

Object: Revision of manuscript "Beta receptor blocker therapy for the elderly in the coronavirus disease 2019 era" (Manuscript NO.: 76923, Minireviews)

Dear Editor of *World Journal of Clinical Cases*

Dear Reviewers

Thank you for receiving and for reviewing our work.

We greatly appreciated your comments, which helped us to optimize the quality of our manuscript. Indeed, we made a revision of the manuscript along the lines you have suggested, applying all of your suggestions as you can evaluate in following "point by point" reply. We hope the revised manuscript will meet the requirements of academic publishing in *World Journal of Clinical Cases*.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: It is a very interesting and well researched article on outcomes of beta blocker therapy in COVID-19 era. The authors have highlighted all major studies to this effect that show the possible positive outcomes in patients on beta blocker therapy in COVID -19. Though there are no major trials to this effect the studies presented are mainly retrospective or observational in nature. The authors have referenced a study on page 6/17 which has been cited as reference # 55. The authors have referred to this study of infusion of beta blocker metoprolol in 20 patients with mechanical ventilation as a case control study. It appears that the study type for this a randomized clinical trial for a pilot study. The authors should elaborate on this study as it is one of the few interventional studies to this effect. Also, references are missing at certain places e.g on page 5/17 it is mentioned that "Beta blockers downregulate ACE2, thereby reducing the virus' ability to attack cells". Please add a suitable reference to this statement. The authors have referenced a study (reference # 56) on page 7/17 and mention that beta blocker was paradoxically associated with increased mortality. On the review of the complete text of the cited article it appears that authors have tried to link increased mortality to age and co-morbidities in patients with COVID-19. They have also associated beta blockers and ACE I as associated with increased mortality, but they appear to be confounders in this situation being the most commonly used medications for elderly. Also, it is confusing as two conflicting statements are made regarding effect of beta blockers on renin production which is claimed to have a protective effect on page 5/17 and harmful effect on page 7/17. Overall, the article is very good and definitely adds to the existing literature.

REPLY:

Thank you for all your valuable advices.

The manuscript was edited for proper English language, by highly qualified Editors at Filipodia.

The Certificate Service Confirmation will be uploaded with the revised manuscript.

Contents of the manuscript have been significantly improved according to your fundamental suggestions as described in the following points:

- 1) We have elaborated on the study cited as reference # 55. In particular, in the text we emphasized how critically ill COVID19 patients can obtain hemodynamic benefits from the infusion of beta-blockers in addition to the anti-inflammatory benefits.
- 2) A reference to the statement "Beta blockers downregulate ACE2, thereby reducing the

virus'ability to attack cells" on page 5/17 has been added as required. This is reference #33: Vasanthakumar N. Can beta-adrenergic blockers be used in the treatment of COVID-19? Med Hypotheses 2020; 142:109809. [PMID: 32388480doi: 10.1016/j.mehy.2020.109809]

- 3) As regard to the mention that beta blocker was paradoxically associated with increased mortality (reference # 56) on page 7/17, we have followed your valuable advice of underlining the confounding effect of other drugs. Indeed, we have reported that “the concurrent use of other drugs may have confounded the results”
- 4) 4) On page 7/17 we omitted the statement about the harmful effect of beta-blockers on the production of renin, which was in conflict with what was previously stated. Thank you for noticing this conflictual sentence.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: congratulation this is veru intersting paper.

REPLY

Thank you for the positive comment.

We have revised the manuscript very carefully. We have the revision further edited by professional English editor.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Thanks to the author's efforts on the manuscript, which provides effective information. I don't think there is any problem with the manuscript

REPLY

Thank you for your recognition.

We have made a careful revision of the manuscript and have the revision further edited by professional English editor.

Reviewer #4:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The manuscript entitled " Beta receptor blocker therapy for the elderly in the coronavirus disease 2019 era" aims to outline the most important evidence available in the literature on the usefulness of beta blocker therapy for older patients in the context of the COVID-19 pandemic. The manuscript is written well; however, it has a number of limitations. 1. The current review just summarized the published results and conclusions. No perspective views were included. 2. Figure 1 is not clear enough. 3. Lack of therapy strategies discussion. 4. Lack of large-scale clinical trials results and discussion.

REPLY:

Thank you very much for your crucial comments and observations.

Professional editors at Filipodia carefully revised the manuscript in order to optimize the readability of the paper. We will upload the Certificate Service Confirmation with the revised manuscript.

- 1) A new section entitled “Actual strategies and future perspectives for beta blocker use” has been added (Page 7/18) in order to expand the information on beta blockers for readers. In this section, we have reported perspective views and discussed therapy strategies of beta blockers treatment in COVID-19 context.
- 2) Figure 1 has been reworked in PPT format. It has been made clearer and supplemented with messages about COVID-19 triggered ventricular tachyarrhythmias treatment
- 3) In the new section on therapeutic strategies (page 7/18), current indications for the use of beta blockers for myocarditis related to COVID-19 and for tachyarrhythmias related to Sars-Cov infection 2 were reported.
- 4) In the absence of available large-scale clinical trials on the treated topic, the difficulties related to their design and conduction have been clarified in the text.
In fact, on page 8/18 we have reported: “Indeed, evidence from specific, large clinical trials is lacking. Unfortunately, the design and conduction of these studies appear very problematic for the difficulties of having control groups during pandemic waves, and discriminating the effect of beta blocker from those of other drugs.^[66]” We provided a specific reference to these statements: i.e. reference 66: Brüssow H. COVID-19: From pathogenesis models to the first drug trials. *Microb Biotechnol* 2020;13:1289-1299 [PMID: 32573950 DOI: 10.1111/1751-7915.13611]

Thank you for your time and attention.

If you should require further clarification, please do not hesitate to contact me.
We look forward to hearing from you soon.

With best regards, on behalf of all authors

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