conditions. This manuscript should not be accepted for publication in the World Journal of Hepatology for the following reasons:

1. Lack of Novel Insights: The manuscript provides an extensive overview of the existing literature on the complement system's role in liver diseases but fails to offer new insights or significant advancements in the field. For a review article, it is crucial to provide a fresh perspective or new hypothesis that can advance the understanding or treatment of liver diseases, which this manuscript does not sufficiently achieve.

2. Incomplete Coverage of Recent Studies: The review does not adequately incorporate the latest research and findings, especially from the last one to two years. This omission is particularly notable in the sections on non-alcoholic fatty liver disease and viral hepatitis, where recent advancements have been pivotal.

3. Superficial Analysis: The manuscript often lists findings from various studies without deep analytical integration or discussion about the implications of these findings. A more thorough analysis and synthesis of how the complement system interactions vary between different types of liver diseases would be beneficial.

4. Methodological Concerns: There is a lack of transparency regarding the criteria for selecting studies included in the review, which raises concerns about

the potential for selection bias. A more rigorous methodological approach to literature selection and analysis is needed.

5. Theoretical and Practical Implications: The discussion section lacks a critical examination of how the findings might influence current clinical practices or future research directions. The manuscript would benefit from a stronger focus on practical applications and potential therapeutic targets. Given these significant concerns, I do not find the manuscript suitable for publication in its current form. It would need substantial revisions to address the above points comprehensively.

Response:

1. We have revised the manuscript to focus on new insights and significant advancements in understanding the role of the complement system in liver diseases.

2-4 Additionally, we have supplemented the manuscript with the latest research and findings from recent years, conducted an in-depth analysis and synthesis of the interactions of the complement system in different types of liver diseases, and described the methods used to select and analyze the literature to enhance methodological transparency (**Abstract**).

5 Furthermore, we have emphasized practical applications and potential therapeutic targets and once again revised the manuscript.

Reviewer #2:

Thanks for the editor invited me to review the manuscript. It is my pleasure to review this manuscript. The manuscript " Research Progress on the Roles of Complement in Liver Diseases " offers a summary of the complex interplay between the complement system and liver homeostasis, emphasizing its dual role in liver disease pathology. The authors do not have academic integrity

problems according to the peer-review rules, priorities, and standards. The manuscript topic fall within the scope of the journal. The manuscript structure is clear. The references consistent with or closely related to the subject of the manuscript. This is a very interesting study that will appeal to a lot of readers. This is a meaningful and interesting review. I still have the following questions about this manuscript.

1. First of all, the title of the article “Research Progress on the Roles of Complement in Liver Diseases” is too large. This review main summarizes the involvement of the complement system in liver injury, providing references and directions for future research. Therefore, the title of the article is not suitable and needs to be modified.

2. In fact the liver is responsible for producing 80%-90% of plasma complement components. The effects of complement and liver injury are mutual. However, this review only reviewed the effect of complement on liver injury, but did not mention the effect of liver injury on complement.

3. This review mainly reviews the relationship between complement and liver injury. Many studies are just phenomena, lacking the mechanism of complement in liver injury.

4. It is suggested that hepatitis B virus induced liver injury and hepatitis C virus induced liver injury should not be reviewed separately.

5. Finally, the primary and secondary titles of the article are not clear. For example “Complement and Alcoholic Liver disease (ALD)” including “The complement system is involved in alcoholic liver fibrosis and cirrhosis”.

Response:

1-3 We have revised the title and supplemented the discussion on the impact of liver injury on complement as well as the mechanisms by which the complement system participates in liver injury.

4 The review of hepatitis B virus- and hepatitis C virus-induced liver injury has been reorganized.

5 Additionally, we have optimized the manuscript structure to ensure smooth transitions between different sections.

Reviewer #3:

This study provides a comprehensive review of the roles of the complement system in various liver diseases, including chronic hepatitis B, non-alcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma. The manuscript not only summarizes current research advancements but also explores how different components of the complement system contribute to the pathogenesis of these diseases. By citing a substantial body of relevant literature from basic scientific research to clinical applications, it underscores the importance of interdisciplinary collaboration. For instance, it highlights molecular mechanisms linking viral hepatitis and hepatocellular carcinoma. The strength of this article lies in its comprehensive literature review, citing a large number of high-quality studies that cover a wide range from basic science to clinical applications. Examples include the study on complement C5a as a indicator of significant fibrosis and early cirrhosis in chronic hepatitis B patients [Deng et al., 2017], and a cross-sectional study on the association between complement C3 and the incidence of NAFLD in adults [Jia et al., 2015]. This provides readers with a detailed and up-to-date knowledge framework. Additionally, the article delves into the specific mechanisms by which the complement system operates in different liver diseases, revealing its dual role in immune responses, both enhancing immune reactions and potentially exacerbating liver damage through altered liver cell function. This in-depth analysis aids in understanding the complexity of the complement system and its critical role in disease progression.

The paper also mentions the potential of the complement system as a new therapeutic target, listing promising directions for drug development, such as the protective effects of C5a receptor antagonists in reducing ischemia-reperfusion injury [Arumugam et al., 2004], providing valuable references for future treatment strategies. Finally, the authors not only summarize existing research findings but also point out important directions for future research and potential drug targets, such as exploring the role of the complement system in liver regeneration and repair [Mastellos et al., 2001], offering clear guidance for subsequent studies. Although the paper mentions several potential therapeutic targets, there is limited discussion on how these findings can be translated into practical clinical treatment strategies. Additionally, some sections lack clear logical connections between paragraphs. The authors are recommended to further explore the potential of the complement system as a therapeutic target and the challenges it faces, as well as refine the manuscript structure to ensure a smooth transition between different sections.

Overall, this manuscript offers valuable insights into the role of the complement system in liver diseases, contributing significantly to the advancement of research in this field. However, addressing the aforementioned limitations would strengthen the manuscript and better serve both the academic community and clinical practice. By refining these aspects, the authors can provide a more robust foundation for understanding the complement system's role in liver diseases and potentially guide future research towards developing novel therapeutic strategies.

Response: We appreciate your advice.

We have optimized the manuscript structure to ensure smooth transitions between different sections and supplemented the exploration of the complement system as a therapeutic target and its associated challenges.

Round 2

Thanks for the editor invited me to review the manuscript. It is my pleasure to review this manuscript. The manuscript "Research progress on the roles of complement in liver injury " offers a summary of the complex interplay between the complement system and liver homeostasis, emphasizing its dual role in liver disease pathology. The authors do not have academic integrity problems according to the peer-review rules, priorities, and standards. The manuscript topic fall within the scope of the journal. The manuscript structure is clear. The references consistent with or closely related to the subject of the manuscript. This is a very interesting study that will appeal to a lot of readers. This is a meaningful and interesting review. The authors changed the title of the article "Research Progress on the Roles of Complement in Liver Diseases" to "Research progress on the roles of complement in liver injury". It is very good. In fact the liver is responsible for producing 80%-90% of plasma complement components. The effects of complement and liver injury are mutual. This review reviewed the effect of complement on liver injury and the effect of liver injury on complement. It is interesting.

Response: Thank you for your recognition of our revision