Author’s response to reviews

Title: Clinical determinants of the severity of Middle East respiratory syndrome (MERS): A systematic review and meta-analysis

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Point-by-point responses to the reviewers (PUBH-D-16-02946)

[Response to Reviewer 1]

Reviewer #1: The authors have performed an important piece of work synthesising evidence on the clinical determinants of the severity of Middle East Respiratory Syndrome (MERS). My comments relate mainly to the conduct and presentation of this systematic review. A number of issues exist with presentation of this systematic review that the authors will need to address. I list them out in the order in which they appear in the manuscript: 1) Title: PRISMA checklist item #1 recommends that the report be identified as "a systematic review, meta-analysis, or both". The authors have performed a meta-analysis but do not state this in their title. Please amend.

We appreciated the reviewer’s comment. The title was amended as suggested (P1L3).

2) Abstract: PRISMA guidelines (checklist item #2) recommend that a structured summary is provided in the abstract that includes details on "data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods". Please revise the abstract accordingly.

We have adhered to the guideline as much as possible (P2L30-L32), documenting data sources, study eligibility criteria and participants. We checked other similar publications in BMC Public
Health, and they have not used these pieces of information as independent headers of abstract, and thus, we adhered to those published studies.

3) Abstract: Under 'Results', the authors state that "In ICU case studies, the expected odds ratio (OR) of death among patients with underlying heart disease or renal disease to patients without such comorbidities was less than 1.0, while the OR was greater than 1.0 in studies with other types of designs. This sentence is not very clear. It would be easier to present the actual ORs with their 95% CI.

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We agree and the corresponding part was corrected accordingly (P3L46-L48).

4) Methods: While the authors state that this systematic review was performed in accordance with PRISMA guidelines, they appear to have missed a few points on the PRISMA checklist. It would improve this manuscript significantly to address all of them. For example, was a protocol registered for this review (PRISMA checklist #5)? List the objectives of the review using the PICO framework (PRISMA checklist #4).

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We thank the reviewer for raising these important points. We have added a protocol summary to the revised manuscript. Moreover, PICO is now clarified in Methods (P5L103-L107).

5) Methods: Were any non-English language manuscripts identified? Were translations obtained? Or did the authors limit studies to English language studies only? If so, given that the MERS primarily affected non-English-speaking countries, could it be possible that some potential studies may have been missed?

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We added a sentence “We restricted ourselves to publications written in English” to Methods section (P6L123). At the same time, it is true that we missed a few non-English manuscripts and that point was highlighted as one of limitations (P12L283-L285).

6) Methods (Data extraction and analysis): The authors do not state if they used a Fixed Effects or a Random Effects inverse variance weighted model. This is important to mention; please add.

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We added a corresponding sentence accordingly (P7L159).

7) Results: The numbers described in the first paragraph of the 'Results' do not match what has been presented in Figure 1. The Results section states that "Among 571 potentially relevant articles, 547 and 13 articles were excluded". However, Figure 1 shows 575 articles being excluded after screening of titles of 599 potentially eligible articles. Please clarify. Also, please
add an additional compartment to the flow chart indicating how many studies were included in the meta-analysis.

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We apologize for the confusion. Our update of the numbers in manuscript was insufficient. Figures in Figure 1 are correct, and the numbers in the revised manuscript reflect correct ones (P8L168). Also, we mention that all included articles were subject to meta-analysis (P8L171-L172).

8) Figures: The text on some of the forest plots are barely legible. Please consider providing higher quality images for the forest plots. This could potentially be an important systematic review and I do believe that by using the PRISMA guidelines and making sure that this review conforms to them, this review can be improved substantially.

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We thank the reviewer for this suggestion. We will make sure that all the figures will be published in good resolutions.

[Response to Reviewer 2]

Interesting analyses of the information. The major concern for me is (as the authors conceded) that some cases were at least more than once. This could have been 10%-20%. Using data generated by others and combining them to form a consistent report is difficult. Multiple counting of cases weakens any article statement. How can this be minimized? What is an acceptable amount/percent of multiple counting?

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We agree with the reviewer that the overlap of cases in Korea has had an impact on pooled estimate of the case fatality or the risk of ICU admission. Rather than pooled estimate, we value the present study by presenting country-specific differences in ascertainment biases: Korea with lower CFR compared to estimates in the Middle East. This point has been emphasized in P12L278-L280. Moreover, possible idea to avoid multiple counting of cases was mentioned from P12L280-L283.

[Editorial policies]

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For the 'Availability of data and materials' section, please provide information about where the data supporting your findings can be found. We encourage authors to deposit their datasets in publicly available repositories (where available and appropriate), or to be presented within the manuscript and/or additional supporting files. Please note that identifying/confidential patient data should not be shared. Authors who do not wish to share their data must state that data will not be shared, and provide reasons for this in the manuscript text. For further guidance on how to format this section, please refer to BioMed Central's editorial policies page - http://www.biomedcentral.com/submissions/editorial-policies#availability+of+data+and+materials.

Declarations

- Ethics approval and consent to participate
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- Availability of data and materials
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- Funding
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We have ensured that all these subsections are documented from P13-P15.