

Peer Review File

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Reviewer A

Comment 0. This is an interesting systematic review of the most recently published trials of chloroquine/ hydrochloroquine in the treatment of hospitalized patients with COVID-19. The subject of the study is timely and clinically relevant. Nevertheless, some specific points need clarification in order to improve the manuscript.

Reply 0. Your thoughtful comments are greatly appreciated.

Changes in the text: No change was made for this comment.

Major comments:

Major Comment 1. Page 6; Line 86: Why did you include a specific observational retrospective study when your inclusion criteria consider only randomized and non-randomized trials? Either you include all observational studies or you do not include any of them. If this specific study is relevant for corroborating data it may be commented within the discussion.

Major Reply 1: Thank you for your concern regarding inclusion criteria. Page 6; Line 86 (previous numbering), which is a part of Outcome section, explains why viral clearance was selected as one of the primary outcomes. This Outcome section is not describing publication type that we included. Page 5, Line 63, Publication type section indicates that a randomized controlled trial, a non-randomized controlled trial, and a retrospective study are eligible for our analysis.

We agree with you that we should either include or exclude all observational studies and we did include all observational studies that satisfied inclusion criteria shown in the method section.

Changes in the text: No change was made for this comment.

Major Comment 2. Page 7; Line 101: The quality assessment paragraph should be presented right before or after that of data extraction.

Major Reply 2: The section was placed right after data extraction section. Thank you.

Change in the text: Page 7 Line 110.

Major Comment 3. Page 8; line 120: The subtitle should be "Study selection and data extraction" instead of simply "Data extraction"

Major Reply 3. The subtitle was changed. Thank you.

Change in the text: Page 6 Line 99.

Major Comment 4. Results: Please do not use expressions such as "control-favored" or "favorable trend" (e.g., Page 11, line 182; Page 11, line 188).

Major Reply 4. These wordings were deleted or modified. Thank you.

Change in the text: Page 10 Line 167; Page 10, Line 172; Page 12, Line 220; Page 16, Line 265; Page 16, Line 270.

Minor comments: (including English needed revisions)

Abstract

Minor comment 1. Lines 25-26 – “We need to evaluate...COVID-19”. Suggested: we aimed to evaluate... treatment for COVID-19 by a systematic review and meta-analysis of published controlled trials.

Minor Reply 1: The wording was changed following your advice. Thank you.

Changes in the text: Page 3. Line 5.

Minor comment 2. Line 28 – “...and MOOSE.” Suggested: ...and MOOSE reporting recommendations.

Minor Reply 2: The wording was changed following your advice. Thank you.

Changes in the text: Page 3. Line 8.

Minor comment 3. Line 31 – “UMIN0...”. Suggested: delete.

Minor Reply 3: We believe presenting registration information in the abstract is common. Nonetheless, we deleted it based on your recommendation.

Changes in the text: Page 3. Line 11.

Minor comment 4. Line 34 – “Improvement...time-to-event”. Suggested: No improvement of viral clearance was found neither by time-to-event analysis ... nor...

Minor Reply 4: The wording was changed following your advice. Thank you.

Changes in the text: Page 3. Line 14.

Minor comment 5. Line 38 – “...did not facilitate viral clearance”. Suggested: did not improved viral clearance.

Minor Reply 5: The wording was changed following your advice. Thank you.

Changes in the text: Page 3. Line 19.

Introduction

Minor comment 6. Line 49 – “studie” – studied

Minor Reply 6: The wording was changed following your advice. Thank you.

Changes in the text: Page 4. Line 30.

Minor comment 7. Lines 52/53 – “In the mid-March...” – In mid-March...

Minor Reply 7: The wording was changed following your advice. Thank you.

Changes in the text: Page 4. Line 33.

Minor comment 8. Line 62 – “QT prolongation.” – Suggested: ...arrhythmia due to QT prolongation

Minor Reply 8: The wording was changed following your advice. Thank you.

Changes in the text: Page 4. Line 42.

Minor comment 9. Line 63- “..shortage of CQ...” – Suggested: ...shortage of CQ and HCQ for well-established treatment indications, which...

Minor Reply 9: The sentence was modified following your advice. Thank you.

Changes in the text: Page 4. Line 44

Methods

Minor comment 10. Line 93 – “...studies...was...” – ...were included

Minor Reply 10: The wording was changed following your advice. Thank you.

Changes in the text: Page 6, Line 72.

Minor comment 11. Line 127 – “...because expedited reporting was required.” Suggested: ...because we aimed to an expedited reporting.

Minor Reply 11: The wording was changed following your advice. Thank you.

Changes in the text: Page 8, Line 107.

Results

Minor comment 12. Line 134- shere – where...

Minor Reply 12: The spelling was modified following your advice. Thank you.

Changes in the text: Page 8, Line 118.

Minor comment 13. Line 164 – “Tang...Huang et al” – please include references numbers.

Minor Reply 13: We added references. Thank you.

Changes in the text: Page 10, Line 150.

Discussion

Minor comment 14. Line 243 – “...QTc interval...” – before referred as QT; please clarify/uniform

Minor Reply 14: The wording was changed following your advice. Thank you.

Changes in the text: Page 13. Line 234.

Minor comment 15. Line 254 – “...dermatological erythematous.” – please clarify, review English proper terminology.

Minor Reply 15: The wording was changed following your advice. Thank you.

Changes in the text: Page 14. Line 245.

Reviewer B

Comment 0. This is an extremely well conducted systematic review on a timely topic of great interest. The use of chloroquine and hydroxychloroquine has gained tremendous attention due to the pandemics of COVID-19.

Authors implemented robust systematic and meta-analyses approaches as well as unbiased statistical approaches for their studies.

In general, conclusions that chloroquine and hydroxychloroquine do not seem to offer any major advantage to subjects with COVID-19 infection, while potentially being detrimental, are strongly supported by the data presented and the statistical analyses.

Reply 0. Your thoughtful comments are greatly appreciated.

Changes in the text: No change was made for this comment.

Despite this major strengths there are some areas of concerns:

Comment. a) A potential major problem is that authors include as source studies from MedRxiv. Unless there was confirmation and follow up that these studies were also published and not only published online without peer-review; these references should be removed. While many good studies are published in these online sites, many poor and incorrect studies are also published, which can provide incorrect or skewed information. They should not be part of a systematic, meta-analysis review as an authoritative source.

Reply a) We agree with you that quality of articles from MedRxiv website is sometimes questionable. However, our protocol allowed an article from MedRxiv. Besides, some

readers may be interested in analysis using data from MedRxiv. In any case, if we accept your suggestion as it is, as many as four out of seven articles will be excluded from analysis, which may diminish the statistical robustness based on the moderate sample size. After careful consideration, we decided not to exclude MedRxiv articles from our main analysis. However, to respond your suggestion, we conducted a sensitivity analysis excluding data from MedRxiv and presented the data as eFigure 7. Thank you for your considerate advice.

Changes in the text: Page 13 Line 206. Supplementary eFigure 7.

Comment. b) It is really unclear as to where and how the systematic review was registered. Normally a systematic review is registered under a specific protocol. This is not clear from the Methods.

Reply b) Thank for your concern concerning protocol registration. As shown Methods Overview section, the simple version of protocol was registered in ICMJE certified UMIN-CTR web site with registration ID of UMIN000040188. You can see the URL from the reference list. Thank you for your considerate suggestion.

Changes in the text: the text was not changed for this comment.

Comment. c) There is usually a Statement and a Protocol of record; for example PRISMA and PROSPERO.

Reply c) We agree with the reviewer that a systematic review is usually performed following some statement such as PRISMA and that the protocol is preferred to be registered in some website such as PROSPERO. As Methods/Overview section of our previous manuscript clearly indicated, our study was performed based on PRISMA and MOOSE methodology. We know that PROSPERO is most commonly used registration website for a systematic review protocol. However, we noticed that the response from the PROSPERO group is not sufficiently quick probably due to work overload. Therefore, we decided to register our protocol in ICMJE certified UMIN-CTR website. Thank you for your considerate suggestion.

Changes in the text: the text was not changed for this comment.

Comment. d) From the methods as stated it is not easy to determine the inclusion and exclusion criteria for these studies

Reply d) We are so grateful for your inquiry concerning the inclusion criteria. On the other hand, our previous manuscript presented inclusion criteria with subheadings like "Publication type," "Patient," "Treatment," "Outcome." To our understanding, these

presentations are quite commonly accepted for the description of inclusion criteria of a systematic review. PRISMA checklist #6 requires "Eligibility criteria" but does not specifically demand exclusion criteria. If the Editor requests us to clarify specific item regarding inclusion and exclusion criteria, we are happy to provide the information.

Changes in the text: the text was not changed for this comment.

Comment. e) It is also very helpful when authors inform the primary and secondary outcomes.

Reply e) Methods/Outcome section of our previous manuscript clearly indicated that " primary outcomes were all-cause mortality and viral clearance" and that " Secondary outcomes included time to discharge, symptom alleviation, CT image improvement, disease progression defined as a composite outcome with death and intensive care unit (ICU) admission, any adverse event, and serious adverse event." Corresponding results were presented in the result section with each subheading. Thank you.

Changes in the text: the text was not changed for this comment.

Reviewer C

Comment 0: This manuscript focuses on the treatment of COVID-19 with Chloroquine and Hydroxychloroquine, as a systemic review. Although the quality of this study is fairly good to publish, the manuscript needs to be revised. The included studies in this review are seven, four of them are non-peer review. Furthermore, there are many very important studies more related to the topic but didn't include here. There are many places in this manuscript that need to revise. There is a similar study, already published on October 8, 2020, entitle "Efficacy of chloroquine or hydroxychloroquine in COVID-19 patients: a systematic review and meta-analysis". As the authors searched for studies in April, I think it considers a little bit long time before. So I suggest to add more recent peer-reviewed studies.

The suggestions are as follows:

Reply 0: We appreciate your understanding that the first draft of our manuscript was submitted in May and some important article has been published after our submission. The manuscript was amended based on your advices. Point-by-point replies are described below.

Change in the text: no change was made for this comment.

Comment 1. In the title, “of treatment of” should be changed to “for treatment of”.

Reply 1. The wording was changed. Thank you.

Change in the text: P1 L1.

Comment 2. In the keywords, it is suggested to add “COVID-19” or “SAR-CoV-2” word to this part.

Reply 2: COVID-19 was added in the keywords. Thank you.

Change in the text: P2 L33

Comment 3. In the abstract, the “background” part should be revised and re-write.

Reply 3: The background part was revised. Thank you.

Change in the text: P3 L3

Comment 4. In the abstract, line 23, the “hydrochloroquine” should be substituted by “hydroxychloroquine”.

Reply 4: The spelling was corrected. Thank you.

Change in the text P3 L3

Comment 5. In the abstract, line 23, add coma after 2020,

Reply 5: A comma was added after 2020. Thank you.

Change in the text: P3 L7

Comment 6. In the abstract, line 30, “were” should be changed to “was”

Reply: This grammatical error was corrected. Thank you.

Change in the text: P3 L11

Comment 7. In the abstract, define the abbreviations of PRISMA, MOOSE, and RCTs.

Reply 7: They were spelled out. Thank you.

Change in the text: P3 L8/L13

Comment 8. In the introduction, lines 53-55, the author should cite this sentence from the original study, which is the ref. 13.

Reply 8: Ref. 13 was cited here, and the references were renumbered. Thank you.

Change in the text: P4, L36

Comment 9. The references should be arranged as described in the author’s instruction

of the journal.

Reply 9: Since "sources should be referenced according to the Vancouver reference style" according to the instruction, the reference style was set for Vancouver.

Change in the text: P18

Comment 10. In the introduction, line 49, "studies" should modify to "studied", and "chinese" should be changed to "Chinese".

Reply 10: "chinese" was corrected in this revision. "studies" was already amended in the previous revision round. Thank you.

Change in the text: P4, L31

Comment 11. In the methods, line 82: Please clarify this sentence "Search formulas are presented in eText 1", it is not understandable.

Reply 11: The sentence was modified. Thank you.

Change in the text: P6, L65

Comment 12. In the methods, study search part, to be more understandable, it is suggested to add search terms or search key words.

Reply 12: The search strategy is presented in eText 1.

Change in the text: no change was made for this comment.

Comment 13. In the methods, "Publication type": Please re-write this part clearly.

Reply 13: The "Publication type" section was re-written. Thank you.

Change in the text: P6, L68

Comment 14. In the methods, line 121, add a comma after PubMed.

Reply 14: A comma was added. Thank you.

Change in the text: P7, L99

Comment 15. In the methods, line 121, "WOS" what do you mean by this abbreviation? If you mean Web of Science, you should define it in the first place you mention it in the manuscript or write it as it is "Web of Science".

Reply 15: WOS was spelled out. Thank you.

Change in the text: P7, L99

Comment 16. It is suggested to add more related studies. For example, these three

important studies are more related to this topic:

(1) DOI: 10.1001/jama.2020.8630

(2) DOI: 10.1136/bmj.m1849

(3) DOI: 10.1056/NEJMoa2016638

Reply 16:

(1)JAMA was added, and the result section was modified accordingly.

(2)BMJ was already included in the previous manuscript as medRxiv article but the reference was changed to BMJ.

(3)NEJM was not added because this study randomized contact person, not COVID-19 patients. However, this article was commented in the discussion section since this document is important,

Change in the text: Many parts of the result section, figures, tables, and discussion

Comment 17. In the Result, Line 166, “by of ChenX” should be modified to “by Chen X”.

Reply 17: It was amended. Thank you.

Change in the text: P10, L151

Comment 18. In the Result, line 217, “outcomes” should be changed to “outcome”.

Reply 18: The grammar was amended. Thank you.

Change in the text: P12, L203

Comment 19. In the discussion, line 225, “from France. on March 20, 2020”, delete full stop before on March.

Reply 19: The full stop was removed. Thank you

Change in the text: P14, L217

Comment 20. In the discussion, lines 35-36, the sentence, “HCQ has been shown to have in vitro activity against multiple RNA viruses including SARS-CoV-1” doesn't related to Ref. 23. This reference is related only to CQ, not HCQ. Please cite this information from another reference or replace HCQ by CQ.

Reply 20: HCQ was changed to CQ. Thank you.

Change in the text: P14, L228

Comment 21. In the discussion, lines 36-38, also Ref. 25 is related to CQ, not HCQ. So HCQ should be replaced by CQ in this sentence.

Reply 21: HCQ was changed to "HCQ and CQ". Thank you.

Change in the text: P14, L230

Comment 22. In the discussion, line 251, "RA" define this abbreviation. If you mean rheumatoid arthritis, add this abbreviation in introduction part line 65.

Reply 22: SLE and RA were spelled out. Thank you.

Change in the text: P15, L247

Comment 23. In the discussion, line 267, add full stop before "For example".

Reply 23: A full stop was added. Thank you.

Change in the text: P16, L262

Comment 24. On the figure 1, the fifth square, (Record excluded n = 234), you should be clarified by short explanation how you excluded here.

Reply 24: We explained as "excluded by screening. Please note that detailed reason for exclusion by the screening process is not requested by PRISMA statement.

Change in the text: Figure 1.