

## **AUTHOR RESPONSE TO REVIEWERS AND EDITORS**

We are extremely thankful to the reviewers and the editors for their comments on our manuscript. Please find below the responses to comments raised. We have revised the manuscript taking into consideration all of the pertinent suggestions and comments.

Reviewer #1:

Comment 1: On a general view, the introduction section is good, whereas the following two chapters (ACLF and liver regeneration; stem cells and their use in diseases of the liver) are somewhat redundant.

Authors response 1: Thank you for the comments. The description on regeneration of the liver with respect to ACLF was thought to be important for the manuscript as it would provide better idea on the use of stem cells for the reader. We agree that these descriptions are known and widely published, but our concise and to the point descriptions add value to the manuscript since it briefly, but strongly described pathomechanisms. Hence we would like to keep this section as is, to ensure reader understanding of disease mechanisms with brief clarity.

Comment 2: The most important section (stem cell therapy for ACLF) should be widened, with a deeper discussion on pros and cons of all studies reported in Table 1. For instance, the first study cited in this chapter (Ref 22) evaluated the role of adipose tissue derived stem cells in rabbits, whereas the second study (ref 23) used umbilical-cord derived MSCs in humans; another study dealt with pediatric patients.

Authors response 2: Thank you for the comments. The section on stem cell therapy in ACLF is short since clinical studies on the same have been seldom performed. All of the studies of stem cells in ACLF until 2020 including basic science work has been already described. The current data has been fully updated. The major points of each pertinent study have been described in the Table 1, while in the revised version, we have added the important shortcomings to the main text. The differences in studies describe the heterogeneity in clinical use of stem cells in ACLF and this is an important point for the 'ineffectiveness' described in our narrative and conclusions.

Comment 3: Moreover, the Authors cited a metanalysis by Chen et al, on three studies. Two of them were cited in Table 1, but not the third one (PMiD 27687792).

Authors response: Thank you for the comments. We have purposefully omitted the third study and provided reasons for the same in the revised manuscript. The third study utilized plasma exchange along with MSC transplantation and hence could not be discussed further in the manuscript as it was not purely stem cell-based therapy for ACLF.

Comment 4: I suggest to look for recently published studies on this field. I suggest to more deeply describe adverse events reported throughout the studies.

Authors response 4: Thank you for the comments. All current data including pros and cons of the study as well as adverse events have been discussed in the manuscript.

Reviewer #2:

Comment 1: This is very interesting study on stem cell therapy for chronic liver failure. It is not clear what "stem cell therapy for acute on chronic liver failure" means in the title, legend texts and figures. The term acute-on-chronic liver failure (ACLF) may be better in a whole manuscript. Proofreading is needed.

Authors response 1: Thank you for the comments. We have described stem cell therapy, the different types of stem cells and the clinically utilized types of stem cells based on tissue of derivation in the manuscript. Our manuscript in this regard focuses on all types of stem cells utilized specifically for ACLF and includes current data in all its aspects.

Editorial Office's comments

Comment 1: The study was supported by Akdeniz University Research Foundation.

Authors response 1: Please note that this study did not receive any support or funding.

Comment 2: The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Authors response 2: Thank you, we have included raw editable PPT as advised.

Comment 3: The author should number the references in Arabic numerals according to the citation order in the text. The reference numbers will be superscripted in square brackets at the end of the sentence with the citation content or after the cited author's name, with no spaces.

Authors response 3: Thank you, we have revised the manuscript as suggested.

We hope all revisions are as expected and would like to sincerely thank the reviewers and editors for helping us improve our manuscript.

Cyriac Abby Philips

Corresponding author.