Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript

entitled "Acute Liver Failure: A Systematic Review and Network Meta-Analysis of Optimal Type Based on Nine Types of Stem Cells in Animal Models" (Manuscript NO.: 79492, Meta-Analysis). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in highlight in the paper. The main corrections in the paper and the responds to the reviewer's comments are as flowing:

Responds to the reviewer's comments:

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: 1)The original findings of this manuscript is comparision of prevous research of the therapeutic potential of different types of stem cells in the treatment of acute liver failure through subgroup analysis of traditional meta-analysis and network meta-analysis, in order to explore the optimal types of stem cells and provide reference for animal experiments and clinical research in the future. Manuscript meets the all criteria according to the criteria checklist (the title, abstract, key words, etc). In the introduction, I sugest a better and more detailed definition of acute liver failure in accordance with the guidelines. Until today, it is not clear which kind of stem cells has the most therapeutic potential. This meta-analysis, has found that although mesenchymal stem cells are the current research hotspot, liver stem cells have

the greatest therapeutic potential among the stem cells included in the analysis, which need to be paid more attention in the future. 2) The quality and importance of this manuscript is very good (grade B) since it is a meta analysis. The new findings of this study (meta-analysis)indicate that liver stem cells have the greatest therapeutic potential among the stem cells included in the analysis. The conclusions appropriately summarize the data that this study provided. Although mesenchymal stem cells are the current research hotspot, liver stem cells have the greatest therapeutic potential among the stem cells included in the analysis, which need to be paid more attention in the future. Authors found that stem cell therapy could significantly reduce the levels of ALT, AST, TNF- and IL-6 in animals with acute liver failure through a comprehensive analysis of 72 studies included. As the first study in the current field, this research is carried out from four aspects of ALT, AST, TNF- alfa and IL-6, and the results are consistent. Limitations of the study:1) Due to the small number of studies and the large differences in the treatment strategies of stem cells in different studies, it is difficult for us to further conduct subgroup analysis on the transplantation dose and route of stem cells to obtain more information.2) Search only in English database, which may lead to certain linguistic bias. 3) Failure to search grey literature and conference abstracts may lead to publication bias. The future directions of the topic described in this manuscript: because of the low quality of evidence on the internal and external authenticity of animal studies, more high-quality animal studies are needed in the future to explore the most promising stem cells. This publication should be an incentive for further research and application of stem cells in acute liver failure in the future in the clinical practice.

Response 1): Thank you for your suggestion. We have added more detail in the introduction of the manuscript to describe the definition of acute liver failure according to the guidelines. See page 3, lines 2-9 for details.

Response 2, 3): Thank you very much for taking the time to review our manuscript, and thank you for acknowledging our research. You insightfully summarized the main findings of our study and pointed out its strengths and limitations. We have made further revisions to the manuscript based on your suggestions. In addition, for the comprehensiveness and reliability of the

results, we performed an updated search of the databases and searched more databases. We therefore included 17 new articles, which we also reanalyzed. The newly included literature did not change our original results and conclusions. We also added sensitivity analysis in the results section to explore the reliability of the Meta-analysis results. The results showed that our meta-analysis results are very reliable. See page 11, lines 228-236 for details.

In conclusion, thank you again for your appreciation of our research. Your comments and suggestions have improved the quality of our manuscript and given us great encouragement and help.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear authors The search strategy presented needs to be even more robust because PRISMA standards require minimum 4 database of literature search the study keywords does not account for alternate terms for stem cells such as stromal cells and cellular therapy which might miss some studies with alternative names used for the stem cells although the authors claim the LSC to be the most promising subtype for further analysis, the traditional meta-analytic framework identified the LSC to be no way different from the placebo in terms of all outcomes other than IL-6 and how does the result vary in case of the network analysis Moreover, the title says 9 subtypes and only 6 types were analyzed so it needs to be changed authors did not explain the method of evaluation of the bias in the network assesed using meta-analytic bias assessment approach such as CiNeMA approach which is needed to validate the findings of the individual network assessed.

1)The search strategy presented needs to be even more robust because PRISMA standards require minimum 4 database of literature search. The study keywords does

not account for alternate terms for stem cells such as stromal cells and cellular therapy
which might miss some studies with alternative names used for the stem cells.

Response 1) Thank you for your suggestion. Indeed, as you said, the number of databases we searched did not meet the standard requirements of PRISMA. At your suggestion, we re-searched 5 databases including PubMed, Web of science, Embase, Cochrane, and Scopus, and updated the literature at the same time. We have also revised our search strategy based on your suggestions to comprehensively collect all relevant studies in the current field. The search terms are as follows: ("stem cell" OR "stem cells" OR "stromal cells" OR "stromal cell" OR "mesenchymal cell" OR "mesenchymal cells" OR "cell therapy" OR "cellular therapy" OR "progenitor cell" OR "progenitor cells" OR "cytotherapy") AND ("liver failure" OR "hepatic failure"). See page 5, lines 75-82 for details.

As you expected and as we presented in the results, we initially obtained 5436 documents after re-searching. After careful inclusion and exclusion, we included 17 new articles on the basis of the original 72 articles. Therefore, we also re-analyzed the results. The new addition to the literature did not change the original results and conclusions. Anyway, thanks again for your very important advice.

2. Although the authors claim the LSC to be the most promising subtype for further analysis, the traditional meta-analytic framework identified the LSC to be no way different from the placebo in terms of all outcomes other than IL-6 and how does the result vary in case of the network analysis.

Response 2) Thank you for your suggestion. Here we misused the analysis method, for which we are very sorry. Because our network meta-analysis uses WMD to pool effect sizes, but we used SMD when performing traditional meta-analysis. In fact, when performing meta-analysis, WMD eliminates the influence of the absolute value on the results, so that the original weight and

measure can truly reflect the experimental effect, and it is easy to understand when applied. However, SMD not only eliminates the influence of the absolute value, but also eliminates the influence of weights and measures on the results, which makes the results difficult to interpret and requires caution when interpreting the results. Therefore, it is a better practice to choose WMD in our study.   When we chose WMD for analysis, the traditional Meta-analysis results showed that the treatment effect of LSC was significantly better than that of the placebo group.

This also leads to another problem. When we used WMD, the results of the conventional Meta-analysis showed that the treatment effect of LSC was statistically different compared to placebo, whereas when we used SMD, the results of the conventional Meta-analysis showed no statistical difference between the treatment effect of LSC and placebo. This is explainable. As we mentioned earlier, SMD results can introduce greater bias, making the results difficult to interpret and even anomalous results. For example, in the included studies, the results of the individual studies all showed a better treatment effect for LSC than for placebo, but when SMD was used for the combined analysis, the results did not differ anymore. This is a limitation of SMD, which to some extent eliminates the therapeutic effect of the intervention.

In addition, compared with the traditional Meta-analysis, the reticulated Meta-analysis combined the results of direct and indirect comparisons, and also considered the effect of other kinds of stem cells on the treatment effect of LSC, which made the Meta-analysis results modified and more relevant to the actual situation. Therefore, we believe that the network Meta-analysis results in this study are more reliable.   Moreover, when the results of our traditional Meta-analysis using WMD were combined, the treatment effect of LSC was significantly better than that of placebo, which was consistent with the results of the network Meta-analysis.

In conclusion, thank you for your queries and suggestions, which fill in the shortcomings of our manuscript. When we conduct traditional Meta analysis,

we will use WMD to combine the results to make the results more in line with the real situation.

3)The title says 9 subtypes and only 6 types were analyzed so it needs to be changed.

Response 3) Thank you for your suggestion. After your reminder, we found that this title is inappropriate, and we have modified it. In addition, we have further revised the title to meet the requirement of journal (title no more than 18 words).

4) Authors did not explain the method of evaluation of the bias in the network assesed using meta-analytic bias assessment approach such as CiNeMA approach which is needed to validate the findings of the individual network assessed.

Response 4) Thank you for your suggestion. After consulting with experts in the fields of evidence-based medicine and statistics, we decided to use the following approach to assess the risk of bias of the meta-analysis and the robustness of the results.

We used sensitivity analysis to test the reliability of traditional meta-analysis results, and PSRF to judge the fitting effect of the model to test the reliability of network meta-analysis results. The results of our sensitivity analysis showed that the direction of the confidence intervals for the pooled results of the remaining studies did not change after individual articles were excluded. In addition, PSRF can be equal to 1 after a certain number of iterations, indicating that the robustness and reliability of the network Meta-analysis results are very good. See page 11, lines 228-236 for details.

In conclusion, thank you for taking your precious time to review our manuscript and for providing very constructive review comments. We have made careful revisions based on your comments, which have greatly improved the quality of our manuscript.

JOURNAL EDITOR-IN-CHIEF'S REVIEW REPORT

Name of journal: World Journal of Stem Cells

Manuscript NO: 79492

Title: Acute liver failure: A systematic review and network meta-analysis of optimal type of stem cells in animal models

Journal Editor-in-Chief (**Associate Editor**)**:** Shengwen Calvin Li

Country/Territory: United States

Editorial Director: Jia-Ru Fan

Date accepted review: 2022-12-15 17:57

Date reviewed: 2022-12-15 18:02

Review time: 1 Hour

SCIENTIFIC QUALITY	LANGUAGE QUALITY	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	[ ] Accept
[Y] Grade B: Very good		[ ] High priority for publication
[ ] Grade C: Good	[Y] Grade B: Minor language polishing	
[ ] Grade D: Fair		[ ] Rejection
[ ] Grade E: Poor	[ ] Grade C: A great deal of language polishing	[Y] Minor revision
		[ ] Major revision
	[ ] Grade D: Rejected	

JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS TO AUTHORS

EIC-specific comments: 1) Both Figure 1 flow chart and Figure 2 Risk of bias assessment results: A summarized interpretation of the figure should be provided in the figure legend rather than forcing the reader to search for the illustration. Note that an ideal figure legend should allow the reader to grasp the meaning of the figure without getting to the text: the same principles

applied to the other figures (Fig 3, Fig 4, Fig 5, Fig 6, Fig 7). 2) This meta-analysis has found that although mesenchymal stem cells are the current research hotspot, liver stem cells have the most significant therapeutic potential among the stem cells included in the analysis, which needs to be paid more attention to in the future. Why did they state that "liver stem cells have the greatest therapeutic potential?" The authors need to highlight the whys in the Results and conclusion in the abstract. 3) Table 1. League table of network meta-analysis estimations: Corresponding citations should be provided. 4) Reviewer #2: "Although the authors claim the LSC to be the most promising subtype for further analysis, the traditional meta-analytic framework identified the LSC to be no way different from the placebo in terms of all outcomes other than IL-6, and how does the result vary in case of the network analysis." The authors' rebuttal thoroughly addressed the argument, which should be made in the manuscript, thereby alerting the bias might come from different approaches.

Dear Editors:

Thank you for your comments concerning our manuscript entitled "Acute liver failure: A systematic review and network meta-analysis of optimal type of stem cells in animal models" (Manuscript NO.: 79492, Meta-Analysis). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval.

1) Both Figure 1 flow chart and Figure 2 Risk of bias assessment results: A summarized interpretation of the figure should be provided in the figure

legend rather than forcing the reader to search for the illustration. Note that an ideal figure legend should allow the reader to grasp the meaning of the figure without getting to the text: the same principles applied to the other figures (Fig 3, Fig 4, Fig 5, Fig 6, Fig 7).

Response 1) Thank you for your suggestion. We have added legends to each figure for the convenience of readers.

2) This meta-analysis has found that although mesenchymal stem cells are the current research hotspot, liver stem cells have the most significant therapeutic potential among the stem cells included in the analysis, which needs to be paid more attention to in the future. Why did they state that "liver stem cells have the greatest therapeutic potential?" The authors need to highlight the whys in the Results and conclusion in the abstract.

Response 2) Thank you for your suggestion. We have added relevant information in the Abstract to highlight why liver stem cells have significant therapeutic potential.

3) Table 1. League table of network meta-analysis estimations: Corresponding citations should be provided.

Response 3) Thank you for your suggestion. The corresponding citation is provided in the methodology section of our manuscript.

4) Reviewer #2: "Although the authors claim the LSC to be the most promising subtype for further analysis, the traditional meta-analytic framework identified the LSC to be no way different from the placebo in terms of all outcomes other than IL-6, and how does the result vary in case of the network analysis." The authors' rebuttal thoroughly addressed the argument, which should be made in the manuscript, thereby alerting the bias might come from different approaches.

Response 4) Thank you for your suggestion. We have added corresponding

content to the methodology section of the manuscript to clarify this situation. Additionally, we have re-polished the language.

We appreciate for Editors' warm work earnestly, and hope that the correction will meet with approval.
Once again, thank you very much for your comments and suggestions.

We also thank the editor for the timely handling of our manuscript, and we have found the "Impact Index Per Article" in this field according to the Reference Citation Analysis (RCA) system. Based on these articles, we wrote highlights of the latest cutting-edge research results. This helps us a lot in writing articles.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we did not list the changes but marked in highlight in revised paper.

We appreciate for Editors/Reviewers' warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.