PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Thematic analysis to explore patients' experiences with long COVID-19: a conceptual model of symptoms and impacts on daily lives
AUTHORS	Rofail, Diana; Somersan-Karakaya, Selin; Choi, Julia; Przydzial, Krystian; Zhao, Yuming; Hussein, Mohamed; Norton, Thomas; Podolanczuk, Anna; Mylonakis, Eleftherios; Geba, Gregory

VERSION 1 – REVIEW

REVIEWER	Dharmendra Singh Hamdard Institute of Medical Science and Research, General Medicine
REVIEW RETURNED	20-Aug-2023

GENERAL COMMENTS	This is a well-done study, and I've included a separate review file. Abstract section: add saturation analysis details to the abstract, and abbreviate the conclusion section. For research ethics: My one significant criticism is that the Hospitailsed acute COVID-19 exclusion criteria don't reflect back on the methods and results, but rather the opposite. references no: 2, 18, 28, and 38 need minor changes as suggested in the attached file. Some minor comments are made in the remaining review.

REVIEWER	Bárbara Olivan-Blázquez Universidad de Zaragoza, Department of Psychology and Sociology.
REVIEW RETURNED	24-Aug-2023

GENERAL COMMENTS	Thank you for giving me the opportunity to review this article, which deals with a very interesting and useful topic to delve into the pathology of persistent covid. However, it would be necessary to clarify some aspects to improve its quality. I will now proceed to make some comments or considerations in the hope that they will be useful to the authors. Title: Perhaps it is not relevant to use the word results in the title, since original research articles present results. Abstract: it is not clear in the abstract the part of the systematic review study, nor the results in relation to the disease model obtained. Bullet points: Since the systematic review part is not clear beforehand, it is complicated for the reader to understand the first point presented. The second point presented as a bullet point, given the speed with which it is published in relation to persistent covid, has become obsolete, since there are several articles that use qualitative methodology. On the other hand, it is presented as a limitation that mainly women participate in the study, but the pathology affects mostly women, and it would have been desirable

	to slightly increase the sample of men so that the percentage of affectation by gender would have been representative. Introduction: The introduction is well constructed and written, following an adequate thread. Methodology: The systematic review study of the subject is not clear, since later its use is not detailed when constructing the model, and therefore this part is hardly replicable. On the other hand, in any research study that is carried out, in order to have a good theoretical framework and as a basis for the study, an information search is carried out beforehand, which can be more or less systematic. It is not clear whether this bibliographic search (which can be carried out as a systematic search) is what the authors explain in this section. On the other hand, it would not be necessary to place a time limit of ten years on the search, since the disease has not existed for such a long time. Regarding the qualitative part, the interviews with patients were conducted online, and the interviews with professionals were conducted by telephone. Why were they conducted telematically, and could this have affected the results? On the other hand, it would be necessary to specify what was the topic list (script of open questions asked) to know the depth of the interviews. The authors can show it in a table if they consider it appropriate. Did the authors ask about the intensity of the symptoms? This aspect is essential to understand the dimension of the persistent covid disease, and to include it in the model. In relation to the analysis it would be necessary to include more information such as whether the coding was established a priori or whether grounded theory or some other theory was used for data analysis. Did these diseases appear after covid-19 infection? Results: Regarding the results of the qualitative study, It would be necessary to go deeper into the model obtained. On the other hand, all the quotes shown belong to female patients. There was nothing differential in the discourse of men and women? It would be interesting if this could be explored further. The authors have used numerous quotes or literal quotations to illustrate the results obtained; however, this sometimes complicates the reading of the results. The authors could consider the possibility of putting the quotes in a table ((specifying scope to which they refer in one column and in another column, the qoutes). The words "difficulties finding the right word" can be substituted for verbal fluency. Discussion and conclussions: It would be necessary to go deeper into the discussion about the proposed model since it is the novelty of this study and it is hardly discussed. The conclusions that are shown are not specifically conclusions of the study carried out. Tables: In Table 1 it would be convenient to, at least, show the p-value in the comparison between the participants coming from the different recruitment methods. In table 2, the word "solo" appears.(Solo private practice). is it a mistake? Figures: Figure 2 shows the model obtained but perhaps it would be more interesting to show another figure that presents the interdependence of the different areas. Since it is a relevant result of the study, perhaps another more complete and complex figure could be made.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 Comments

This is a well-done study, and I've included a separate review file.

We thank Reviewer 1 for their positive response to our manuscript. We have included point-by-point responses here to Reviewer 1's main comments as well as those provided in the separate review file.

Abstract section: add saturation analysis details to the abstract.

We thank the reviewer for this suggestion. In the 'Participants' section of the abstract, we have added the following sentence (page 3):

'Concept saturation was also assessed.'

In the 'Results' section of the abstract, we have added the following sentence (page 4):

'Saturation was achieved for the reported impacts.'

Abstract section: abbreviate the conclusion section.

We have revised the Conclusions sections as follows (page 4):

'The conceptual model, developed based on patient experience data of long COVID-19, highlighted numerous symptoms that impact patients' physical and mental wellbeing, and suggest humanistic unmet needs. Prospective real-world studies are warranted to understand the pattern of long COVID-19 experienced in larger samples over longer periods of time.'

For research ethics: My one significant criticism is that the Hospitailsed acute COVID-19 exclusion criteria don't reflect back on the methods and results, but rather the opposite.

We thank Reviewer 1 for pointing out this discrepancy. This was an oversight on our part. The most recent study eligibility criteria did not exclude patients who were hospitalised during the initial COVID-19 infection. This exclusion criterion had been removed from our study due to difficulties with patient recruitment. We have revised the supplemental materials accordingly.

References no: 2, 18, 28, and 38 need minor changes as suggested in the attached file.

These changes, listed individually below, have been actioned.

Some minor comments are made in the remaining review.

We thank Reviewer 1 for this feedback; each point is addressed below.

Page 1 keywords, INFECTIOUS DISEASES

Please write in lower case, Please confirm it's the appropriate MeSH search word or it needs replacement.

Please note that the keywords were selected from a list provided within the manuscript submission site. If possible, we will change to lower case letters when resubmitting the manuscript.

Page 3 word count. Word count: 4860/4000 words.

Word count is more than allowed, please try to concise material and methods, and results section.

We have revised text in the Methods and Results. In addition, at the suggestion of Reviewer 2, we have placed the quotation text in new Tables 3 and 4. However, additional text has been added to provide clarification, at the request of the Reviewers. Therefore, we have also moved some of the text from the Methods section to the Supplement to reduce the overall word count to 4091 after addressing the Reviewer comments.

Page 5,6 Abstract

Add saturation analysis details to the abstract part, and abbreviate the conclusion section.

This comment has been addressed above.

Page 8, line 23

Written: National Institute for Health Excellence (NICE)
Suggest: National Institute for Health and Care Excellence (NICE)
Revised as suggested (page 6).

Page 9, lines 49-51
Written: Trouble speaking, and memory, concentration or sleep problems
Suggest: Trouble speaking, memory, concentration, and/or sleep problems
Revised as suggested (page 6).

Page 9, line 13
Written: From 8 to 57%
Suggest: From 8% to 57%
Revised as suggested (page 7).

Page 11, lines 13-16
An electronic search was performed using PubMed to identify qualitative papers exploring the patient experience of long COVID-19 in the last 10 years.
When the COVID-19 infection has only been present for a little over 4 years, why was a duration of 10 years considered?
We have amended the relevant text in the Methods, as follows (page 9):
'An electronic search was performed on July 23, 2021 using PubMed to identify qualitative papers published up to that date that explored the patient experience of long COVID-19.'

Page 11, line 43
Pharmaceuticals Inc.'s clinical trial programme (COV-2066) in hospitalised participants (NCT04426695)
But as per exclusion criteria:
Point 2: patient was hospitalised during initial COVID-19 infection need to be excluded.
Please confirm whether hospitalised patients were excluded or included. Change in methodology or results will be needed accordingly
As described in more detail above, we have removed the exclusion criterion relating to hospitalisation during initial COVID-19 infection from the supplemental materials. Patients who were hospitalised during the initial COVID-19 infection, such those who participated in the COV-2066 trial, were eligible to enrol in our study.

Page 18, line 49
They also reported that a small number of patients who presented with severe respiratory symptoms were hospitalised, but as per exclusion criteria:
Point 2. Patient was hospitalised during initial COVID-19 infection need to be excluded.
Please confirm whether hospitalised patients were excluded or included. Change in methodology or results will be needed accordingly
As described in more detail above, we have removed the exclusion criterion relating to hospitalisation during initial COVID-19 infection from the supplemental materials. Patients who were hospitalised during the initial COVID-19 infection, such those who participated in the COV-2066 trial, were eligible to enrol in our study.

Page 18, lines 54-56
Clinicians suggested that most symptoms would eventually resolve, though they found it challenging to say exactly when this would happen.
It should be a part of discussion not results.
We have rephrased this sentence to clarify that symptom resolution was part of the clinician interview and therefore is included in the Results section (page 17).

‘During the interviews, clinicians suggested that most symptoms would eventually resolve, though they found it challenging to say exactly when this would happen.’

Page 26, line 41
Written: however, this study highlighted the emphasis on longer-term impacts.
Suggest: however, this study highlighted the emphasis on long-term impacts.
Revised as suggested (page 27).

Page 26, lines 41-46
As the impacts of daily living occurred simultaneously with symptoms, one might infer that by reducing symptoms and/or their severity there might in turn also be a reduction of some, if not all, impacts.
Consider rephrasing
Thank you for the suggestion. We have rephrased this sentence as follows (page 27):
‘A reduction in the number and/or severity of symptoms may mitigate the negative impact of long COVID-19 on patient health-related quality of life.’

Page 32, line 15
Ref 2: Suppl 1:S93-S99.
Suggest: Suppl 1: S93-9.
Formatting of all references has been checked prior to resubmission.

Page 34, line 39
Ref 18: JAMA 2020;324:1495-96.
Suggest: JAMA 2020;324:1495-6.
Formatting of all references has been checked prior to resubmission.

Page 36, line 24
Ref 28: 2016;5:147-49.
Suggest: 2016;5:147-9.
Formatting of all references has been checked prior to resubmission.

Page 37, line 52
Ref 38: 2009;9:11-18.
Suggest: Ref 38: 2009;9:11-8.
Formatting of all references has been checked prior to resubmission.

Page 40, lines 18-30
Race, n (%)*
Where * means:
Patient can select more than one choice
Total counting of patients in race section is more than 41 in all section and more than 23 in recruited section.
Is it correct to say that subject belong to more than race/ethnicity?
The reviewer is correct that each participant could select more than one choice of race. We have amended the footnote as follows for clarity (Table 1, page 42):
‘*Patients could select more than one choice to reflect individuals with mixed race.’

Page 41, line 16
Time between hospitalisation due to COVID-19 and interview (months) but as exclusion criteria:
Point 2: Patient was hospitalised during initial COVID-19 infection need to be excluded.
Please confirm whether hospitalised patients were excluded or included.
Change in methodology or results will be needed accordingly

As described in more detail above, we have removed the exclusion criterion relating to hospitalisation during initial COVID-19 infection from the supplemental materials. Patients who were hospitalised during the initial COVID-19 infection, such those who participated in the COV-2066 trial, were eligible to enrol in our study.

Reviewer 2 Comments
Thank you for giving me the opportunity to review this article, which deals with a very interesting and useful topic to delve into the pathology of persistent covid.
However, it would be necessary to clarify some aspects to improve its quality. I will now proceed to make some comments or considerations in the hope that they will be useful to the authors.
We thank the reviewer for their feedback and suggestions to improve our manuscript.

Title: Perhaps it is not relevant to use the word results in the title, since original research articles present results.
Revised as suggested (page 1).

Bullet points: Since the systematic review part is not clear beforehand, it is complicated for the reader to understand the first point presented.
Whilst this review was not a systematic review, it was comprehensive to address the research questions of interest that were focused on developing a preliminary conceptual model that was then further refined with data from patient and clinician interviews. We have revised the first bullet point of the strengths and limitations section to make the scope and purpose of the literature review clearer as follows (page 5):
'This study included a comprehensive review of published literature related to long coronavirus disease 2019 (COVID-19), alongside, in-depth, qualitative interviews with patients recruited from both clinical trials and healthcare research firms, as well as interviews with independent clinicians, to understand the patient experience of long COVID-19.'

Bullet points: The second point presented as a bullet point, given the speed with which it is published in relation to persistent covid, has become obsolete, since there are several articles that use qualitative methodology.
We agree that several articles regarding the patient experience of long COVID have been published and have revised the second bullet of the strengths and limitations section as follows (page 5):
'While knowledge about acute COVID-19 symptoms and patient experience is relatively comprehensive, this study adds to the limited literature on the patient experience of long COVID-19 and its impacts on daily life, including neurocognitive, physical and emotional functioning.'

Bullet points: On the other hand, it is presented as a limitation that mainly women participate in the study, but the pathology affects mostly women, and it would have been desirable to slightly increase the sample of men so that the percentage of affectation by gender would have been representative.
We thank the reviewer for pointing this out. We have revised the last bullet to read (page 5):
'A limitation of this study is that the participants were predominantly White and female. Whilst the pathology of long COVID-19 is known to affect mostly women, it would be desirable to perform additional research in males and more diverse patient groups for better representation of the affected population.'

Introduction:
The introduction is well constructed and written, following an adequate thread.
We thank the reviewer for their positive feedback.

Methodology:

The systematic review study of the subject is not clear, since later its use is not detailed when constructing the model, and therefore this part is hardly replicable. On the other hand, in any research study that is carried out, in order to have a good theoretical framework and as a basis for the study, an information search is carried out beforehand, which can be more or less systematic. It is not clear whether this bibliographic search (which can be carried out as a systematic search) is what the authors explain in this section.
We conducted a comprehensive literature review to address the research questions of interest rather a systematic review. This approach is common in patient-centered outcomes research and the development of conceptual models to capture, from a patient perspective, rich qualitative insights from populations of interest (Cook DA. 2019 Systematic and nonsystematic reviews: Choosing an approach. Healthcare Simulation Research: A Practical Guide). We previously published a conceptual model of the symptoms and impacts associated with acute COVID-19 (Rofail D et al. 2022 BMJ Open: PMID 35501077). For the current and prior study, we followed the US Food and Administration (FDA) guidelines (2009) that recommend that conceptual models are informed by a comprehensive literature search.

Methodology: On the other hand, it would not be necessary to place a time limit of ten years on the search, since the disease has not existed for such a long time.
We have amended the relevant text in the Methods to reflect that the literature search covered several years (page 9):
'An electronic search was performed on July 23, 2021 using PubMed to identify qualitative papers published up to that date that explored the patient experience of long COVID-19.'

Methodology: Regarding the qualitative part, the interviews with patients were conducted online, and the interviews with professionals were conducted by telephone. Why were they conducted telematically, and could this have affected the results?
The FDA 2022 guidelines on patient-focussed drug development state that one-on-one interviews can be conducted in person or remotely using either computers or telephones. We appreciate that in-person interviews would have allowed for greater attention to non-verbal cues; however, the study participants were from former clinical trials that were conducted at over 100 sites in the US. Although the FDA does not have a single recommended administration method; the guidelines state that the selected method should be appropriate for the target population. Both the patient and clinician interviews were conducted using Microsoft Teams, for which camera use was optional. Patients and clinicians also had the option to dial-in to the interviews by telephone only. We do not believe that the administration of the interview by telephone only would have negatively impacted the study.
We have revised the Methods to clarify that the patient interviews, conducted using Microsoft teams, were audio-recorded but patients had the optional use of the camera (page 12).
'Audio-recorded patient interviews were conducted via Microsoft Teams (use of camera optional by patient) by four experienced qualitative researchers who received specific training for this study, and who had backgrounds in psychology and anthropology as well as ≥2 years' experience in qualitative research.'

Methodology: On the other hand, it would be necessary to specify what was the topic list (script of open questions asked) to know the depth of the interviews. The authors can show it in a table if they consider it appropriate. Did the authors ask about the intensity of the symptoms? This aspect is essential to understand the dimension of the persistent covid disease, and to include it in the model.
As requested by the reviewer, we've added more detail to the patient interview section in the manuscript. We added the following text to describe how the semi-structured interview guide was developed (page 11):
'Semi-structured patient interview guides were developed in line with best practices outlined in the FDA patient-focussed drug development guidance. The patient interview guides provided the researcher with a general outline for the semi-structured interview, but each interview was unique

based on spontaneous patient responses to questions about symptoms and the impacts of long COVID-19 on daily activities and health-related quality of life.'
The focus of this manuscript was on symptom manifestation and impact, although symptom severity was included. We have added several examples of questions that the interviewer used in the patient interviews (page 12).

Methodology: In relation to the analysis it would be necessary to include more information such as whether the coding was established a priori or whether grounded theory or some other theory was used for data analysis.
No a priori coding frame was applied as we used open and inductive coding that was tailored to symptoms and impacts of long COVID-19, including those spontaneously mentioned by patients and those revealed from additional probing questions from the interviewer. Inductive categorisation enabled us to identify higher-order overarching symptoms and impacts concepts, domains, and sub-domains. An inductive approach to analyzing qualitative data is an accepted approach to generate reliable observations (Thomas DR [2006] American Journal of Evaluation; https://doi.org/10.1177/1098214005283748). A grounded-theory approach was applied to our thematic analysis, in that the process of categorizing symptoms and impacts included a critical review of responses before coding was finalized.
We have added the following sentence in the Methods to expand on the categorisation process (page 14):
'This categorisation was an iterative process performed by a research team that involved comparison and cross-referencing between different analytic categories.'

Methodology: Did these diseases appear after covid-19 infection?
We have clarified the time frame of symptoms associated with long COVID-19 in the Methods by the addition of text in brackets in the following sentence (page 12):
'During the semi-structured interview, patients were asked open-ended questions to provide spontaneous inputs regarding the symptoms of long COVID-19 (experienced after the first 4 weeks of acute COVID-19).'

Results: Regarding the results of the qualitative study, It would be necessary to go deeper into the model obtained. On the other hand, all the quotes shown belong to female patients. There was nothing differential in the discourse of men and women? It would be interesting if this could be explored further.
We thank the reviewer for their feedback. We have added quotations from males to Table 3 and Table 4. The focus of the current study was a grounded thematic analysis intended to generate rich qualitative insights directly from patients to describe concepts important to patients as part of the lived experience of long COVID-19. Conceptual models are used to convey key components for health research (Brady et al. 2020 Health Promotion Practice: PMID 31910039) and have been previously developed in qualitative studies (Klassen et al. 2009 BMC Womens Health: PMID 19409078; Armstrong et al. 2018 Implementation Science: PMID 29661195; Di Tosto et al. 2023 BMC Health Services Research: PMID 37563581). Conceptual models facilitate the visual representation of descriptive data of the patient experience (Rofal D et al. 2022 BMJ Open), which importantly reflects the increased involvement that patients have in disease management. We agree that it could be interesting to explore any potential differential discourse between males and females in future research.

Results: The authors have used numerous quotes or literal quotations to illustrate the results obtained; however, this sometimes complicates the reading of the results. The authors could consider the possibility of putting the quotes in a table (specifying scope to which they refer in one column and in another column, the quotes).

We thank the reviewer for this valuable suggestion. We have moved the quotations on symptoms and impacts to new Tables 3 and 4, respectively. We used separate tables for signs and impacts as we acknowledge that BMJ Open requires tables more than two pages in length to be placed in online Supplemental Materials. We appreciate that we now have six figures/tables in the main manuscript. We agree with the reviewer that this important change makes the reading of the results much easier and appreciate the suggestion since the quotations are a fundamental part of the documentation and unique contributions to this field.

Results: The words "difficulties finding the right word" can be substituted for verbal fluency.
We thank the reviewer for this suggestion and understand why this may have been proposed. However, on this occasion we would prefer to keep 'difficulties finding the right word' to reflect the wording that the study participants used. The rationale is that in the field of patient-centered outcomes research and measurement science, as much as possible, we try to avoid placing our own interpretation and rather keep as close as possible to the voice of the patient.

Discussion: It would be necessary to go deeper into the discussion about the proposed model since it is the novelty of this study and it is hardly discussed
We thank the reviewer for this suggestion. Our intent for this study was to develop a clinically grounded model of the symptoms and associated impacts that may negatively affect the quality of life of people with long COVID-19. In the manuscript, we have discussed how this patient-relevant empirical model of long COVID-19 is similar or different to another model that we developed for acute COVID-19. Owing to the preliminary nature of our data, we feel that further studies are needed for more in-depth interpretation.
To emphasise the wide range of symptoms reported by patients, we have added the following sentence to the Discussion (page 28):
'We found that patients typically experienced symptoms across of number of clinical domains during long COVID-19.'

Conclusions: The conclusions that are shown are not specifically conclusions of the study carried out.
The Conclusions section has been revised to emphasise the results of this study and their application to the clinical and real-world settings as follows (page 30):
'Our qualitative research reveals that long COVID-19 impacts all aspects of patients' daily life, particularly neurocognitive and mental health issues. To the best of our knowledge, this is the first study to report a conceptual model of long COVID-19 with neurocognitive and emotional concepts, based on empirical evidence from patient and clinician interviews. The model highlights, from a patient perspective, symptoms and impacts associated with long COVID-19, all of which showed significant negative effects on patient health-related quality of life.'

Tables: In Table 1 it would be convenient to, at least, show the p-value in the comparison between the participants coming from the different recruitment methods.
We used a purposive sampling approach. Our focus was on patient characteristics using our screener, and, given the nature of qualitative work, we do not believe p values based on any descriptive characteristics are useful to understand the patient experience of the disease (Palinkas LA et al. 2015 Adm Policy Ment Health and Fisher MJ & Marshall AP. 2009 Australian Critical Care).

Tables: In table 2, the word "solo" appears.(Solo private practice). is it a mistake?
The term 'solo' referred to clinicians that had an independent consulting practice. We have revised to 'Private practice' for clarity. Please note that in order to reduce the total number of figures and tables to below the maximum of 5, we have moved Table 2 to the Supplement and it is now Table S2.

Figures: Figure 2 shows the model obtained but perhaps it would be more interesting to show another figure that presents the interdependence of the different areas. Since it is a relevant result of the study, perhaps another more complete and complex figure could be made.
The purpose of the current study was to build a visual representation of patient-reported experience of long COVID-19. We agree with the reviewers that the independence of the concepts would be interesting to explore; however, this was beyond the scope of the current study and would require a different study design to address adequately. For example, a large quantitative dataset with structural equation modeling could determine relationships between the patient-report concepts we reveal to be associated with long COVID-10.

Author-initiated amend
We have added a citation of a recently published paper (Bowe et al. 2023 Nature Medicine; PMID: 37605079) in the Introduction as follows (page 7):
'A recent study reported an elevated risk of both hospitalisation and death during two years of follow up for patients who were hospitalised during acute COVID-19 infection.'
Furthermore, to ensure that the manuscript is close to the maximum word limit of 4000 words, we have moved some of the text in the Methods section to the Supplement (word count of main text: 4091/4000 words).

VERSION 2 – REVIEW

REVIEWER	Bárbara Olivan-Blázquez Universidad de Zaragoza, Department of Psychology and Sociology.
REVIEW RETURNED	04-Oct-2023

GENERAL COMMENTS	The authors have modified or explained the performed changes in the manuscript. From my point of view, this manuscritp can be useful to address the pathology of persistent covid from a multidisciplinary and person-centered approach.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2 Comments

The authors have modified or explained the performed changes in the manuscript. From my point of view, this manuscript can be useful to address the pathology of persistent covid from a multidisciplinary and person-centered approach.

Thank you for the positive assessment of our revised manuscript.