

Peer-review Comments and Author Responses

Reviewer A

1. *It would be ideal if more details could be provided in the methods section, specifically about inclusion/exclusion criteria.*

Thank you for your comment. The section for the search criteria was further detailed in the supplementary appendix and in the manuscript in the “materials and methods” section.

Reviewer B

2. *The principal objective of this study is to assess the current knowledge of UC-MSCs treatment for COVID-19-induced ARDS by reviewing the results of published phase I-II clinical trials. Totally, 10 studies are included in this mini-review, however 1 study is an observational study. The authors should remove the cohort study in line with the eligibility criteria. Thus, figure 1 and table 1 should be revised regarding the eligibility criteria.*

We removed 2 articles from the study, the observational study as you suggested and removed the article from Matthay, et al 2019, Because the origin from the mesenchymal stromal cells were not derived from the umbilical cord based on our eligibility criteria. In addition, we modified the eligibility criteria from the supplementary appendix and figure 1.

Matthay, M. A., Calfee, C. S., Zhuo, H., Thompson, B. T., Wilson, J. G., Levitt, J. E., Rogers, A. J., Gotts, J. E., Wiener-Kronish, J. P., Bajwa, E. K., Donahoe, M. P., McVerry, B. J., Ortiz, L. A., Exline, M., Christman, J. W., Abbott, J., Delucchi, K. L., Caballero, L., McMillan, M., McKenna, D. H., ... Liu, K. D. (2019). Treatment with allogeneic mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome (START study): a randomised phase 2a safety trial. *The Lancet. Respiratory medicine*, 7(2), 154–162. [https://doi.org/10.1016/S2213-2600\(18\)30418-1](https://doi.org/10.1016/S2213-2600(18)30418-1).

3. *The Results require major style revision. All relevant data should be presented in the Results section, although major results can be summarized as part of the Discussion. For instance, a sentence such as "the duration from admission to discharge in the treated group and control group was the same (20.00 vs 23.00 days, P = 0.306) (Meng et al., 2020)" belongs to the results. Nevertheless, a*

sentence such as " there were no significant differences between the corresponding intervention and control groups for length of stay" is allowable in the Discussion. I would suggest using the subheadings in the results and describe them in a concise manner addressing each relevant study's results.

Results section: we changed the results with the suggested format. Therefore, we included the “immunological markers outcomes”, “clinical performance outcomes”, and “primary safety outcomes” in this section and described the findings.

4. *The discussion also needs major style revision. There should be a focus only on the key findings from the review, and the clinical / research implications (mention how the study's results might influence future research) and limitations. Comparisons with literature can also be presented (e.g., here the authors can describe the results of the cohort study, previously mentioned, and compare the findings from UC-MSCs therapy to current findings of other studies on this topic or other types of MSCs therapy for COVID-19). A structured "discussion" model is presented, as follows: "This mini-review found that ... (add a summary of the important or interesting results). In turn, in agreement with other studies... Previous evidence has indicated an overall beneficial effect of To our knowledge, this is the first mini-review that assessed the The present findings are clinically important, notably Some controversy exists on ... Further research is thus needed to determine.... Limitations must be acknowledged, particularly.... " I suggest that the authors consider the above suggestion and modify accordingly.*

Discussion: we changed our discussion. We followed your suggestions and added only the key findings from our review and limitations.

5. *The conclusion requires more concise writing. Special care must be taken to avoid overstating the importance of the findings. In fact, early phase trials have shown the "promising" efficacy and safety of UC-MSc therapy for COVID-19 associated moderate-to-severe ARDS. The authors should highlight the word "promising" in the manuscript. This shows the reader that further studies are required.*

Conclusion: we modified it with the suggested changes such as highlighting the “promising” word in the manuscript.

6. *The references demand style revision. The PPCR Journal uses the APA system (see tutorial: <https://www.utoledo.edu/library/help/guides/docs/apastyle.pdf>).*

For instance, entries in the reference list are arranged in alphabetical order by surname of the first author. Furthermore, there is no comma between the surname and "et al." and there is a period after the "al."

We revised the references to APA7 style format.

- 7. Another general comment is that there are grammatical errors in the manuscript. Abbreviations are used haphazardly. Lowercase letters should be used as default, and capital letters with proper nouns / abbreviations and at the beginning of each sentence. Significant language editing is required to bring this manuscript to publication standard.*

Grammatical, language and abbreviation errors were addressed.

- 8. Please review the summary below: Title: The title provides a succinct description of the content of the study. Minor changes were required. Abstract: The Abstract is attractive, providing a brief description of the aim of the study and its major results and conclusion. However, revisions were made for an appropriate clarification given the results and conclusion of the study. Adjustments were also necessary for clarity, conciseness, and formal tone. Introduction: The Introduction provides adequate scientific background and rationale, giving a deeper understanding of the intent of the study. Changes were necessary for conciseness and formal tone. Methods: The methods are reported clearly, and more information about the eligibility criteria can be found in the supplementary appendix. Data regarding the total number of studies included in the review should be described in the results section. Revisions were made for conciseness and formal tone. Results: Narrative should be used to describe the results clearly. Structural changes were necessary. I provided my suggestions and arguments for the same. Discussion: The discussion needs to be rewritten as it mainly contains parts of results without interpretation of them. The first thing to do in the discussion is to identify the major findings of the study. Once the authors have described their key findings, they should critically interpret them and provide a comparison with different studies on the same topic. The consistencies and contradictions should be presented. The strengths and novelty should be emphasized. Care was taken in acknowledging some limitations of the study. Conclusion: An effective conclusion needs to be clear and succinct, presenting a summary of the study and an effective take-home message.*

Reviewer C

9. *Given the nature of the review, the last sentence of the "methods and results" part in the abstract that reads "a statistically significant difference (...)" should be discarded, as no statistical analysis was actually ran in the study.*

We revised our abstract and highlighted only the statistically significant findings.

10. *The conclusion stated in the abstract about results being "more promising" is a term too subjective and should be changed.*

Conclusion: we highlighted the word promising to inform readers further studies should be done.

11. *The limitations have been well addressed. Given that the inclusion criteria only allowed for phase I and II studies to be included, the limitation that studies were performed at single centers and which in turn lead to a lack of external validity is probably not necessary. PHase I and II studies are supposed to be focused on internal validity, with a small sample size precisely to prioritize internal validity.*

We mentioned small sample size one-centered lacked generalizability.

12. *It is mentioned that missing data was handled properly but there isn't any further explanation about this. If the word limit is a challenge, then consider ignoring to mention this as it adds no stringent information.*

Discussion: we removed the missing data part. There was not enough information in these papers regarding missing data handling. Thus, we removed it.

Reviewer D

13. *The manuscript is comprehensible and follows a logical order. However, there are some sentences that are unclear and need to be phrased differently (some of which are marked in the attached revised manuscript). The authors may consider proofreading by an English speaker to improve the manuscript's fluency and syntax.*

14. If the intervention in the included studies was UC-MSCs therapy along with standard of care, this should be mentioned, because in the current manuscript the intervention appears to be UC-MSCs alone vs. placebo + standard of care.

Intervention: we mentioned in the manuscript some studies compared placebo to UC-MSCs, and others compared with Standard of care.

15. Was the decision to include only Phase I and Phase II trials in the search strategy made a priori? Or is the lack of Phase III trials part of the authors' findings? The authors should provide justification behind only including Phase I-II trials in their eligibility criteria a priori (before the results of the search strategy) or remove this criterion if all trials were intended to be searched but no Phase III trial was found. This should be explicitly mentioned as this may be one of the most relevant findings in terms of future research.

Eligibility criteria: we specified in “materials and methods” we didn’t include phase III trials due to lack of performed studies at the time of our search strategy. The eligibility criteria in the supplementary material mentions Phase I and Phase II trials because there were also pilot studies available. To achieve homogeneity, we excluded pilot studies.

16. Methods: The way the results are going to be presented is missing. Even if no meta-analysis or other statistical analysis is to be done, and just a narrative review is intended, this should be explicitly stated. Also, “[...] from the date of their inception to October 4, 2022 [...]”: The authors use a rather non-specific timeframe for review. Since COVID-19 was first reported in December 2019, the authors may try to limit their time frame to be more efficient and specific. In the interest of replicability, the authors are encouraged to report the specific combination of keywords that they used for the search strategy in the Supplementary Appendix. In the Supplementary Appendix, the authors provide the MeSH terms that were used. The MeSH term “acute lung injury” was included, but not the MeSH term “respiratory distress syndrome”, which is more compatible with the population of interest. Both terms might be different and might yield different results in the search strategy.

Methods: we included studies from February 1, 2020- October 4, 2022 with the available studies. We addressed the MeSH terms issue by specifying the terms we used in our search strategy for reproducibility and replicability purposes in the Methods section. Furthermore, this section was modified to integrate all the advice suggested by you and other reviewers. More detail in the process and clearance on some steps was developed. Including the PRISMA checklist and the items that were included/absent in our mini review, as suggested.

17. Results: The Table provided in the Supplementary appendix should be included in the main manuscript, as it offers valuable information regarding the results (including the characteristics of the studies). Furthermore, a brief description of the outcomes of each study should be included in the Table. The authors should mention how many studies addressed clinical outcomes and how many studies addressed inflammatory outcomes. These outcomes, and how they were determined, should also be specified in the Methods section. The authors should provide a summary of the relevant characteristics of the included studies (randomization, blinding, intervention, control, follow-up, outcomes, etc.). Quality assessment, if performed, should also be specified, or mentioned otherwise if not performed.

Results: we modified the results section, including study outcomes divided into the following subtitles: “clinical performance outcomes”, “immunological markers outcomes”, and “Primary safety outcomes”. The table from the supplementary material was modified to include the information suggested. We summarized the table as follows: reference, country, study population, intervention, primary outcome measured and main findings. This table is included now in the manuscript.

18. Discussion: The authors should specify which studies they are referring to in each specific sentence when describing the different outcomes. Discussion, 10th paragraph: The authors should be commended for their efforts in pointing out the limitations of the included studies and how they affect the authors’ interpretation of their findings. However, the authors should also mention if they perceive any limitation in their review (e.g. potentially ambiguous terms, unpublished data, publication bias, etc.).

Discussion: we added the limitations from our mini-review.

19. Conclusions, first paragraph, “[...] a 1-year follow-up comparing the clinical outcomes showed no statistically significant differences between the two groups.”: This sentence might underestimate the importance and future directions of the results, given that this is an acute condition and long-term follow-up is not really the goal of this treatment. Is this long-term outcome relevant given that the disease is acute in nature? The authors may instead consider mentioning the lack of clinical outcomes such as mortality (or mention these results, if existing).

Conclusion: we already modified the conclusion as suggested.

20. PRISMA reporting guidelines should be followed, and a completed checklist is encouraged as an attached file for submission. Specifically, Items No. 5, 6, 9, 10, 11, 12, 13, 14, 15, 19, 20, 22 from the PRISMA checklist are absent or incomplete to a certain degree and should be reviewed.

21. Whole manuscript: Abbreviations should be explained in detail the first time they are used in the manuscript.

The abbreviations were explained in a cohesive manner. Additionally, the references were modified to maintain the same format, and ordered alphabetically.

22. Abstract: The authors should avoid using citations in the abstract. Besides from taking valuable characters for the extension limit, the abstract should be a stand-alone summary of the authors' work, not a review of existing literature.

Citations from the abstracted were removed, and it was edited properly to summarize our work.

23. Abstract: Methods and Results are perhaps the most important sections in the manuscript. As such, authors should consider to provide them separately in the abstract as well.

24. Introduction, last paragraph: The authors should not address the limitations of their findings in the Introduction section.

The paragraph about limitations was removed from the introduction.

25. Methods, first paragraph, "Ultimately, 10 trials were included [...]": The number of studies that were included is part of the Results section, as this is the output of your search strategy.

The number of studies included in our study was modified, we appreciated a discrepancy in our research strategy and the two studies that we included (details on why we eliminated them were explained above).