

Reviewer A

Major:

1. Title- Instead of Psychiatric involvement- Please use inclusive term- Behavioral health, please make this edit throughout the manuscript (Eg: instead of Psychiatric illness- say- Behavioral Health issues)

Reply 1: Amended as suggested

2. Please include the % or number of some objective data in abstract background section to denote – how big is the problem?

Reply 2: Amended as suggested

3. Main Body- please use heading as Result

Reply 3: Amended as suggested

4. Line 50-51: Fatigue, headache are very generalized symptoms, not related with neuropsychiatry and attention disorder needs to be specified.

Reply 4: Amended as suggested

5. Line 89-95- have no information about Suicide, please consider deleting them

Reply 5: Thank you for your suggestion. According to this suggestion, we deleted it.

6. Please use- one term- as behavioral health- not psychiatric, not mental

Reply 6: Amended as suggested.

7. Line 101- how much increase, what %, in each sub-group, please go in a little bit of depth

Reply 7: Amended as suggested. Although data are very scarce, now more information is available.

8. Line 116- again how much increase, Odds Ratio, % increase, numbers please.

Reply 8: Amended as suggested. Although data are very scarce, now more information is available.

9. Line 121, you have not discussed anything on pathophysiology, how can you wrap up, please add more details or delete 121-123.

Reply 9: Amended as suggested. It is now deleted.

10. Your whole Neuroinflammation section starting at 124- is talking only about COVID-19, your manuscript title and aim is talking about long COVID-19, there is a huge mismatch, please rectify and make major changes

Reply 10: We thank the reviewer for his/her comment. Post COVID syndrome is of course very closely related to acute COVID-19. Data we could retrieve on neuroinflammation in post COVID syndrome are mostly published after the date of search, or analyze non-human beings (e.g. primates, mice). Still, as suggested by the Reviewer, and thanks to the Editorial team, that provided relevant literature to enrich this paper (see Editorial comment), we now included data on this specific topic and reorganized the section according to his/her suggestions. Now data are available in a continuum from acute covid to post-COVID syndrome. Thank to reviewer and editorial team suggestion, we are now more satisfied with the manuscript that has certainly improved for what pertains its completeness. We specified the reasons for adding this information from different papers now cited in the reference list in the Methods section.

11. Please provide a succinct conclusion- usually no citations needed there, your conclusion should not be more than 50-75 words, please re-write.

Reply 11: We thank the reviewer for his/her comment. Amended as suggested

12. Here is a good template to follow (even though you didn't do the systematic review - <https://pubmed.ncbi.nlm.nih.gov/32771837/>)

Reply 12: We followed the template as suggested by the reviewer

13. Please check the grammar thought-out paper

Reply 13: Thank you for your comment. Now the paper has been checked for grammar through-out.

Minor:

1. Line 73. 1th June, it should be June 1st, 2022.

Reply 1: Amended as suggested

2. Line 52 lung related symptom, defined it further

Reply 2: Amended as suggested

3. Line 57-58-seems to have affected massively.....it is grammatically incorrect

Reply 3: Now amended.

Reviewer B

On page 5, in paragraph ,“Several studies have been performed to examine the impact of the COVID-19 pandemic on the mental health of the general population while still few data are available concerning the mental health sequelae in the post-COVID syndrome and the correlation with increased suicidal risk.”. There are no bibliographical references. Two are recommended that have specifically worked on this aspect:

Irigoyen-Otiñano M., Nicolau-Subires E., González-Pinto A., Adrados-Pérez M., Buil-Reiné E., Ibarra-Pertusa L., et al. Characteristics of patients treated for suicidal behavior during the pandemic in a psychiatric emergency department in a Spanish province. *Rev de Psiquiatría y Salud Ment.* 2022 doi: 10.1016/j.rpsm.2022.03.004. ISSN 1888-9891.

Irigoyen-Otiñano M, Porrás-Segovia A, Vega-Sánchez D, Arenas-Pijoan L, Agraz-Bota M, Torterolo G, Sánchez-Cazalilla M, Fuentes-Casany D, Adrados-Pérez M, Puigdevall-Ruestes M. Psychiatric Emergencies and Suicide Attempts Before and During COVID-19 Lockdown in Spain. *Crisis.* 2023 Jan 13. doi: 10.1027/0227-5910/a000896. Epub ahead of print. PMID: 36637085.

On page 5, in paragraph, “Evidence on the increase in suicidal thoughts and behaviours is weak, except in young people, where a higher risk of suicidal behaviours is confirmed.” there is little bibliography so it is recommended to add more bibliography:

Llorca-Bofi V, Irigoyen-Otiñano M, Sánchez-Cazalilla M, Torterolo G, Arenas-Pijoan L, Buil-Reiné E, Adrados-Pérez M, Nicolau-Subires E, Albert-Porcar C, Ibarra-Pertusa L, Puigdevall-Ruestes M. Urgent care and suicidal behavior in the child and adolescent population in a psychiatric emergency department in a Spanish province during the two COVID-19 states of alarm. *Rev Psiquiatr Salud Ment.* 2022 Jun 15. doi: 10.1016/j.rpsm.2022.03.003. Epub ahead of print. PMID: 35755490; PMCID: PMC9212908.

The rest of the manuscript is correctly structured and clarifies the objectives of the research and its results. I recommend that you add a section on limitations and strengths of the study.

Reply: We thank the reviewer for his insightful and helpful references, which we added in the manuscript.

Reviewer C

Main Consideration

Introduction

1. The introduction does not clearly explain why it is only for "post-COVID syndrome".

Reply 1: We thank the reviewer for his comment. To concentrate on post-COVID syndrome was an Editorial choice that was shared with the working and writing group. This choice was motivated by the interest on the potential long-term consequences of the COVID-19 pandemic. Moreover, the reviewer can find a large continuum between acute and post-COVID syndrome in the manuscript.

2. Lines 62-63: "Previous literature described evidences of long-lasting neuropsychiatric consequences after viral infections (11), and indeed a possible role of COVID-19 as a trigger of neuropsychiatric impairment is under investigation". Besides this, there are many similar articles reviewing post-COVID syndrome and suicide risk (e.g., PMID: 33486531, 34994790, 36556240, 34976149, 36321004, 36192553). How does this review differ from previous reviews? What does this review add to existing knowledge? Please cite similar reviews for comparison and state this clearly to avoid confusing readers.

Reply 2: We extend our appreciation to the reviewer for their insightful comment. In response, we have included more articles from their suggested list, enriching the overall content and completeness of our paper. The unique aspect of this review is its infectious disease perspective within the context of distinctive public health circumstances. Additionally, we have incorporated data on neuro-analysis, particularly addressing neuroinflammation in both acute and post-COVID-19 syndrome. Furthermore, our study encompasses a comprehensive analysis, resuming available evidence on behavioral health issues in COVID and post-COVID syndrome. That view is shared by the Editorial team, that provided relevant literature to enrich this paper (see Editorial comment).

Main Body- 1) Suicide and post COVID-19 syndrome

3. Lines 97-98: "while still few data are available concerning the mental health sequelae in the post-COVID syndrome and the correlation with increased suicidal risk". This contradicts what was mentioned in the introduction (lines 59-60).

Reply 3: We thank the reviewer for his/her comment. Now the whole paper is more homogenous.

4. The section is brief and the discussion is not in-depth enough. Since the purpose of this article is to review the relationship between post-COVID syndrome and suicide risk, it is suggested that the authors could explore the factors that influence suicide after infection with COVID. For example, different populations (health care workers, adolescents, women), different countries (policy, culture, health care system), history of illness, economic level (unemployed), mental health, history of suicide, family (violence, childhood shadows), alcohol consumption, drug use, etc.

Reply 4: We thank the reviewer for his/her suggestion. As for it is disclosed in the methods section, we focused on the potential role of COVID related issues in driving behavioral health complications, and the potential role of neuroinflammation. Still, thanks to reviewer suggestion we now included a more in-depth discussion, touching on different factors that we did not consider initially, and we think that thanks to these suggestions the narrative review is now more complete.

5. It is also suggested that the authors could discuss the reasons why similar studies have reached different conclusions. For example, studies conducted in Japan have shown a significant increase in suicide rates; could this be related to the higher number of people living alone in Japan (prone to loneliness, which raises the risk of depression, anxiety, and even suicide)?

Reply 5: We express our gratitude to the reviewer for their suggestion. To the best of our knowledge, we currently lack similar data that the reviewer could recommend citing relevant papers. It would be highly beneficial if the reviewer could provide specific references to enhance the depth and relevance of our paper.

6. In addition, it would be more meaningful to summarize the available post-COVID syndrome suicide prevention measures. The conclusion only briefly mentions some of them.

Reply 6: We thank the reviewer for his/her comment. We added a comment on this.

7. Given the clinical condition of post-COVID syndrome mentioned in the introduction, it is recommended the authors also report the duration when citing the literature, i.e., how long do patients remain suicidal after COVID infection?

Reply 7: We thank the reviewer for the suggestion. No consensus exists upon this from the data we could retrieve. To the best of our knowledge, we currently lack similar data that the reviewer could recommend citing relevant papers. It would be highly beneficial if the reviewer could provide specific references to enhance the depth and relevance of our paper. We included a comment on this lack of consensus.

8. It is highly recommended that the authors draw a table to summarize the main findings for the convenience of the reader.

Reply 8: We thank the reviewer for his/her comment. Given the narrative nature of this review, there is no obligation to summarize findings in the manner typically seen in systematic reviews. Methodologically, such an approach would not be deemed appropriate from our perspective, specifically in view of the very high heterogeneity of data we could retrieve.

More discussion, deeper thoughts.

Main Body- 2) Neuroinflammation, COVID-19 and psychiatric involvement

9. Why not about "post COVID syndrome"?

Reply 9: we now included post COVID syndrome in the title, and in the text.

10. Why discuss only neuroinflammation as a mechanism (also only "neuroinflammation" or "hyperinflammation" was searched in the Methods)? It is suggested that the authors list the existing relevant neurobiological mechanisms and explain each one in relation to suicide (whether supported by clinical data or not). I do believe that this would help the readers to have a comprehensive understanding of the field rather than a one-sided one.

Reply 10:

We thank the reviewer for his/her comment. We restructured the paper accordingly.

11. It is recommended to include a separate section on the STRENGTHS and LIMITATIONS of this review to promote a more intellectual interpretation.

Reply 11: we included a section on strengths and limitations.

Minor Suggestions

Methods

12. Line 29: "A search was run on PubMed using the appropriate mesh terms". However, the MeSH terms are not seen in the detailed search strategy provided in the method (lines 73-77).

Reply 12: We thank the reviewer to his/her comment. We are not able to include all mesh terms in the abstract, as it is requested from the journal to include a 250-300 words abstract. Search strategy is further defined in the method section.

13. Table 1-Date of Search "01 July 2022": should it be "Initial search on June 1, 2022, update search on July 1, 2022"?

Reply 13: We thank the reviewer for his/her comment. That was a typo, we amended the text.

14. Reference 31 is a case series. Did the authors perform a supplemental search? If so, please indicate it in the Methods.

Reply 14: We thank the reviewer for his/her comment. That was a case series we used for comparison (post mortem findings) and not an article retrieved by the initial search strategy. Similarly, the Editorial team provided relevant literature to enrich this paper (see Editorial comment).

Reference & Citations

15. Lines 41-43: "Generally speaking, the definition of 'long COVID' has been proposed to identify signs and symptoms that continue or develop after acute COVID-19 (2)". It is suggested the authors consider updating the reference from the clinical case definition established by the WHO: "post-COVID-19 condition occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include, but are not limited to, fatigue, shortness of breath, and cognitive dysfunction, and generally have an impact on everyday functioning".

- Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV; WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis.* 2022 Apr;22(4):e102-e107.

Reply 15: we thank the reviewer for his/her suggestion. We included the updated definition.

16. Lines 96-97: "Several studies have been performed to examine the impact of the COVID-19 pandemic on the mental health of the general population". Please add citations.

Reply 16: We thank the reviewer for the comment. We added relevant citations.