

Peer Review File

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**Review Comment**

- Second paragraph: I recommend the authors to provide the current estimated mortality rate as a percentage on the total diagnosed cases worldwide.

**Reply:** We provided the recent data on total diagnosed COVID-19 cases and current estimated mortality rate in text. We added some data (see page 4, line 63-68)

- moreover, I suggest providing a few and clear data about the mortality risk in relation to the age class and (multiple) comorbidity.

**Reply:** We provided some data on age and comorbidity related mortality rate. We added some data (see page 4-5, line 68-94)

- the third paragraph is unclear. I recommend rephrasing it completely. Moreover, I recommend the authors to clarify what is the methods of this review. Is that a narrative review (as it seems to be) or is it a systematic review (since they try to provide a kind of methodology...)? Of course, there is no systematic approach in this review and, thus, I do not see the need to specify the database used. In detail, they included Google scholar, but not all papers indexed in this database are peer-reviewed. I would suggest replying only on the articles indexed in Pubmed and/or Scopus and/or WOS. Therefore, I think the authors should clarify this point rather than providing imprecise and approximative mention to their methodology, which is not applicable to a narrative review.

**Reply:** Yes, this is a narrative review and we rephrased this paragraph completely. we have modified the text as advised (see page 5, line 95-102)

THERAPEUTIC INTERVENTIONS

- this paragraph as an independent section of the manuscript makes no sense. The authors should place it in the introduction after the appropriate revision of the last paragraph, as explained above.

**Reply:** We removed this independent paragraph and rephrased it in last paragraph of introduction. We have modified the text as advised (see page 5, line 95-102).

- can the authors clarify if they considered only the clinical trial for this review?

**Reply:** Yes, only clinical trials. We modified our text as advised (see page 5, line 97-99)

LOPINAVIR/RITONAVIR

- it's a good summary. In order to increase the scientific value of this paper, I recommend the authors to include a table with the main characteristics (authors, year, country, trial design, number of participants in each study groups, main findings, etc.)

for each drug considered in this review.

**Reply:** We include a table on all clinical trials that we explained in text. We provided the table as advised (see Table 1)

ARBIDOL:

- Indeed, all these paragraphs are a good summary, but a better and precise overview should be provided to the readership. These sections are a good comment as far as a table is provided.

**Reply:** We provided a table including all studies included in summary. We provided the table as advised (see Table 2)

FAVIPRAVIR/REMDESIVIR

- same comments as above (lopinavir/ritonavir)

**Reply:** we provided a table with all studies included in the summary. We provided the table as advised (see Tables 3 and 4)

Chloroquine and Hydroxychloroquine:

- same comments as above (lopinavir/ritonavir)

**Reply:** We provided the table as advised (see Table 5)

- as the authors reported several trials investigating the effectiveness of HCQ were coupled with macrolides and, especially, azithromycin. In this regard, in this discussion, a few rows may be dedicated to the potential role claimed for macrolides as antiviral agents, which is actually not strongly supported, even if cannot be ruled out completely at the moment. A very recent review addressed this issue and the authors may mention its main conclusions (refer to: Clinical evidences on the antiviral properties of macrolide antibiotics in the COVID-19 era and beyond. *Antivir Chem Chemother.* 2020 Jan-Dec;28:2040206620961712. doi: 10.1177/2040206620961712).

**Reply:** We included some direct as well as indirect role of azithromycin as antiviral therapy in the text summary. we modified our text as advised (see page 10, line 288-293)

FOLLOWING SECTION:

- there are not so many trials (at least not finalized) like the previous drugs. Therefore, in these cases, a table may not be necessary.

**Reply:** Ok.

TOCILIZUMAB

- the authors should provide some more details to present this biological therapy. Indeed, the readership of this journal may not be very familiar. A few more biochemical characteristics of TCZ as well as biological actions of IL-6 should be provided (this article provides a good overview: *Curr Med Chem.* 2018;25(42):5860-5893. doi: 10.2174/0929867325666180522085716.).

**Reply:** We have elaborated the biological properties of tocilizumab as well as IL-6.

We have modified the text as advised. (see page 12, line 365-374)

- moreover, the authors may mention also some initial experiences with other biologics and, in detail, those blocking IL-1 (see: Proc Natl Acad Sci U S A. 2020 Aug 11;117(32):18951-18953. doi: 10.1073/pnas.2009017117. Epub 2020 Jul 22; & Lancet Rheumatol. 2020 Jun;2(6):e325-e331. doi: 10.1016/S2665-9913(20)30127-2. Epub 2020)

**Reply:** Regarding this comment we try to give a good overview of IL-1 in COVID 19 pathogenesis and biologics to block its action. (see page 13, line 401-414)

#### CONVALESCENT PLASMA THERAPY

- This section may be expanded. Indeed, there are mismatching experiences with this therapy. Some more details about the clinical indication and the level of neutralizing antibodies used in the available trials should be described. In this case, a table providing an overview may be helpful as well.

**Reply:** Regarding this comment we expanded this section with some more studies. We also described the level of neutralizing antibodies that used in trials. We also provided the table for overview of summary. We added some data and modified our text as advised (see page 14, line 434-436 & line 439-454). We also provided the table as advised (see Table 6)

#### INTERFERON:

- a few rows to introduce the molecule structure and the biological role should be added (e.g. Clin Microbiol Rev. 2001 Oct;14(4):778-809, table of contents. doi: 10.1128/CMR.14.4.778-809.2001.)

**Reply:** The molecular structure and biological role of interferons are explained in this section. We modified our text as advised (see page 22, lines 460- 471)

#### CONCLUSION

- “Many of above-mentioned antivirals seems to have some therapeutic effects...”. Clearly states the most effective ones.

**Reply:** We clarified this with the names of most effective molecules based included studies in this review. (see page 16, line 509-518)

- “...language barrier...” Clarify what do the authors mean exactly.

**Reply:** We found some literature in some local languages thus cannot reviewed for this review writing.

- provide clear take home messages.

**Reply:** We clarified this with the names of most effective molecules based included studies in this review. (see page 16, line 509-518)

#### REFERENCES

- to be completed and updated according to the comments and recommendations

above

**Reply:** We updated references as your comments and recommendations. More recent references were added.

- double check that all references are from peer-reviewed and Scopus/WOS indexed journals, since the authors mentioned also Google Scholar as literature search database (see previous comments about the introduction)

**Reply:** We have checked all references for peer-review and we found two such references and removed from this review. We also found a study which had been retracted by publisher, related reference has been removed from this study.