Peer Review File

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Reviewer A

The authors will perform a systematic review to collect comprehensive evidences of current available therapeutic options in SARS-CoV, MERS-CoV and SARS-CoV-2 infected patients (both for randomized controlled trials and controlled cohort studies). Right now, this is a very urgent and important topic. Overall, this study is relatively advanced and well designed, but main limitation is its extrapolation. Research on COVID-19 is limited. Although SARS-CoV, MERS-CoV, and SARS-CoV-2 share similar viral structures, it is not known whether the drug treatment conclusions drawn from SARS or MERS can be used for COVID-19. Whereas, considering the lack of available evidence and the value that this study can bring, this protocol can be considered for publication after firstly addressing the following comments.

Reply:

We really appreciate reviewer's positive comments on our study. Indeed, the results drawn from SARS or MERS might not be directly extrapolated to COVID-19, despite SARS-CoV and MERS-CoV were closely related with SARS-CoV-2. Therefore, we plan to conduct subgroup analysis based on indication to evaluate the reliability of results (kindly see Page 11, Line 224-225): We will overcome this issue through subgroup analyses of distinct situations, such as indications, interventions, and study designs.

In addition, we have followed your suggestions and revised our manuscript to address the reviewer's comments. The revisions are marked in red. Detailed responses are as follows:

Comment 1:

1. "Abstract" part, "SARS-CoV, MERS-CoV and SARS-CoV-2 infected patients", should be "SARS-CoV, MERS-CoV or SARS-CoV-2 infected patients".

Reply 1:

We really appreciate your suggestions, and we have replaced the "and" with "or". (kindly see Page 4, Line 59-61).

Changes in the text:

This systematic review and meta-analysis will summarize all the evidences for efficacy and safety of current therapeutic options in SARS-CoV, MERS-CoV or SARS-CoV-2 infected patients.

Comment 2:

2. Line 60, is there a PROSPERO number? And the description should be “the PROSPERO”.

Reply 2:

Thank you for your advices. We added the PROSPERO number (CRD42020168639), and we added “the” before “PROSPERO” as well. (kindly see Page 4, Line 63-65)

Changes in the text:

The protocol of this study has been submitted in the PROSPERO platform (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is CRD42020168639.

Comment 3:

3. Line 67, I guess “a total of 105,586 confirmed infections” is not correct.

Reply 3:

Thank you for your advices. We have modified our text as advised. (kindly see Page 4, Line 72-73)

Changes in the text:

As of 5 July 2020, a total of 11,125,245 confirmed COVID-19 cases were reported with 528,204 fatal cases.

Comment 4:

4. Line 174, the authors may be able to add some additional sensitivity analyses, e.g. excluding high-risk bias studies or studies with a small sample size.

Reply 4:

Thank you for your advices. We have added some additional sensitivity analyses as advised. (kindly see Page 10, Line 189-190)

Changes in the text:

We also plan to conduct sensitivity analyses by omitting individual study orderly to assess the confidence of the results. In condition, sensitivity analyses will also be conducted by excluding studies with high-risk of bias or small sample size.

Comment 5:

5. Line 184-205, the use of too many adversative conjunctions may result in readers not being able to better understand what the authors are trying to say. Please simplify some sentences. Additionally, please clarify what types of studies were included in the previous systematic reviews, RCT? Or only cohort studies or others?

Reply 5:

We really appreciate your suggestions. We have simplified the discussion section and reduced the description of previous systematic reviews as advised (see Page 10-11, Line 202-218). In addition, we have described the types of inclusive studies of previous systematic reviews (see Page 10-11, Line 207, 211-212, 217).

Changes in the text:

Momattin et al. have conducted a systematic review to summarize potential treatments for MERS based on earlier studies of SARS (22). They figured out that ribavirin may improve the SARS-CoV infection in 71.4%-80% of patients, and reduce the ICU admission rates to 13%-20%. Meanwhile, ribavirin showed a benefit in decreasing mortality rate of SARS patients. However, there were some limitations: (1) Most of the inclusive studies were cohort studies despite one RCT; (2) Treatment dosage, frequency and administration routes were variable (22). Latterly, Morra et al. revealed that monitoring adverse effects carefully, especially anemia, bradycardia, diarrhea and transaminitis, the rapid initiation of ribavirin and interferon combination may have effects in MERS patients. However, this study included only case reports, case series and observational studies. And it was limited by the small sample size of included studies, requiring further large-scale clinical studies (32). Recently, Zhang et al. conducted a systematic review for all therapeutic options associated with coronavirus infections. They suggest a variety of nutrients, antivirus agents, Ribonucleic Acid (RNA) virus vaccines and convalescent plasma based on evidences of SARS/MERS experiences, SARS-CoV-2 in vitro results, or COVID-19 cases. No conclusive therapy could be implemented to treat COVID-19 (20).

Comment 6:

6. Line 222, what do they suggest these agents for? Please clarify.

Reply 6:

Thank you for your advices, we have clarified “these agents” as “these antiviral agents, such as remdesivir, chloroquine and hydroxychloroquine, lopinavir/ritonavir, ribavirin, arbidol, and interferon”. (kindly see Page 12, Line 245-246)

Changes in the text:

The meta-analysis will evaluate efficacy and safety of these antiviral agents, such as remdesivir, chloroquine and hydroxychloroquine, lopinavir/ritonavir, ribavirin, arbidol, and interferon, based on retrieved studies.

Comment 7:

7. Line 244, so far, there have been some randomized controlled trials of covid-19. Could the authors briefly discuss the available results?

Reply 7:

Thank you for your suggestions, we have added brief discussion of the available RCTs of COVID-19. (kindly see Page 11-12, Line 227-239)

Changes in the text:

We have conducted a preliminary search showing that limited number of RCTs reporting efficacy and safety of antiviral agents for patients with confirmed COVID-19. Three RCTs documented inconsistent results of hydroxychloroquine (33-35). Chen et al documented that hydroxychloroquine therapy showed radiographical benefit (34). Tang et al and Chen et al revealed hydroxychloroquine observed no benefit in SARS-CoV-2 eradication (33,35), and it caused more adverse events especially diarrhea (33). Two RCTs showed that lopinavir/ritonavir monotherapy did not observe significant benefit in lowering virus load of SARS-CoV-2 and improving clinical outcomes over supportive care for hospitalized adult patients with mild/moderate (36) or severe COVID-19 (37). Recently, three RCTs documented that remdesivir was associated with shorter time to recovery (38,39) rather than clinical benefits (39) in hospitalized adult patients with COVID-19. No significant difference was noted between short course (5 days) and long course (10 days) of remdesivir (40). In addition, we will perform quality analysis of retrieved evidences to evaluate the reliability of recommendations.

Comment 8:

8. Line 245, I don't think a quality analysis can solve the problem of the lack of large-scale clinical trials.

Reply 8:

We really appreciate your suggestion. We have modified the description as advised. (see Page 12, Line 240-241)

Changes in the text:

In addition, we will perform quality analysis of retrieved evidences to evaluate the reliability of recommendations.

Reviewer B

Major comments:

This study protocol for a systematic review mainly evaluates efficacy and safety of current therapeutic options for COVID-19 based on previous clinical evidences. Generally, this study protocol is well designed, and fulfill the gap of rigorously conducted investigation for COVID-19 antiviral therapies. However, the major limitation of the present study is its heterogeneity of included studies. The indications and interventions are both variable. Moreover, cohort studies are also included which may downgrade the evidence quality. In order to make this study more convincing, the author can make subgroup analysis based on indications, interventions, and study designs. Overall, this study protocol might be considered for publication after minor revision. The following minor comments should be addressed by the authors.

Reply:

We really appreciate Reviewer's positive comments on our study. We have modified the subgroup analysis as you advised (kindly see Page 9-10, Line 183-187). Additionally, we have followed your suggestions and revised our manuscript to address these concerns. The revisions are marked in red. Detailed responses are as follows.

Minor comments:

Comment 1:

1. In abstract, methods section, the author described "Manual searches will be conducted by searching preprinting websites, clinical trial registers, et al." Please clarify what does the abbreviation "et al" stand for? Does it mean other sources be manually searched?

Reply 1:

Thank you for your suggestions. We have replaced the "et al" as "and screening the reference lists of inclusive studies." (see Page 3, Line 46-47)

Changes in the text:

Manual searches will be conducted by searching preprinting websites, clinical trial registers, and screening the reference lists of inclusive studies.

Comment 2:

2. In abstract, methods section, the author described "Randomized controlled trials (RCTs) and controlled cohort studies reporting therapy for SARS, MERS, and COVID-19 will be included." Please elucidate what kind of therapy was investigated.

Reply 2:

We really appreciate your advices. We have modified as advised. (kindly see Page 3, Line 49-50)

Changes in the text:

Randomized controlled trials (RCTs) and controlled cohort studies reporting antiviral therapies, including ribavirin, remdesivir, lopinavir/ritonavir, arbidol, chloroquine, hydroxychloroquine, interferon, and so on, for SARS, MERS, and COVID-19 will be included.

Comment 3:

3. In abstract, study registration section, please add the website address of PROSPERO platform as well as the registration number.

Reply 3:

Thank you for your advice. We have added the website address of PROSPERO platform and the registration number. (kindly see Page 4, Line 63-65)

Changes in the text:

The protocol of this study has been submitted in the PROSPERO platform (https://www.crd.york.ac.uk/PROSPERO/), and the registration number is CRD42020168639.

Comment 4:

4. In introduction section, the pandemic of COVID-19 has spread rapidly, the author needs to update the epidemiological data of COVID-19.

Reply 4:

Thank you for your reminder, we have updated the epidemiological data of COVID-19. (see Page 4, Line 72-73)

Changes in the text:

As of 5 July 2020, a total of 11,125,245 confirmed COVID-19 cases were reported with 528,204 fatal cases.

Comment 5:

5. In methods section, the registration information in PROSPERO platform should also be described in detail.

Reply 5:

Thank you for your advice, we have added the registration information in PROSPERO platform in method section. (kindly see Page 6, Line 108-109)

Changes in the text:

This study will be conducted following the statement of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (23) and previously registered protocol (PROSPERO: CRD42020168639).

Comment 6:

6. In methods, data extraction section, the comprehensive data should be extracted with no detail information skipped.

Reply 6:

Thank you for your suggestion. We have described the comprehensive data as advised. (kindly see Page 8, Line 154-160)

Changes in the text:

We will extract data with an well-designed form, involving study characteristics (investigator, publication year, study location, study design, sample size), population characteristics (gender, age, diagnosis, comorbidities), intervention characteristics (therapeutic agents, administration start date, dosage, treatment duration, concomitant

medication), clinical outcomes (mortality, incidence of ARDS, mechanical ventilation usage, ICU admission, hospital stay, reduced viral load, clinical improvement, improvement of symptoms, time to become afebrile).

Comment 7:

7. In methods, quality assessment section, the author described "For each study, the quality characteristics will be rated as low risk of bias, moderate risk of bias, high risk of bias or unclear." Then, please clarify how to appraise the quality through the NOS?

Reply 7:

Thank you for your suggestion. We have clarified the scale method of NOS. (kindly see Page 9, Line 170-171)

Changes in the text:

The risk of bias of individual study was rated as low (NOS scores≥7), moderate (4≤NOS scores≤6), or high (NOS scores≤3).

Comment 8:

8. In the discussion section, please state the prevalence of COVID-19 and the potential effective anti-coronavirus agents.

Reply 8:

We really appreciate your kindly suggestion. We have added the description of prevalence of COVID-19 and the potential effective anti-coronavirus agents at the beginning of discussion. (kindly see Page 10, Line 195-198)

Changes in the text:

The COVID-19 has become a global pandemic (3), and numerous antiviral agents has been considered for fighting against the new virus SARS-CoV-2. Amongst, remdesivir (30) (31), chloroquine and hydroxychloroquine (16,17), lopinavir/ritonavir (12,13), ribavirin (9), arbidol (19), and interferon (10,11) were most extensively used.

Comment 9:

9. In the discussion section, the author summarized previously published systematic reviews reporting efficacy and safety of antiviral agents in patients with coronavirus infection. However, the strengths and limitations of these systematic reviews should be documented briefly, while the strengths and limitations of the present study should be highlighted.

Reply 9:

We really appreciate your suggestions. We have simplified the discussion section and reduced the description of previous systematic reviews as advised (kindly see Page 10-11, Line 202-218).

Changes in the text:

Momattin et al. have conducted a systematic review to summarize potential treatments for MERS based on earlier studies of SARS (22). They figured out that ribavirin may improve the SARS-CoV infection in 71.4%-80% of patients, and reduce the ICU admission rates to 13%-20%. Meanwhile, ribavirin showed a benefit in decreasing mortality rate of SARS patients. However, there were some limitations: (1) Most of the inclusive studies were cohort studies despite one RCT; (2) Treatment dosage, frequency and administration routes were variable (22). Latterly, Morra et al. revealed that monitoring adverse effects carefully, especially anemia, bradycardia, diarrhea and transaminitis, the rapid initiation of ribavirin and interferon combination may have effects in MERS patients. However, this study included only case reports, case series and observational studies. And it was limited by the small sample size of included studies, requiring further large-scale clinical studies (32). Recently, Zhang et al. conducted a systematic review for all therapeutic options associated with coronavirus infections. They suggest a variety of nutrients, antivirus agents, Ribonucleic Acid (RNA) virus vaccines and convalescent plasma based on evidences of SARS/MERS experiences, SARS-CoV-2 in vitro results, or COVID-19 cases. No conclusive therapy could be implemented to treat COVID-19 (20).

Comment 10:

10. In the discussion section, please add references to the citations, such as "The first systematic review focused on this topic was reported by Stockman LJ, et al." "Momattin H, et al. have conducted a systematic review to summarize potential treatments for MERS based on earlier studies of SARS." and "As of MERS patients, Morra ME, et al. conducted a systematic review reporting relatively constant mortality between interferon treatment and supportive treatment."

Reply 10:

Thank you for your advice. We have added references as advised. (kindly see Page 10-11, Line 203, 211)

Changes in the text:

Momattin et al. have conducted a systematic review to summarize potential treatments for MERS based on earlier studies of SARS (22).

Latterly, Morra et al. revealed that monitoring adverse effects carefully, especially anemia, bradycardia, diarrhea and transaminitis, the rapid initiation of ribavirin and interferon combination may have effects in MERS patients (32).

Comment 11:

11. Why the study of Stockman LJ, et al could not lead to convincing conclusion that ribavirin improved recovery rate? Please illustrate clearly.

Reply 11:

Thank you for your suggestion. We have deleted this systematic review of Stockman LJ, et al to reduce the description of previous systematic review.

Comment 12:

12. In the third paragraph of discussion, the author claimed "Monitoring adverse effects carefully, the rapid initiation of ribavirin and interferon combination may have effects." What kind of adverse effects should be monitored for ribavirin administration? Please clarify in detail.

Reply 12:

Thank you for your advice. We have described the monitoring adverse effects detailly. (kindly see Page 11, Line 209-210)

Changes in the text:

Latterly, Morra et al. revealed that monitoring adverse effects carefully, especially anemia, bradycardia, diarrhea and transaminitis, the rapid initiation of ribavirin and interferon combination may have effects in MERS patients (32).