

## Detailed Response to Reviewers' Comments

Dear Editors and Reviewers:

We feel great thanks for your professional feedback that we have used to improve the quality of our manuscript. According to your valuable suggestions, we have made extensive corrections to our previous draft, the detailed corrections are listed below. The reviewer comments are laid out in italicized font and numbered. Our changes and additions to the manuscript are highlighted in yellow.

Reviewer #1

1. In the paragraph: MSCs-Exo also enhanced macrophage phagocytosis and TNF- $\alpha$  and IL-8 secretion, thereby ameliorating LPS-induced lung injury in mice [67]. Please correct to MSCs-Exo also enhanced macrophage phagocytosis and significantly diminished TNF- $\alpha$  and IL-8 secretion, thereby ameliorating LPS-induced lung injury in mice [67] to cope with the cited reference.

Response to the reviewer:

We are so sorry for our careless mistakes. Thank you for your reminder. We have made the appropriate corrections in the paragraph under the subheading "MSCs-Exo" on page 10 of the manuscript, highlighted in yellow. To avoid any inconsistency regarding page numbers, it is noted that the corrected sentence references citation number [57], titled "Mesenchymal stromal cells modulate macrophages in clinically relevant lung injury models by extracellular vesicle mitochondrial transfer".

2. In the paragraph: Studies have shown that patients show significant signs of recovery in radiologic parameters on lung computed tomography scans after 60 days of MSCs infusion, with significant subsidence of turbidity in the lungs. One patient presented with acute renal failure, pulmonary edema,

and bilateral multiple effusions, and the turbidity associated with COVID-19 was significantly reduced after treatment [94]. Please be noticed that the cited reference by Yao et al. has nothing to relate with your citation. Furthermore, please add more citations to cope with your suggestion in this paragraph.

Response to the reviewer:

Thank you for your valuable feedback regarding our manuscript. We apologize for the previous citation error. In accordance with your request, we have made corrections on page 21 of the manuscript, under the subheading "Monitoring", specifically to the 3rd, 4th, and 5th sentences of this paragraph, highlighted in yellow for clarity. To avoid any inconsistencies regarding page numbers, it should be noted that the corrected sentences now reference citation number [106], titled "Mesenchymal stem cells derived from perinatal tissues for treatment of critically ill COVID-19-induced ARDS patients: A case series".

Regarding the concern about citation, I understand your point. It has been clearly noted that the study by Yao et al. is unrelated to the content of this section. Since the case mentioned in this paragraph specifically refers to a particular study, no additional references were cited here. This was done to highlight the findings of that specific research rather than to provide a broad literature review. However, I have ensured that more studies are appropriately cited in other parts of the document to support the arguments and provide a more comprehensive perspective.

3. In the paragraph: A clinical study by Chu[96] et al. demonstrated that a mildly ill patient's first chest CT examination revealed an isolated nodule outside the lower lobe of the left lung after MSCs-Exo nebulization treatment. Please check the reference as it doesn't belong to Chu and it dosen't cope with your citation.

Response to the reviewer:

Thank you for bringing this to our attention. Upon reviewing our manuscript, we recognize that the reference attributed to Chu does not

correspond correctly with the cited content, and we apologize for this oversight. In accordance with your request, we have made corrections on page 21 of the manuscript, under the subheading "Monitoring", specifically to the 11th and 12th sentences of this paragraph, highlighted in yellow for clarity. To avoid any inconsistencies regarding page numbers, it should be noted that the corrected sentences now reference citation number [115], titled "Nebulization therapy with umbilical cord mesenchymal stem cell-derived exosomes for covid-19 pneumonia."

4. Please check all the other references.

Response to the reviewer:

Thank you for your suggestion. We have thoroughly reviewed our sources and identified the correct reference that supports our claims.

5. Finally, the discussion of the "various therapeutic approaches for COVID-19" could be enriched by considering the Egyptian and African immune-modulatory approach.

Response to the reviewer:

Thank you for your valuable suggestions to enhance our discussion on the various treatment methods for COVID-19. Following your guidance, we have added a discussion on immunomodulatory approaches in the African region on page 4 of the manuscript, in the Introduction section of our manuscript, highlighted in yellow for clarity. To avoid any inconsistencies regarding page numbers, it should be noted that the added sentences now reference citation number [5], titled "Unproven herbal remedy against covid-19 could fuel drug-resistant malaria, scientists warn". We have also compared the existing treatment methods for COVID-19 across different countries and regions, including those in the African region, and summarized this in a table (Table 1). We are grateful for your insightful suggestions, which have enriched our discussion on the diverse treatment approaches for COVID-19. We believe these additions will significantly improve the manuscript.

6. As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).

Response to the reviewer:

We have sent the revised manuscript to a professional English editing company or a native English speaker for further touch-ups and a new language certificate.

7. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs, rows, or text portions can be reprocessed by the editor. Suppose the author has used a figure published elsewhere or that is copyrighted. In that case, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e., generated de novo by the author(s) for this paper). If the picture is 'original,' the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT):  
Copyright ©The Author(s) 2024.

Response to the reviewer:

Thank you for your detailed instructions regarding the submission of original figure documents. I have carefully reviewed your requirements and obtained authorization from the previous publisher or the copyright holder. These charts have been credited with references and copyrights, and the content within the tables has been clearly marked with corresponding references. All our figures were created in Fig draw (<https://www.figdraw.com>) and each submitted image is original. Accordingly, I have added the required copyright information "Copyright ©The Author(s) 2024" to the bottom right-hand side of each figure. In addition,

we organized the tables and pictures into separate documents as required and submitted them to the system in the form requested.

9. The main text of the manuscript must include two parts: "Introduction" and "Conclusion".

Response to the reviewer:

Thank you for your attention to detail and for guiding us through refining our manuscript. Based on your suggestion, we have added a "Conclusion" section, highlighted in yellow for clarity. I hope these revisions meet your expectations. If there are any further adjustments needed, please let me know, and I will be happy to comply.