

Dear Editor in Chief of World Journal of Clinical Cases

Thank you for your interest in our manuscript. We have made the recommended changes and we are resubmitting the manuscript to the World Journal of Clinical Cases.

We hope that all the changes suffice and our article is strongly considered for publication.

Sincerely yours

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05246699      Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

1. This article is a brief discussion of the use of Adipose-Derived Stem Cells in The Treatment of Hepatobiliary Diseases and Sepsis. In this review the authors have aimed to addresses the use of Adipose-Derived Stem Cells in The Treatment of Hepatobiliary Diseases and Sepsis. And critically evaluated whether Adipose-Derived Stem Cells can augment clinical efficacy for Hepatobiliary Diseases and Sepsis. Even though this review is reasonably synthesized, there are several potential pitfalls that need to be addressed before this publication can possibly be considered for an immediate publication.

**Response:** Thank you for your kind remarks regarding our article. In our opinion, ADSC will be in the future of treatment of hepatobiliary diseases and liver transplantation. Currently all the studies are in the initial phases. Protocols are not established firmly. However, the COVID era has shown the effectiveness of mesenchymal stem cells in controlling uncontrolled inflammatory response. The scarce case reports and series will show us the efficacy of mesenchymal stem cells (and ADSC) in regeneration of large parenchymal organs such as the liver.

2. Authors are strongly encouraged to address the following indicated concerns and are mandatory. Some references missing. For example, "Mesenchymal stem cells have an intricate cell biology and are amenable to being utilized in tissue engineering"; "SVF contains a mixture of red blood cells, fibroblasts, endothelial cells, smooth muscle cells, pericytes, and fat cells. SVF can be cultures, forming a fibroblast like cells that are adherent to the culture flask. These cells were originally named as the pre-adipocytes."; "There are some advantages to using the ADSC in regenerative medicine. The most important one is the abundance of stem cells in the adipose tissue."; "There is a uniform pattern of surface marker expression for ADSC which are presence of CD90, CD73, CD105, and CD44."; "Liver resection

and transplantation are among the definitive treatments of life-threatening chronic liver disease and primary/secondary liver tumors. The most frequent complication following liver disease is the biliary complications. Some of these complications may even cause mortality in the patients. Stenosis is one of the biliary complications that are observed following hepatobiliary surgery.” and etc. The following references may help the authors: a) Mazini L, Rochette L, Amine M, Malka G. Regenerative Capacity of Adipose Derived Stem Cells (ADSCs), Comparison with Mesenchymal Stem Cells (MSCs). *Int J Mol Sci.* 2019 May 22;20(10):2523. doi: 10.3390/ijms20102523. PMID: 31121953; PMCID: PMC6566837., b) Samadi P, Saki S, Manoochehri H, Sheykhhasan M. Therapeutic applications of mesenchymal stem cells: A comprehensive review. *Curr Stem Cell Res Ther* 2021; 16(3): 323-53. <http://dx.doi.org/10.2174/1574888X15666200914142709> PMID: 32928093.

**Response:** The references that the reviewer has suggested have been used in addition to other new references have been added to the necessary places.

3. In the Conclusion Remarks, please include clearly the current gaps in the knowledge base, for example current challenges, evolving challenges, and the next frontiers (suggestions by authors, how using the state-of-the-art technology one can improve the efficacy of the ADSC in the treatment of hepatobiliary diseases, i.e., authors own futuristic perspective and how to address those shortfalls rather than general and vague conclusions, for the benefit of audience.

**Response:** We have tried to make revisions in the conclusion part of the manuscript according to the recommendations of the reviewer.

4. I suggest drawing at least two schematics/figures illustrating (for example, (i) how adipose-derived stem cells operate in The Treatment of Hepatobiliary Diseases and Sepsis and (ii) feature of adipose-derived stem cells) for explaining the data. It will help to understand the findings.

**Response:** Figure 2 have been added to the manuscript and figure 1 has been changed and developed.

5. Authors must include at least two tables (i) a List of in vitro studies that use ADSC for Hepatobiliary Diseases and Sepsis treatment (ii) a List of preclinical trial that use ADSC for Hepatobiliary Diseases and Sepsis treatment. The review should cover all the different studies into some key points that can guide the reader into the next set of studies, and point out what is missing in the literature as well.

**Response:** Two tables that the reviewer has suggested also s added. Unfortunately, clinical trials regarding ADSC is very scarce so all mesenchymal stem cell trials have been searched and appropriate ones are added.

03700188      Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

1. The text is well written, the title well describes the topic covered. References are relevant and 1/3 very recent (< 3 years). I think this is a topic that will stimulate further research. Sepsis and chronic liver disease are frequent challenges in clinical practice and with great morbidity and even mortality.

**Response:** Thank you for your kind comments.