

Response to comments

We would like to thank the Editors and Reviewers for taking the time to provide insightful inputs to our paper. In accordance with the suggestions, we have made changes to the manuscript. We look forward to your response and hope the revision will enable the acceptance of the manuscript.

Editor-in-chief:

- **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.**

Thank you. We have provided editable PowerPoint files for figures among our resubmission files.

- **Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.**

Thank you. We have updated the tables as per your instructions.

Science editor:

- **Please modify the article format according to the requirements of the journal, for example, the beginning of the paragraph should be uniform, and the font and label should be accurate.**

Thank you very much for the feedback. The format is changed accordingly.

- **Some descriptions of materials and methods are not professional enough, please correct them carefully.**

Thank you very much for your comment. Accordingly, we have expanded our Methods section to provide further information, which we think tremendously increased the quality of our manuscript. The Methods section in the revised version has a subheading named “*Study population and data collection*” which reads as follows:

“All subjects hospitalized with a COVID-19 associated indication (laboratory-confirmed or clinically diagnosed infection) at participating institutions were eligible for inclusion in the VIRUS: COVID-19 registry. The exclusion criteria for the VIRUS Registry study are non-COVID-19 related admissions, Minnesota patients who have not provided research authorization, and readmissions of already included patients. De-identified data were collected through Research Electronic Data Capture software (REDCap, version 8.11.11, Vanderbilt University, Nashville, Tennessee) and stored in a central database hosted by Mayo Clinic.”

With regards to the analysis for this particular study, all adult subjects admitted between March 15, 2020, and January 15, 2021, were screened for inclusion. Although enrolled in the VIRUS: COVID-19 registry, we excluded pediatric patients (<18 years old) from this project. Another exclusion criterion was patients enrolled from institutions reporting fewer than 65% of subjects with hospital discharge status. Since those participating centers were unlikely to represent a realistic distribution of outcomes, they were omitted as non-participating. After the application of exclusion criteria, patients of 143 participating hospitals in 21 countries were found to be eligible for inclusion. Detailed inclusion and exclusion criteria for the VIRUS Registry and this project is provided in Supplementary Figure 1.

The patients' residential addresses at the time of diagnosis were not accessible due to the de-identified database. As a surrogate, the location of the participating institutions, which was available for all enrolled patients, was used to determine geographical variables. Latitude and altitude information was retrieved from the Google Earth software. Based on their locations, subjects were grouped according to the elevation above the sea level and the distance from the Equator, regardless of the hemisphere of location. Baseline information and disease related specifics were gathered from the VIRUS Registry.”

– **The inclusion and exclusion criteria in articles should remain uniform.**

Thank you. While revising the Methods section we have grouped the inclusion and exclusion criteria for both the Registry as well as this study (please see our response to the above comment). Furthermore, we have included a new supplementary figure (Supplementary Figure 1) to provide further clarification.

– **Does "S. Figure, S. Table" mentioned in the results refer to supplementary figure and supplementary table? If yes, please provide relevant figures and tables.**

Thank you. The labels are updated as “Supplementary Figures (1 and 2, in the current version)” and “Supplementary Table” in both text body and legends.

– **The coverage of the discussion was too narrow to reveal the correlation between the outcome of the patients with COVID-19 and other factors.**

Thank you. We appreciate this constructive comment. Correspondingly, the Discussion section has been expanded with relevant information. Alongside other additions, we have included a new paragraph discussing the association of COVID-19 outcomes and certain factors. Below please find the newly added passage:

“Older age and certain comorbidities were shown to be associated with unfavorable disease outcomes for COVID-19 patients. Populations living in higher latitudes were shown to have a higher median age and more frequent comorbid conditions.

Furthermore, individuals living at higher elevations from the sea-level were shown to have less comorbidity burdens. Our study sample also noted a similar distribution of median age and comorbidities to different latitude and altitude levels.”

Reviewer #1:

- **The beginning of the paragraphs needs to be unified. Besides, adjustment of the manuscript writing is necessary.**
Thanks. The formatting has been changed to comply with the Journal guidelines.
- **Abstract: "(49-74)" should be rewritten as follows "(the age ranged from 49-74 year)"**
Thank you very much for indicating the ambiguous language. The statement has been updated as “(interquartile range: 49-74)”.
- **Materials and methods section: It is better to replace the word "sex" by "gender".**
Thanks. The term “sex” in the methods has been replaced by “gender”.
- **I see these sentences "Institutions reporting fewer than 65% of patients with hospital discharge status were omitted as non-participating because they were unlikely to represent a realistic distribution of outcomes. After the application of this rule, 143 participating hospitals in 21 countries were found to be eligible for inclusion". Should be moved and united with the inclusion and exclusion criteria.**
Thank you very much for your attentive review. The statement has been unified with other inclusion and exclusion criteria. Also, inclusion and exclusion criteria for the VIRUS Registry and for this specific project have been grouped together, and a new Supplementary Figure is included to provide further clarification (*Supplementary Figure I*).
- **It is better to write this abbreviation "m.a.s.l." as "MASL".**
Thanks. The abbreviation has been updated accordingly.
- **What you mean by " S.Figure, S.Table "?. Please clarify or numbering them similar to other figures and tables.**
Thank you very much for stating the confusing numbering with regards to figure and table legends. The labels are updated as “Supplementary Figure” and “Supplementary Table”.
- **These sentences were repeated "For Mortality, Odds Ratio (OR) are displayed per 10 degrees of latitude and 250 meters of altitude. For Hospital-free days, the estimate is the expected difference in mean days, similarly displayed per 10 degrees of latitude and 250 meters of altitude. Findings were adjusted for age, gender, race, body mass index, number of days with symptoms prior to admission, symptom groups, timing of admission, and comorbidities", in the materials and methods section and just below Table 2.**
Thank you very much for your careful review. The statements are compiled so as to be disclosed in the Materials and Methods section solely. The repetition has been deleted from the Table footnotes.
- **There is no mention of the factor "body mass index" in Table 1, despite, you mentioned it in the materials and methods section.**
Thank you for noticing the missing information. We have updated the table with relevant information.

- **Discussion: "report" in the first paragraph needs to change to "reported".**
Thanks. sorry for typo, it has been changed to ‘reported’.
- **I don’t see a discussion on all the studied socio-clinical factors and their relationship to the outcome of the patients with COVID-19.**
Thank you. We appreciate this careful observation. Correspondingly, the discussion section is updated with relevant information. The following passage was included:
“Older age and certain comorbidities were shown to be associated with unfavorable disease outcomes for COVID-19 patients. Populations living in higher latitudes were shown to have a higher median age and more frequent comorbid conditions. Furthermore, individuals living at higher elevations from the sea-level were shown to have less comorbidity burdens. Our study sample also noted a similar distribution of median age and comorbidities to different latitude and altitude levels.”
- **Supplementary table: a. Please rewrite it as " Supplementary Table: Distribution of subjects to the countries" b. It is better to add two columns, the Latitude and Altitude, to give an overview of these factors according to the mentioned countries.**
Thanks. The table headings are changed as per your suggestion. Many thanks for pointing out the missing information. Supplementary table is updated with location information.
- **SUPPLEMENTARY FIGURE, please rewrite it as "Supplementary Figure: Flowchart of included patients."**
Thanks. The expression is changed accordingly.

Reviewer #2:

- **No changes in atmospheric O2 are detectable at this altitude. How do you reconcile the increase in mortality between 125-145 masl? The number of patients above 1,500 masl must be minute to draw any meaningful conclusions.**
What is discussed as altitude is really not a real, O2-wise meaningful altitude elevation. To elicit physiological changes altitudes over 1,000 masl are required and in the current study it appears that the numbers of patients above this limit is very low.
Thanks. We agree with the Reviewer’s comment. In the discussion section, now we have included an explanation to the paragraph in which we address the altitude’s effect. The end of the paragraph reads as follows:
“Although our results might suggest an impact of different elevation levels on disease outcomes, not having enough variation in altitude to test the impact of atmospheric oxygen pressure impedes our ability to conclude the actual effect of higher altitudes. Thus, our analysis results should be interpreted with caution.”
- **The study included patients over a 10 month period, with 7 of those (March to September) with enough sunlight hours to allow for “normal” vitamin D-levels in the northern hemisphere.**

Thank you very much for providing the idea to improve our discussion. The statement is included in the limitations section, which, in the updated version, reads as follows:

“Furthermore, although it was suggested as a contributor to disease severity, especially in higher latitudes, vitamin D levels were not included in the analysis due to the unavailability of the data. However, the timing of the study encompassing enough sunlight hours for the Northern Hemisphere might mitigate this limitation’s impact.”

- **I think this is the most severe limitation. Extremely low numbers at geographical extremes makes it impossible to perform valid statistical calculations and draw meaningful conclusions. The altitude significances are not making sense at such low masl locations.**

Thank you very much for your valuable comment indicating this limitation’s importance. The inadequate variability in the elevation levels is now listed as the first and foremost limitation. The section now reads as follows:

“The most important limitation of our study was the small sample variety in lower latitude and higher altitude environments. Especially not having patients from a wide range of altitude levels precluded drawing definitive conclusions about the impact of higher altitudes.”