

HOWARD UNIVERSITY

College of Medicine
Department of Biochemistry &
Molecular Biology

July 24, 2023

Dear Editor,

I am writing to submit our modified article with a revised title "**Potential long-term neurological and gastrointestinal effects of COVID-19: A review of adult cohorts**" to *World Journal of Methodology*.

The article synthesizes findings from five studies and highlights the major symptoms of PASC, including anxiety, depression, dysphagia, dyspnea, and headache. The review also notes that most of the symptoms are neurological in origin and suggests the need for more research on African American patients, who have been underrepresented in the studies reviewed.

REVISIONS:

We have included the Core Tip in the revised manuscript. As per the reviewers' feedback, we modified (highlighted in **red text**) the title and streamlined the presentation of data for clarity as follows:

Reviewer #1: "The style of presentation by the Tables and Figures of this study is complicated and not standard. On the Table 2, fever is not GI and Neuro symptom. The percentage of symptoms shown on the Fig 3 is unclear as to whether it is the percentage of all symptoms or all patients. If the authors make a critical review and analyze data from all include studies, it will make this study more interesting. The information in this study is only descriptive data from the included studies".

Response #1: The figures that are presented with tables are meant to highlight the cardinal datasets extracted from the tables for quick reading and comprehension. The figures do not entirely duplicate the tables. It is true that "fever" is neither a neurological nor a GI symptom. We therefore, removed it from Table 2. In Fig. 3, we relabeled the legend as "**Percentages of PASC – GI/ Neurological symptoms in all patients of the five studies reviewed.**". We thank you for your insight.

Reviewer #2: 1. The title should mention the article type. 2. The number of words in the abstract should be revised. 3. The title of the manuscript is not corresponding to the aim of the manuscript. Why did the authors specifically study neurological and gastrointestinal complications of long-term COVID? Why were other systems not included? The authors should explain these questions in the introduction. 4. Methodology. a. It is advised to revise the article type. E.g., retrospective review. b. How was homogeneity assessed among the selected studies? c. What was the statistical software used? d. Logistic regression. Describe the model performed. Describe how the variables were chosen. 5. All the abbreviations should be fully described at first appearance. E.g., NEURO. 6. References should be revised. There are two types of references with different numbers of citations. 7. The articles should be properly referenced. Avoid PMID numbers. 8. Limitations. There was a significant difference among the studies. Minorities were less reported, which could affect data interpretation.



The studies were not particularly assessing the aim of this review. The reviewer would like to ask the authors to provide a clear explanation regarding the aim of the manuscript. In the present form, it isn't easy to understand why the authors studied this specific objective. I believe that this article would be of great interest to your readership, given the current focus on understanding the long-term effects of COVID-19. The insights presented in this review could potentially inform clinical care for PASC patients and pave the way for further research in this area especially as it relates to minority patients. Thank you for your suggestions.

Response #2: The title has been modified (see above). The number of words in the Abstract have been revised to less than 200. The format of the Abstract was altered to adhere to the journal's specifications. There are many reasons why we reviewed the long-term effects of neurological and GI symptoms in COVID-19 patients. The main reason is to understand the full spectrum of this evolving disease with regards to the various neurological and GI symptoms that can persist after the acute phase of the infection. This knowledge is crucial for providing appropriate medical care and support to patients. We also provided two additional statements (marked in red text) reflecting the importance of this study in the Introduction. We revised the title to reflect that this study was a review of the literature in an area that received scant research. We assessed the homogeneity of the five studies selected by clearly defining the specific inclusion and exclusion criteria (see Fig. 1). These criteria are well-defined and explicit, ensuring that the selected studies are relevant to the research question and have similar characteristics. We used SPSS and Excel statistical software to assess descriptive, parametric and non-parametric correlation and Chi-square tests as appropriate. The variables were chosen in line with the objectives of this study. This clarification was added in the Methods section. As suggested, all the abbreviations have been fully described at first appearance (marked by red text). References were also revised by removing duplicates and replacing PMID's with citation numbers. Thank you for pointing out this oversight. It is true that minorities were underrepresented in this review as mentioned in our Discussion. However, the review also highlighted the significant differences presented in the collected data of the five studies necessitating further exploration of the Long COVID experience across the US demographics. Thank you for your feedback.

Reviewer #3: Dear Authors, Thank you very much for this well-written manuscript, regarding an important topic with enormous healthcare implications. Please find below my comments and queries, pertaining to your manuscript: 1. Figure 1: Please include the exclusion criteria of the 1122 patients in the preselection phase to your flow chart and present them also in the text. 2. Statistical analysis: Please provide the statistical analysis used for the assessment of the studies quality and heterogeneity selected for this systematic review. 3. Table 1: Please explain the term PMID. 4. Figure 3: Please define if the percentages are referring to the overall 27,383 included to your review. 5. Figure 6: Please explain all the abbreviations used. 6. Discussion: you don't need to explain the term PASV again if there is already explained above. 7. Discussion: it is confusing to report that you started with 8 studies and then reduced to 5 because you have already mentioned your inclusion and exclusion criteria. This information does not belong to the discussion. Best Regards

Response #3: As per your suggestions, we included the exclusion criteria for the 1,122 articles in Fig. 1. These are also in the methods section. The statistical analysis used was explained in our answer to Reviewer 2's question above. Briefly, the determination of the variability among the results of individual studies to assess heterogeneity was based on chi-square distribution. This was the reason that we evaluated only five of the eight studies that were originally selected for this review and even whether statistical pooling of data was appropriate. We removed PMIDs and replaced them with citation numbers. Yes, the percentages in Fig. 3 are from the total number of patients (i.e., 27,383). In Fig. 6, all abbreviations have been spelled out. We removed the statement regarding the original 8 studies from the Discussion and made a statement to that effect in Fig. 1 (highlighted in red). "Reflex has been corrected to "Reflux". Thank you.

Reviewer #4: Summary: a Review-based study to report the incidence of neuro/GI Long COVID symptoms in US-patients. Major concern: In the conclusions section, the authors stated that this study demonstrated a positive correlation between neuro and GI symptoms. However, I found this study just to sum up and report the number of patients with neuro/GI symptoms, and did not find any analysis in the paper. Comments: 2. It is suggested to revise the manuscript for the minor typographical errors-for example: gastroesophageal reflex => reflux. 3. It is unclear why small case studies (with < 5 cases) were not included in the study. 4. (any study with all or most patients from Western countries including US minority populations). Including studies with non-US participants is acceptable only if the investigators had access to the data. However, this information has not been stated in the manuscript.

Response #4: The conclusion section has been revised. As suggested, we corrected typographical errors. Some off the minor studies were not included in the review because they had missing data. As for inclusion of international cohorts, this was not our intended purpose as we wished to focus on COVID-19 effects on the US population.

We would like to thank all the reviewers for their thoughtful suggestions and feedback. We would also like to thank the editors for your consideration of this revised submission of our manuscript. We have uploaded the revised manuscript in **Draft form** and **Clean version** for your perusal. We look forward to hearing from you.

Sincerely,

Dr. Zaki Sherif
Professor
Howard University College of Medicine
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College of Medicine
Department of Biochemistry &
Molecular Biology

August 9, 2023

Dear Editor,

We are responding to the additional questions raised by the reviewers of our paper "Potential long-term neurological and gastrointestinal effects of COVID-19: A review of adult cohorts" to *World Journal of Methodology*.

Specific Comments to Authors and Responses:

Question 1: Could the authors explain why they assessed COVID-related neurological and gastrointestinal symptoms? Why were not studied neurological and pulmonary symptoms? Or other combination?

Response 1: As we stated in our original rebuttal to this question, there are many reasons why we reviewed the long-term effects of neurological and GI symptoms in COVID-19 patients. The main reason is to understand the full spectrum of this evolving disease with regards to the various neurological and GI symptoms that were observed to persist in our Long-COVID (PASC) study participants after the acute phase of their infection. This knowledge is crucial for providing appropriate medical care and support to minority patients who were the main participants of our study. We also provided two additional statements in the Introduction reflecting the importance of studying the enduring neurological and GI symptoms in minority Long COVID patients who suffered disproportional affliction during the pandemic, which received scant research in the literature. It is true that minorities were underrepresented in the this review as mentioned in our Discussion. We are also reviewing other combinations of symptoms such as neurological and pulmonary symptoms or their variations. Comprehensive research in various symptom domains contributes to a holistic understanding of COVID-19 and its effects on human health.

Question 2: Please provide correct ORCID number of the corresponding author.

Response 2: ORCID for Zaki Sherif: **0000-0002-1772-7041** (<https://orcid.org/0000-0002-1772-7041>)

Question 3: Please upload the PDF version of a statement affirming that the statistical review of the study was performed by a biomedical statistician to the system.

Response 3: The statement and the file have been provided as requested.



Question 4: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as "Manuscript No. -Figures.ppt" on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Response 4: The changes have been made and the figures are now editable in Power Point slides.

Question 5: Please add page numbers of your manuscript to the last column of the table in the file "PRISMA 2009 Checklist" (not tick).

Response 5: Page numbers have been added.

Question 6: Please revise in the attached file "85475 Auto-edited" and reply within seven days, thank you! Only one file is available in F6publishing system, please upload all files with zip format, or send to me by email

Response 6: I sent the file to you by e-mail.

Sincerely,

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