

# Comparative Profile for COVID-19 Cases from China and North America: Clinical Symptoms, Comorbidities and Disease Biomarkers

Alaa Badawi and Denitsa Vasileva

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## RESPONSE TO REVIEWERS AND EDITORIAL COMMENTS

### Authors' Comment

We thank the Reviewers and the Editor-in-Chief for the constructive comments. We sincerely believe that addressing these comments has significantly improved the manuscript. We have addressed every comment and answered every inquiry to the best of our abilities and within the scope of the study and the available information. Reviewers' and Editor-in-Chief 's Comments were faithfully copied and highlighted in red font (below) with our respective responses. All changes made to the manuscript have been highlighted in red font within the revised manuscript.

### Reviewers' Comments

**Specific Comments to Authors:** Thank you for the opportunity of reviewing this interesting research. This study evaluates the differences in profiles of clinical symptoms, comorbidities and disease biomarkers between China and North America. In principle the idea has merit; however, there are some issues with data affecting comprehensibility in full comparative profile.

#### *Major comments:*

1. Provide the details in search strategy and study selection, a PRISMA flowchart of study selection is recommended.

Response: PRISMA flowchart and PRISMA checklist have been added now into the revised version of the manuscript and a statement is added into the Methods section (first two lines). A Figure for PRISMA flowchart (Figure 1) is now added to the text.

2. Please define the timing of blood sample collection (on admission or otherwise?), the timing of classification of disease severity.

Response: Within the context of this study and giving its focus as well as given the fact that the analysis of the selected studies is presented in aggregates, it is not possible or rationale to provide the timing of blood collection, classification and admission.

3. How to assess the risk of bias in individual studies, and publication bias across the body of literature.

Response: We fully agree with the Reviewer's comment that bias analysis should have been explained and included. As suggested, tests for bias assessment are now mentioned in the study (Methods Section). The results are now detailed and presented in the supplementary

materials (Supplement Table 3). In this respect, we used Egger's test to examine the correlation between the effect size and its corresponding sampling variance in the individual studies. A statistical test of funnel plot asymmetry, such as Egger's test for continuous outcomes, assesses whether the association between effect estimates and standard error (which is related to sample size) is statistically significant. We used Kendall's tau with continuity correction test (Begg and Mazumdar correlation rank test) to test the correlation between the ranks of effect sizes and the ranks of their variances across the selected studies.

**4. How did you resolve the discrepancies in collected data.**

Response: the discrepancies in the collected data is resolved by the measures of heterogeneity analyses, i.e.,  $\tau^2$ , Q and  $I^2$ .

**5. The authors state "this observation was apparent in the cases from North America where patients with co-existing medical conditions were, on average, older (40 – 80 years) than their counterparts from China (18 – 75 years)", the subjects of this study are COVID-19 Adults Cases?**

Response: Indeed, only reports with adult cases were included. This statement is now added to the Methods Section, Paragraph 1, "Study Selection".

***Specific Points:***

**Introduction:**

1. The sentence " In December 2019, COVID-19 infection began to spread from Wuhan, Hubei, China where it was declared on January 30, 2020 as a public health emergency of international concern by the World Health Organization (WHO)" (Page3, line5) requires a reference

Response: A reference is added as suggested.

2. To date, the situation of COVID-19 pandemic has changed, the sentence "two of the most affected world populations with COVID-19" (Page4, line12) needs an update.

Response: The sentence is changed to "*highly affected populations*"

**Methods:**

3. Please define "Aggregated Dataset", Please elucidate the search strategy and study selection (databases? Study selection?), did you exclude the studies that examined populations were children or pregnant women?

Response: As stated in the original manuscript, the Aggregated Dataset of Clinical Outcomes for COVID-19 Patients is a publicly accessible dataset which aggregates data from published clinical studies and preprints released between December 2019 and April 2020 ([http://www.covidanalytics.io/dataset\\_documentation](http://www.covidanalytics.io/dataset_documentation)). As mentioned in the text, "*we excluded case reports and studies with patients from countries other than China, and North America*". A statement on the inclusion of report only with adult cases is now included in the revised version. There was no distinction for pregnant women.

4. Loss of smell and taste are two common symptoms of nervous system damage at a pooled prevalence of 35.04% (95% CI, 22.03%-49.26%) (Ibekwe TS, et al. Systematic Review and Meta-

analysis of Smell and Taste Disorders in COVID-19. OTO Open 2020:4:2473974X20957975. doi: 10.1177/2473974X20957975.), are there any differences between China and North America?

Response: We were bound by the data available in the examined studies. There was not enough data to permit a comparison in the loss of smell and taste between the two study regions.

5. Please define the time of clinical laboratory parameters. Significant differences between patients with severe or critical COVID-19 and non-severely ill counterparts were observed for liver enzymes, ALT and AST; kidney function parameters, urea and creatinine; biomarkers of myocardial function, troponin I and CK-MB; measures of coagulation, D-dimer. These laboratory parameters are used to diagnose liver injury, acute kidney injury, myocardial injury and pulmonary embolism. Would you add these laboratory tests results (including ALT, urea, troponin I, CK-MB, and D-dimer) in Table 4? Considered as a potentially fatal complication, acute pulmonary embolism (APE) is recommended to be added in Table 1 if possible.

Response: Again, as with the above comment, we were bound by the data available in the examined studies. There was not enough information or data to permit a comparison between the two study regions in the suggested parameters.

6. What's the mortality rate associated with COVID-19.

Response: The mortality rates are now included into the results section. The following statement is added *"From the selected reports, the mortality rates of COVID-19 ( $\pm$ S.D.) was  $5.9\pm13.4\%$  in China, not significantly different from rates of  $13.9\pm14.8\%$  in North America."*

7. Liver diseases including?

Response: In the studied database (i.e., Aggregated Dataset of Clinical Outcomes for COVID-19 Patients), Liver diseases are defined as "any". This is now added to the results section as *"(any, e.g., alcohol-related liver disease, hepatitis, cirrhosis, hemochromatosis, liver Cysts, non-alcoholic fatty liver disease)"* and to Table 3.

### Discussion:

8. The authors state "the frequency of case severity was significantly higher in North American than China..... This may be due to the higher rates of clinical symptoms such as dyspnea, myalgia, diarrhea and chills noted in the North American cases" (Page13, line12). Dyspnea is associated severe pneumonia or ARDS, however symptoms of myalgia, chills, diarrhea and are not specific symptoms for severity of COVID-19. Diarrhea may indicate an involvement in gastrointestinal tract, which can be find in most non-severe patients. Currently, there is no firm evidence to suggest that severity of digestive symptoms corresponds to severity of COVID-19 clinical course. I totally agree that more organs or system (such as liver, kidney, heart, and coagulation system) are involved and the possibility of severity increases.

Response: We thank the Reviewer for this comment. A statement to the effect of the mentioned clinical symptoms on disease severity (as per the Reviewer's comment and suggestion) is no mentioned in the manuscript. As per this comment, the following sentences were added the manuscript (page 13) *"Dyspnea is associated with severe pneumonia or ARDS whereas symptoms such as diarrhea may indicate an involvement in gastrointestinal tract,*

*particularly in patients with non-severe cases. Currently, there is no firm evidence to suggest that severity of digestive symptoms corresponds to severity of COVID-19 clinical course."*

9. A higher level of creatine kinase is due to a higher prevalence of chronic kidney diseases? How do you differentiate it from acute kidney injury (AKI)?

Response: the examination of the selected studies does not allow for answering the question related to the link between creatine kinase and chronic kidney disease nor it permits for differentiating it from acute kidney injury.

With regard to this comment and Comments 4 and 5 above, we want to stress on the fact that the findings of our study were only limited to the data available in the selected papers. Any further substantiation would not have been appropriate in the context of this study.

10. "Furthermore, the varied prevalence of comorbidities and status of healthcare services between China and North America may be other important factors affecting the COVID-19 profile" (Page16, line19) requires a reference.

Response: We thank the Reviewer for this comment. An additional reference is added as suggested [Gong X. The health care gap between China and America. Ann Transl Med. 2014 2(4):39. doi: 10.3978/j.issn.2305-5839.2014.04.04].

#### **4 LANGUAGE QUALITY**

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

Response: All language issues are now resolved.

#### **5 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

Response: None

##### **(1) Science editor:**

Scientific quality: The manuscript describes a meta-analysis of the comparative profile for covid-19 cases from China and North America. The topic is within the scope of the WJCC.

Response: None

##### **(1) Classification: Grade C;**

Response: None

(2) Summary of the Peer-Review Report: This study evaluates the differences in profiles of clinical symptoms, comorbidities and disease biomarkers between China and North America. The idea has merit. However, there are some issues with data affecting comprehensibility in full

comparative profile. Some references should be added. The questions raised by the reviewer should be answered.

Response: All Reviewers' comments were addressed and answered, and the suggested references are now added in the revised version.

**(3) Format:**

1. There are 4 tables and 1 figure. A total of 66 references are cited, including 38 references published in the last 3 years. There are no self-citations.

Response: To address Reviewers' comments, one additional Figure is added and two additional references.

**2. Language evaluation: Classification: Grade A.**

Response: None

3. Academic norms and rules: The authors provided the Biostatistics Review Certificate, and the PRISMA 2009 Checklist. No academic misconduct was found in the Bing search. However, the highest single-source similarity index showed to be 9% in the CrossCheck report. The authors need to rephrase the repeated parts.

Response: In fact, we checked the document repeatedly for plagiarism using online plagiarism checker. The entire document showed 100% unique content and 0% plagiarized content. We could not spot those 9% similarity and where from.

4. Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJCC.

Response: None

**5. Issues raised:**

(1) The "Author Contributions" section is missing. Please provide the author contributions;

Response: please check at the Editorial Office Director's Comment below. It states, "*The authors have written the "Author Contributions" section*". Indeed, Author Contribution is in the manuscript; last section.

(2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Response: As recommended, the two Figures are now attached as PowerPoint into the submission.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout.

Response: PMID and DOI numbers are added now to the references throughout – to the best of our abilities. Some references, however, do not have PMID and/or DOI (as known).

(4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text; and

Response: As suggested, “Article Highlights” section is now added at the end of the main text.

(5) The abstract should be an informative, structured abstract of no less than 350 words should accompany each manuscript. Abbreviations should be avoided, but if used should be spelled out at first mention. The 5 sections of the structured abstract are: Background, Aims, Methods, Results, and Conclusion. 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Response: The abstract has been restructured into the suggested section and expanded – to the best of our ability – to accommodate the needed number of words.

(2) Editorial office director: have checked the comments written by the science editor. This work was supported by the Public Health Agency of Canada. Please upload the approved grant application form(s) or funding agency copy of any approval document(s). The authors have written the “Author Contributions” section.

Response: The corresponding author is a Senior Research Scientist at the Public Health Agency of Canada (PHAC). By virtue of being affiliated with PHAC, all research work is supported by the Agency. No specific application form(s) or funding agency is available. This is an annual research fund provided to the Senior Author.

(3) Company editor-in-chief: have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors.

Response: All comments are addressed now to the best of our ability and all required documents are attached as per the Journal’s instruction.