

Dear Editor

Thank you for conditionally accepting our review paper. We take this great opportunity to revise the manuscript accordingly based on editors' and reviewers' comments and suggestions.

1. We added author contributions and provided the original figure document separately.
2. We corrected language problems, especially revised some long sentences and repeated sentences.
3. We revised the manuscript based on reviewers suggestions, and answered all questions one by one.

We sincerely hope you find our manuscript acceptable for publication in the World Journal of Stem Cells.

Best Regards

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Dear reviewer (1):

Thank you very much for your helpful comments and excellent suggestions on our paper. We have revised the article according to your suggestions. Here, we have answered your questions as follows:

Question 1: In the abstract, the author does not provide any information about the therapeutic potential of MSCs for SARS-CoV-2 or related infections. The author should add some sentences about the therapeutic potential of MSCs for SARS-CoV-2.

Thank you for pointing this out; we have made this change by adding the following sentence: Mesenchymal stem cell can secrete cytokines to modulate immune cells by inducing anti-inflammatory regulatory T cells, macrophages and neutrophils, reducing the activation of T and B cells, dendritic and NK cells. Thus, they have therapeutic potential for treating severe cases of COVID-19.

Question 2: In the introduction, the most important point in the introduction is “Small studies have shown that MSCs can be effective in COVID-19 ARDS...” but there no references in the text. The author should add references to this information.

The references were added.

Question 3: the introduction has only one sentence about the potential efficacy for COVID-19 and not introduce the other therapeutic strategies of COVID-19 to justify why MSCs show promise for treating COVID-19. Hence, it is suggesting to briefly introduce the different therapeutic strategies for COVID-19 and highlight the most potential point of MSCs therapy.

Thanks for your suggestion, we have revised the Introduction accordingly.

Question 4: In the Pathology, the paragraph “Barton et al. reported two COVID-19 autopsies...”, mentions SARS-CoV-2 spike protein. To be more readable and understandable, this paragraph needs more explanation of the role of SARS-CoV-2 spike protein in the pathogenicity of SARS-CoV-2.

Yes, we have written additional explanation in this revision.

Question 5: I suggest to add the list of the most treatment options in the paragraph “Currently, drugs alone or in combination with....” the link is not working.

We revised it. Thanks!

Question 6: The subtitle “Recent success of MSCs for COVID-19 Patients” needs extensively review and cite the related works in this section.

We have revised the manuscript accordingly.

Question 7: in the figure 1 legend should include a summary of the immunomodulatory effects of MSCs on immune cells.

A summary of MSC immunomodulatory effects on immune cells is included.

Question 8: The figure has not mentioned any potential mechanism of MSCs for SARS-CoV-2. Hence, the author may refer to the possible mechanism MSCs in SARS-CoV-2 infection.

We have revised this accordingly by adding possible mechanisms.

Question 9: To be more understandable, it is suggested to add the specific factors regulation, whether it is up-regulated or down-regulated, etc.

We have added this information to the Figure 1 legend.

Question 10: The author may need to add the most related studies in table 2.

We have revised accordingly by adding related studies.

Sincerely yours,

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Dear reviewer (2):

We would like to thank you for your constructive comments and helpful suggestions on our paper. We have revised the review according to your suggestions. Please see below our responses to your comments:

Reviewer #2:

There are several recent reviews already addressing these issues and that were not cited by the authors, both on broader aspects related to COVID-19 and on more specific to ARDS-like manifestations in the disease (e.g. doi: 10.1007/s12015-020-09999-0; doi: 10.1007/s12015-020-09973-w; doi: 10.1007/s13238-020-00738-2; doi: 10.1183/13993003.00858-2020).

Thank you for pointing this out. We have now cited these reviews accordingly.

The present manuscript was focused on detailed immune mechanisms related to MSC actions and its applicability for reducing COVID-19 complications (e.g. cytokine storm and ARDS-like manifestations). However, the authors need to make clear what the presented novelty compared to the recently published reviews.

In order to make the text more appropriate, major changes need to be made. General points:

a. The language is good, but the punctuation in all text needs to be carefully reviewed. There are some phrases that do not make sense due to the punctuation, or because they have not a proper continuousness of ideas.

We have revised the manuscript accordingly to reflect this.

b. Some excerpts and sentences are far too long, which makes understanding difficult.

Thank you for this suggestion, we have revised accordingly.

c. It is more suitable to initiate a paragraph with no abbreviation of words, using the entire term. (e.g. Introduction, line 1)

The manuscript has been revised accordingly.

d. It is not necessary to enclose abbreviations in quotation marks. (e.g. Introduction: line 3; Mesenchymal stem cell (MSC) immunomodulatory effects: line 4).

Manuscript has been revised.

e. There should be standardization of the 'MSC' term. In the abstract, it appears writing in plural with MSC abbreviation, however, in the keywords section, it appears MSCs. Structural and

content points: a. In the "Abstract" section, it was cited COVID-19 symptoms such as neurological manifestations, and then they not appear in any part of the text, even nor within the topic about its pathology.

Thank you for this suggestion, we have now revised the manuscript to incorporate this suggestion.

b. In the "Introduction" section was used the term "water leakage". Is it an appropriate term in the proposed context?

The manuscript has been revised accordingly.

c. In the topic "COVID-19 and its pathology", a logical sequence of the content is not clear. The first paragraph of this topic would be more appropriate in the introduction section, for instance. Also, there is a lack of information about the COVID-19 general pathology, so it must be clearer than the pathology will be addressed under pulmonary aspects only.

We have revised the manuscript accordingly.

d. In the first paragraph of the topic "Recent success of MSCs for COVID-19 Patients and clinical trials" was pointed out that pharmacotherapy with chloroquine/hydroxychloroquine has promising effects on patients with COVID-19. However, the cited NIH guidelines make clear a position against the use of these drugs and point out that studies showing an improvement in patients who underwent this treatment still do not present substantial data, in addition to using a small sample size. Therefore, it would be appropriate to address these issues when discussing such treatments. Moreover, it is important to highlight the side effects of these treatments.

Thank you for raising this excellent question. Since the focus of our review is on MSC therapy, we have only listed chloroquine/hydroxychloroquine as therapeutic options for reference.

e. In table 2 were included 25 registered clinical trials using MSC for treating of COVID-19 patients. However, there are at least 45 registered clinical trials in the clinicaltrials.gov platform, so the table should be updated.

Thank you again for pointing this out; we updated it to 50 clinical trials ongoing, and only listed the most related studies in the table 2.

f. In the "Conclusion" section was addressed some limitations about the implementation of MSC-based therapy such as dose, delivery times, type of MSCs, efficacy, and cost-effectiveness. It would be interesting whether such limitations were better discussed throughout the text or even in the conclusion.

Thanks for your suggestion, we have revised the manuscript to reflect this change.

Sincerely yours,

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