Dear professor:

We give our sincere thanks to you and to the reviewers for your valuable time and efforts in reviewing our work (Manuscript NO.: 77548, Meta-Analysis). It is our belief that our findings would be interesting and informative for the readers of your prestigious journal.

As suggested by the Editors and the reviewers, we have made the following revisions point by point, and the revisions are denoted by the red color in the tracked manuscript:

Reviewers' comments:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dr Wang and colleagues have submitted a systematic review entitled "The clinical efficacy analysis of mesenchymal stem cell therapy in patients with COVID-19: a systematic review" for publication. I have the following comments.

1.Were the risk of bias assessed by a standardized risk assessment tool? And if not why?

Answer: We have added Figure 2 for the risk of bias assessed by Review Manager Version 5.1 in our manuscript on Page 6 Lines 9-13 (materials and methods section), Page 8 Lines 5-18 (results section), which have been denoted red in the revised manuscript. Thank you very much.

2.The Cochran's Q test had the P value of <0.00001, corresponding quantity I2 was 95%, and a random-effect model was employed. Providing a description of the level of heterogeneity would be better.

Answer: We have analyzed C-reactive protein, D-dimer, IL-6 and the overall survival

and described the level of heterogeneity for each of them. For C-reactive protein, the Cochran's Q test had the P value of<0.00001, corresponding quantity I^2 was 94%, and a random-effect model was employed which have been described on Page 9 Line 4. For D-dimer, the Cochran's Q test had the P value of 0.03, corresponding quantity I^2 was 71%, and a random-effect model was employed which have been described on Page 9 Line 14. For IL-6, the Cochran's Q test had the P value of<0.00001, corresponding quantity I^2 was 95%, and a random-effect model was employed which have been described on Page 10 Line 1. For the overall survival, the Cochran's Q test had the P value of 0.64, corresponding quantity I^2 was 0% and a fixed-effect model was employed which have been described on Page 10 Line 14.

3.In the Discussion section on Page#10, the authors state "········ administered in critically ill patient". Was being critically ill one of the criterion for inclusion in the included studies? And was it an inclusion criterion for this meta-analysis? It does not seem so.

Answer: We have corrected the statement on Page 11 Lines 3-5. Our preliminary results indicated that MSC can be safely administered in patients with COVID-19 and that administration of MSC was followed by clinical improvement.

The critically ill was not one of the criterion for inclusion in the included studies though some of them had mentioned it. And it was not an inclusion criterion for this meta-analysis which has been demonstrated on Page 4 Lines 10-22 (search strategy and selection criteria section).

4.On Page 11, the authors write "In our meta-analysis we used random-effect model for the high heterogeneity of the analysis (Fig. 2, 3 and 4), thus we showed no significant change in the inflammatory markers when synthesising evidence, mostly for the high heterogeneity in the included clinical trials." My question is would the results be different if a fixed-effect model was used? I suggest removing this statement as it indicate the reason for the insignificance of the results was due to the type of model used rather than the actual lack of a difference. When you opted not to

use a fixed-effect model due to the high heterogeneity, you showed methodological rigor.

Answer: Thank you very much, we have deleted this statement on Page 11 Line 20 and agreed with you that the reason for the insignificance of the results was due to the actual lack of a difference rather than the type of model used.

5.According to the authors, their analysis showed no significant decrease in C-reactive protein (CRP) levels, no reduction in D-dimer levels, no decrease in interleukin 6 (IL-6) after the stem cell therapy in COVID-19 but the overall survival (OS) rate improved after the stem cell therapy in COVID-19 patients. I would like the authors to comment on this?

Answer: Yes, we have commented on this on Page 11 line 11, Page 12 and Page 13. We thought the mechanism would be based on stem cell could act in the inflammatory microenvironment of endothelial and alveolar damage by interacting with various targets and should be explained further.

6. Please extensively revise the manuscript for spellings, syntax, and grammar. There is too much redundancy in the text.

Answer: Yes, we have extensively revised themanuscript for spellings, syntax, and grammar according to your advice and deleted much redundancy in the text and provided the certification from professional English language editing companies (AJE). Thank you very much.

Reviewer #2:

  Scientific Quality: Grade C (Good)

  Language Quality: Grade B (Minor language polishing)

  Conclusion: Minor revision

Specific Comments to Authors: Dear authors, This is an interesting and valuable article, but need revisions in: 1. Title: see attach file 2. Abstract ok   3. Keywords ok 4. Backgrond OK 5. Methods: see attached file 6. Result 7. Discussion and conclusion,

11. Ref. See attached file. Others OK.

meta analysis

Answer: We have corrected it according to your advice in the title. Thank you very much.

If possible please add data about the identity of the stem cells: which passage, culture condition: normoxia or hypoxia, whether the MSCs are preconditioned/primed or not, whether serum free medium was used in culture.

Answer: Yes, thank you very much. We have reviewed the information on stem cell of passage, culture condition: normoxia or hypoxia, whether the MSCs are preconditioned/primed or not, whether serum free medium was used in culture in all the included studies. We found that most of the studies reported on stem cells under clinical-grade or GMP conditions and approved by the authorities. Only one study reported that cells at passages P3 to P5 were used (Lei Shu et al. 2020). Other information is even less, so we have not added this information and not added the discussion.

Randomized clinical trial?

Please specify: how many randomized controlled trial (RCT)? Non-randomized trials? Trials without control (case series)?

Answer: We have added the information of randomized clinical trial or non-randomized trials on Page 7 Lines 15-16 and Table 1. And the case report was without control.

please specify: how many treatments and how many controls?

Answer: Yes, we have added these information on Page 7 Lines 5-6. Thank you very much.

Please specify: RCT? Non-randomized trials? Trials without control (case series)? Case-report?

Answer: Yes, we have added these information on Page 7 Lines 10-11. Thank you very much.

What type of study?Please specify how many MSC (source) and how many AT-MSC?

Answer: Yes, thank you very much. We have added these information on Page 7 Lines 13-14.

Source? UC? AT? BM?

Answer: Yes, we have added these information on Page 7 Lines 14-15. Thank you very much.

Randomized or not?

Answer: Yes, we have added these information on Page 7 Line 16. Thank you very much.

Please add: and the studies included in meta-analysis all used UC-MSC

Answer: Yes, we have added these information on Page 11 Line 3. We included the studies used MSC, but not all used MSC. Thank you very much.

Is the total number of treatment and control enough to take this conclusion??

Please discuss how many treatment and controls are needed to get a robust prove and moderate your conclusion:was proven a promising therapy**.**

was proven a promising therapy → was a promising therapy

Answer: Yes, we have concluded that stem cell therapy was proven a promising therapy. If we must get a robust prove it need three more than 100 randomized cohort trials, we think that is enough and moderate.

　　And we have corrected it according to your advice on Page 16 Line 7. Thank you very much.

Inconsistent format

Answer: We have revised our references format according to the Journal's guideline. Thank you very much.

We appreciate your time and effort spent in examining our work again. We look forward to your favorable decision.

Best regards,

Sincerely yours,

Zheng-Xu Wang, MD, PhD

Prof. of Biotherapy Center