PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors and prognosis for COVID-19-induced acute kidney injury : a meta-analysis
AUTHORS	Lin, Lirong; Wang, Xiang; Ren, Jiangwen; Sun, Yan; Yu, Rongjie; Li, Kailong; Zheng, Luquan; yang, jurong

VERSION 1 – REVIEW

REVIEWER	Hamid Nasri Professor of Clinical Nephropathology Department of Nephrology Division of Nephropathology Isfahan University of Medical Sciences Isfahan, Iran
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	Dear authors, Since you conducted your best efforts, however, the paper is not fully up to date. Please take account to the following items; 1- Regarding the sex difference, it was not discussed well. I found the recent paper on this subject. Please see and extend your paper by its content(cite): Zununi Vahed S, Ghiyasvand S, Tolouian R, Noshad H, Tolouian A, Mohajel Shoja M, Ardalan M. The footprint of androgen sensitive serine protease (TMPRSS2) in gender mortality with COVID-19. Immunopathol Persa. 2020;6(2):e27. DOI:10.34172/ipp.2020.27 2- regarding renal involvement, you explained well the tubular involvement and ATN. However on glomerular involvement it is very waek. Thus please see the following recent articles; Yin W, Zhang PL. Infectious pathways of SARS-CoV-2 in renal tissue. J Nephropathol. 2020;9(4):e37. DOI: 10.34172/jnp.2020.37. Mubarak M, Tolouian R, Pezeshgi A. Collapsing glomerulopathy following COVID-19 infection; possible relationship with APOL1 kidney risk alleles in African-Americans. Immunopathol Persa. 2020;6(2):e18. DOI:10.34172/ipp.2020.18. 3- in your paper however, all etiologies of renal involvement was not well described. please accordingly see the following paper, particularly its table to expand your paper; Yalameha B, Roshan B, Bhaskar LVKS, Mohmoodnia L. Perspectives on the relationship of renal disease and coronavirus disease 2019. J Nephropharmacol. 2020;9(2):e22. DOI: 10.34172/npj.2020.22

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

	4- finally the discussion on ACE2 was not satisfactory, since the following paper i

REVIEWER	Sohail Abdul Salim UMMC USA
REVIEW RETURNED	19-Jul-2020

GENERAL COMMENTS	1. Needs English editing with a professional editor. 2. Please add the following reference in page 4, paragraph 3, line 49 Survival rate in acute kidney injury superimposed COVID-19 patients: a systematic review and meta-analysis, Renal Failure, 42:1, 393-397. 3. What was your criteria to define " Severe COVID-19". Please mention that if possible in the paper. 4. Page 20 Table 2 Line 64 and 65 shows a study by Sachin J Shah and Ahmad Khan. Could you send the reference to these manuscripts? 4. Have you included studies that are not published but in review stages in your meta-analysis? If yes please let us know what studies are not yet published 5. Study by Raef Fadel line no 70 Table 2 Page 21: Fadel study had 355 patients total including 214 floor and 141 icu pts. So why did you skip ICU patients? Why are only 213 patients included? 6. Some of the included studies have not mentioned whether CRRT or intermittent HD was used. How do you justify assuming that all these studies have included patients only on CRRT and not IHD in your analysis?. For Example, Page 20 line 72 Table 2 shows a study by Leonidas. Leonidas Paper does not mention CRRT but RRT. So please explain?

VERSION 1 – AUTHOR RESPONSE

Reply to the comments from Reviewer #1:

Thank you very much for your thoughtful comments.

1. Regarding the sex difference, it was not discussed well. I found the recent paper on this subject. Please see and extend your paper by its content (cite): Zununi Vahed S, Ghiyasvand S, Tolouian R, Noshad H, Tolouian A, Mohajel Shoja M, Ardalan M. The footprint of androgen sensitive serine protease (TMPRSS2) in gender mortality with COVID-19. Immunopathol Persa. 2020;6(2):e27. DOI:10.34172/ipp.2020.27.

Response: We have added an explanation of sex differences in COVID-19 infection in the Discussion section, according to your suggestion. Higher rates of smoking and alcohol consumption, and biological differences in immune systems could make males more vulnerable to COVID-19. The role of androgen-responsive elements (AREs) of the transmembrane serine proteases type II (TMPRSS2) gene as one of the major players of male dominancy in severe COVID-19 infection has been underappreciated. Androgen response elements (AREs) of the TMPRSS2 gene are responsible for

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

higher expression of the TMPRSS2 enzyme on the epithelial cell membranes of the respiratory system. The TMPRSS2 enzyme facilitates the non-endosomal entry of SARS CoV-2 into the lung tissue.

2. Regarding renal involvement, you explained well the tubular involvement and ATN. However on glomerular involvement it is very weak. Thus please see the following recent articles;

Yin W, Zhang PL. Infectious pathways of SARS-CoV-2 in renal tissue. J Nephropathol. 2020;9(4):e37. DOI: 10.34172/jnp.2020.37.

Mubarak M, Tolouian R, Pezeshgi A. Collapsing glomerulopathy following COVID-19 infection; possible relationship with APOL1 kidney risk alleles in African-Americans. Immunopathol Persa. 2020;6(2):e18. DOI:10.34172/ipp.2020.18.

Response: We have added an explanation of glomerular involvement in patients with COVID-19 in the Discussion section, according to your suggestion. SAR-CoV-2 can directly infect glomerular endothelia, podocytes, and renal tubules, causing dominant findings of acute tubular injury and occasionally, collapsing focal segmental glomerulopathy in the kidney tissue. Renal biopsies in patients with COVID-19 have shown global collapse of the glomerular capillary loops accompanied by hyperplasia of overlying glomerular epithelial cells, many of which contain abundant eosinophilic intracytoplasmic protein droplets. Collapsing glomerulopathy (CG) is being increasingly reported in African-American patients with COVID-19 infection. It is possible that CG following COVID-19 infection in this population may be linked to underlying APOL1 kidney risk alleles, which are not uncommon in this ethnic group. This lesion should be considered in the differential diagnosis of rapidly declining renal function in association with heavy proteinuria in

the setting of COVID-19 disease, especially in patients of African ancestry.

3. In your paper however, all etiologies of renal involvement was not well described. please accordingly see the following paper, particularly its table to expand your paper;

Yalameha B, Roshan B, Bhaskar LVKS, Mohmoodnia L. Perspectives on the relationship of renal disease and coronavirus disease 2019. J Nephropharmacol. 2020;9(2):e22. DOI: 10.34172/npj.2020.22

Response: We have added an explanation of the etiologies of renal involvement in patients with COVID-19 in the Introduction section, according to your suggestion. The cytokine storm syndrome involved in the pathogenesis of acute respiratory distress syndrome (ARDS) and the failure of various organs during SARS-CoV infection seems to be related to an enormous inflammatory reaction. Viral replication in targeted organs, including the kidneys, induces systematic viral sepsis and inflammatory

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

responses, and subsequently damages cells in multiple organs. In addition, renal failure in patients with COVID-19 may occur due to rhabdomyolysis, hypoxemia, dehydration, presence of underlying diseases, and improper consumption of non-steroidal anti-inflammatory drugs.

4. Finally, the discussion on ACE2 was not satisfactory.

Response: We have added an explanation of ACE2 in patients with COVID-19 in the Discussion section, according to your suggestion. SARS-CoV-2 enters cells using the ACE2 receptor and cellular transmembrane serine proteases (TMPRSSs) as co-receptors, and TMPRSSs activate the spike protein of the viral surface for membrane fusion into host cells. Single-cell RNA sequencing analysis of kidney cells has revealed that ACE2 is expressed along with TMPRSSs in proximal straight tubule cells and podocytes, indicating that the kidney cells are exposed to SARS-CoV-2 infection.

Reply to the comments from Reviewer #2:

Thank you very much for your thoughtful comments.

1. Needs English editing with a professional editor.

Response: Based on your suggestion, we have invited two professional editors, both native speakers of English, to review and correct our manuscript.

2. Please add the following reference in page 4, paragraph 3, line 49.

Response: Thank you for your suggestions. We have added the reference on page 4, paragraph 3, line 49.

3. What was your criteria to define "Severe COVID-19?" Please mention that if possible in the paper.

Response: Thank you for your suggestions. We have added criteria defining severe COVID-19. Stages of disease severity were determined according to the guidelines for diagnosis and treatment of COVID-19 published by NHC China on February 18, 2020 (6th Edition).[16] A severe case was defined as having either: (1) a respiratory rate > 30/min, or (2) an oxygen saturation ≤ 93%, or (3) a PaO_2/FiO_2 ratio ≤ 300 mmHg. Lung imaging showed that the lesions progressed more than 50% within 24–48 hours.

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

4. Page 20 Table 2 Line 64 and 65 shows a study by Sachin J Shah and Ahmad Khan. Could you send the reference to these manuscripts?

Response: Please see the references to these manuscripts listed below.

Sachin J Shah, Peter N Barish, Priya A Prasad, et. al. Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: a comparison of patients with and without COVID-19. MedRxiv 2020 May 6;2020.05.02.20082461. doi: 10.1101/2020.05.02.20082461. Preprint.

Ahmad Khan, Arka Chatterjee, Shailendra Singh. Comorbidities and Disparities in Outcomes of COVID-19 Among Black and White Patients. medRxiv preprint doi: https://doi.org/10.1101/2020.05.10.20090167.

5. Have you included studies that are not published but in review stages in your meta-analysis? If yes please let us know what studies are not yet published

Response: The articles used in our meta-analysis were identified by comprehensive searches in PubMed, Embase, CNKI, and MedRxiv online databases.

6. Study by Raef Fadel line no 70 Table 2 Page 21: Fadel study had 355 patients total including 214 floor and 141 icu pts. So why did you skip ICU patients? Why are only 213 patients included?

Response: The Fadel study is a multicenter clinical study of 213 patients. The reference is: Early Short Course Corticosteroids in Hospitalized Patients with COVID-19.medRxiv preprint doi: https://doi.org/10.1101/2020.05.04.20074609.

7. Some of the included studies have not mentioned whether CRRT or intermittent HD was used. How do you justify assuming that all these studies have included patients only on CRRT and not IHD in your analysis? For Example, Page 20 line 72 Table 2 shows a study by Leonidas. Leonidas Paper does not mention CRRT but RRT. So please explain?

Response: Thank you for your suggestion. The data we show in Table 2 include patients who underwent renal replacement therapy, including RRT and CRRT. We modified this point in the manuscript, based on your suggestions. At the same time, we also provide an analysis of CRRT treatment of severe and non-critical patients in Figure 3.

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

VERSION 2 – REVIEW

REVIEWER	Hamid Nasri Department of Nephrology, Division of Nephropathology, Nour Medical, Educational & Therapeutic Center, Isfahan University of Medical Sciences Isfahan, Iran. Email: hamidnasri@med.mui.ac.ir,
REVIEW RETURNED	07-Sep-2020

GENERAL COMMENTS	Dear Editor-in-Chief, Thank you for sending the paper to re-check. I check. It is now suitable for publication. It should mention that, papers like this one on COVID-19 should publish soon, sine day by day new data are comming, thus the previous ones may become old Thank you

REVIEWER	Sohail Salim University of Mississippi Medical Center USA
REVIEW RETURNED	09-Sep-2020

GENERAL COMMENTS	I see that you have made significant changes to the manuscript incorporating all suggestions except for one issue. When including data in meta-analysis using studies that are not yet published and unreliable it is best to exclude those. But if you definetly want to use unpublished studies or data, you may include and then perform sensitivity analysis excluding data from medrxiv. That would be my recommendation.

VERSION 2 – AUTHOR RESPONSE

Reply to the comments from Reviewer #2:

Thank you very much for your thoughtful comments.

2. If you defiantly want to use unpublished studies or data, you may include and then perform sensitivity analysis excluding data from medrxiv.

Response: Response: Thank you for your suggestion. We carried out sensitivity analyses to identify possible studies explaining the heterogeneity. The exclusion of each study one at a time did not significantly alter the results or the heterogeneity for every factor.

Risk factors for COVID-19 in conjunction with AKI (Figure S1-3).

Incidence of need for CRRT during COVID-19 infection (Figure S4).

Prognostic analysis of COVID-19 combined with AKI (Figure S5).

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.

VERSION 3 – REVIEW

REVIEWER	Sohail Abdul Salim University of Mississippi Jackson MS USA
REVIEW RETURNED	04-Oct-2020

GENERAL COMMENTS	The author has implemented suggested revisions and included sensitivity analysis. I recommend acceptance and publication.

BMJ Open: first published as 10.1136/bmjopen-2020-042573 on 10 November 2020. Downloaded from http://bmjopen.bmj.com/ on April 19, 2024 by guest. Protected by copyright.