PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort profile: the Johns Hopkins COVID Long Study (JHCLS), a United States Nationwide Prospective Cohort Study
AUTHORS	Wentz, Eryka; Ni, Zhanmo; Yenokyan, Karine; Vergara, Candelaria; Pahwa, Jessica; Kammerling, Thea; Xiao, Pu; Duggal, Priya; Lau, Bryan; Mehta, Shruti

VERSION 1 – REVIEW

REVIEWER	Francesca Bai University of Milan, Department of Health Sciences
REVIEW RETURNED	27-Aug-2023

GENERAL COMMENTS	Milan, 27 August 2023 Manuscript: BMJ OPEN-2023-077742 Cohort profile: the Johns Hopkins COVID Long Study (JHCLS), a United States Nationwide Prospective Cohort Study The authors present the baseline characteristics of the Johns Hopkins COVID Long Study. The main strengths of the study are the long follow up and the large number of enrolled patients. The aim of the study is interesting given the current focus on long COVID and its long-term possible consequences. I think that the manuscript is well-written and clear and could add new data about long-term persistence of symptoms after a first episode of COVID-19; according to me, it is suitable for publication after minor revisions. Specifically: Only a subgroup of patients that consented to participate in the study at the beginning entered the follow up; will the authors compare the main demographic, social and clinical characteristic of the patients who declined to participate and patients who completed the follow up? The WHO definition of post COVID-19 condition is nonspecific; the authors in fact found that 63% of patients have long COVID. Have the authors planned to analyze clusters of persisting symptoms that were not present before COVID-19? How will the authors manage possible losses to follow up in the longitudinal study? Some questionnaires/questions do not investigate how was the situation before COVID-19 (for example, questionnaire about anxiety refers to the last two weeks and also sleep or fatigue are not investigated before); how will the authors correct the lack of data about patients' feeling and symptoms before COVID-19 pandemic and SARS COV-2 infection? 84% of participants are female; it's a possible selections bias (females are more commonly affected by myalgic encephalomyelitis and long COVID). They have correctly written in the limitations that

	the study results could be not generalizable for race and socioeconomic status, but they have to better specify also the gender. The authors could report p values of comparison between patients with previous SARS CoV-2 infection and the control group in table 2 and 3.

REVIEWER	Mostafa M Khodeir Cairo University, Pathology
REVIEW RETURNED	24-Sep-2023

GENERAL COMMENTS	First, I would like to thank the research team for their valuable efforts to unveil the COVID-19 sequelae. However, there are points that need further clarification and work on. 1- Why didn't the authors invite all consented participants in the follow-up survey to complete the first cycle of follow-up before starting publication? 2- The Self-designed questionnaires are good work but need to be validated and tested for reliability, being your primary measurement tool. (This is for all domains with self-designed questionnaires) 3- One of the domains, its questionnaire, although published study, is of low-reliability score (Domain limitations and exercise questionnaire for moderate and light exercise) 4- It is better to share your self-designed questionnaire used in the study for more benefit. 5- Mention the process used for the validation of self-designed questionnaires. 6- Tables 2 & 3, I suggest another design by splitting them into tables for baseline data and others for the first follow-up cycle for more clarity. 7- Deeper analysis to find the significance between domains and each other's (if any) and the data collected in each domain, for example: a-Relation between vaccination status and acute and chronic symptoms, b- Socioeconomic status and acute symptoms, c-Severity: hospitalized and non-hospitalized and long-term symptoms and vaccination.

VERSION 1 – AUTHOR RESPONSE

Comments for Reviewer 1

Comment 1: Only a subgroup of patients that consented to participate in the study at the beginning entered the follow up; will the authors compare the main demographic, social and clinical characteristic of the patients who declined to participate and patients who completed the follow up?

Response: We appreciate your comment regarding the differences between those who agreed to be contacted for future studies and those who declined. In response, we have added Supplementary Table 2 that shows demographic and clinical characteristics across these groups at this time. We have also added the following sentences to the baseline characteristics section: "The demographic and clinical characteristics between those who agreed to be contacted for future studies and those who declined were comparable, with the exception of long COVID status (Supplementary Table 2). Unsurprisingly, more individuals who fully recovered declined continued participation in the study.

However, the number of indeterminate individuals (too early to determine long COVID status) was similar."

Comment 2: The WHO definition of post COVID-19 condition is nonspecific; the authors in fact found that 63% of patients have long COVID. Have the authors planned to analyze clusters of persisting symptoms that were not present before COVID-19?

Response: Thank you for this valuable comment. We agree that the WHO definition of post-COVID conditions is intentionally encompassing and only requires an individual to have one persisting symptom and there is no requirement that the symptom impact daily functioning. We are planning a cluster analysis of both initial and persistent symptoms that is beyond the scope of this cohort profile paper. We have added the following sentences to the Future plans section: "In addition, the study team is planning a cluster analysis of both initial and new/continuing COVID-19 symptoms to help address the broad WHO definition of long COVID. We plan to do this by bringing together the rich symptom data we have in our study with data on the impact each reported symptom has on daily functioning."

Comment 3: How will the authors manage possible losses to follow up in the longitudinal study?

Response: We plan to use inverse probability censoring weights to account for potential selection bias due to loss to follow-up.

Comment 4: Some questionnaires/questions do not investigate how was the situation before COVID-19 (for example, questionnaire about anxiety refers to the last two weeks and also sleep or fatigue are not investigated before); how will the authors correct the lack of data about patients' feeling and symptoms before COVID-19 pandemic and SARS COV-2 infection?

Response: Thank you for this important comment. We recognize that many of our questions/validated measures are measured at/after the COVID-19 pandemic or SARS-CoV-2 infection and thus we are lacking data on a person's experience before these events. This concern was one of the main reasons we have included a control population of individuals without SARS-CoV-2 infection. This will allow us to evaluate if a symptom/experience (e.g., fatigue, anxiety, etc.) reflects SARS-CoV-2 infection or the collective experience of living through a global pandemic. We currently address this in part in the Strengths and Limitations section: "Another strength of the JHCLS is the inclusion of participants without a history of SARS-CoV-2 infection which provides a natural control group, while also allowing for the determination of the incidence of long COVID among those who report a SARS-CoV-2 infection during follow-up. Importantly, both samples are comparable in terms of sociodemographic variables and pre-existing health conditions. We also recognize that many of the heterogeneous symptoms reported as long COVID may reflect all of us collectively living through a pandemic (i.e., anxiety, depression). Thus, it is important that we compare those with and without infection to evaluate some of these outcomes during the same time frame (versus retrospective or historical controls)."

Comment 5: 84% of participants are female; it's a possible selections bias (females are more commonly affected by myalgic encephalomyelitis and long COVID). They have correctly written in the limitations that the study results could be not generalizable for race and socioeconomic status, but they have to better specify also the gender.

Response: We appreciate this important comment. We agree that the results may not be generalizable in terms of gender as 84% of our sample with SARS-CoV-2 infection are female and 85% of our sample without SARS-CoV-2 infection are female. One way we plan to address this will be

to do stratified specific analyses by gender that may be representative of participants within that same gender.
We have added the following clarification and sentence to our Strengths and Limitations section: "Finally, there is a risk that findings from the JHCLS are not generalizable as the majority of participants self-reported white race, female gender, and are from a higher socioeconomic status. To address this, we plan to do stratified-specific analyses that may be better representative of individuals within that same stratum."

Comment 6: The authors could report p values of comparison between patients with previous SARS CoV-2 infection and the control group in table 2 and 3.

Response: We appreciate this suggestion. Due to the guidance of the American Statistical Society and the widespread abuse of p-values, we are not reporting p-values, but do present the numbers and percents.

Comments for Reviewer 2

Comment 1: Why didn't the authors invite all consented participants in the follow-up survey to complete the first cycle of follow-up before starting publication?

Response: In our baseline survey, we ask participants if they consent to be contacted for future COVID-19 studies at Johns Hopkins. This includes our follow-up cohort and other studies. If they agree, 3 or 6 months after a participant completes their baseline survey, they are automatically sent an email inviting them to consent into our follow-up cohort. If they consent, they immediately complete their first follow-up survey. As this is an ongoing study with ongoing recruitment, we cannot wait until all participants are consented. At the time of publication, there were individuals who had just completed their baseline survey and who were not scheduled to receive their invitation to consent into follow-up until the pre-defined interval of 3 or 6 months had passed.

Comment 2: The Self-designed questionnaires are good work but need to be validated and tested for reliability, being your primary measurement tool. (This is for all domains with self-designed questionnaires)

Response: We appreciate the importance of using validated instruments. At the start of the pandemic, we and others were part of several groups that developed questions for COVID-19 research studies quickly and efficiently. While we drew upon experience and validated instruments for other infectious diseases, some questions needed to be developed de novo. We shared our questions and approach for development along with sources with other researchers and organizations. Our baseline questions are available on the National Institute of Environmental Health Sciences Disaster Research Response (DR2) Resources Portal (https://tools.niehs.nih.gov/dr2/index.cfm/resource/24278) and have been shared with other researchers.

In addition, we used validated questionnaires that targeted several specific domains (anxiety, sleep, mental fatigue, physical limitations, and exercise). To the best of our knowledge, there were no validated questionnaires to capture COVID-specific data when we launched our baseline study in February of 2021.

Comment 3: One of the domains, its questionnaire, although published study, is of low-reliability score (Domain limitations and exercise questionnaire for moderate and light exercise).

Response: We appreciate your comment. In determining which questionnaires to administer at baseline, we had to consider the overall length of the survey and aimed to keep it as short and

concise as possible. Our overall goal for the exercise questions was to measure changes in a person's self-reported level of activity (amount and type) before the pandemic/COVID-19 illness and since the pandemic/COVID-19 illness. The Godin-Shephard Leisure-Time Physical Activity Questionnaire is a short instrument that was originally developed to measure the correlation between two objective measures of physical condition (V02 max, body fat percentile) and the authors' subjective exercise questionnaire. Since we were mostly interested in self-reported changes, we felt that the Godin-Shephard Leisure-Time Physical Activity Questionnaire was a good fit for our study and allowed us to collect this data in just a few questions.

Comment 4: It is better to share your self-designed questionnaire used in the study for more benefit.

Response: Thank you for your suggestion. All of our survey questions can be found on the National Institute of Environmental Health Sciences Disaster Research Response (DR2) Resources Portal. In response to your suggestion, we have added the following sentence into our Study procedures section: "All self-designed questionnaires are available on the National Institute of Environmental Health Sciences Disaster Research Response (DR2) Resources Portal (https://tools.niehs.nih.gov/dr2/index.cfm/resource/24278)."

Comment 5: Mention the process used for the validation of self-designed questionnaires.

Response: Please see comment 2.

Comment 6: Tables 2 & 3, I suggest another design by splitting them into tables for baseline data and others for the first follow-up cycle for more clarity.

Response: We appreciate this suggestion. We are currently in the process of analyzing our follow-up data. Therefore, we kept the focus of our cohort profile paper on the baseline measures and data which have been curated and analyzed.

Comment 7: Deeper analysis to find the significance between domains and each other's (if any) and the data collected in each domain, for example:
a-Relation between vaccination status and acute and chronic symptoms,
b- Socioeconomic status and acute symptoms,
c-Severity: hospitalized and non-hospitalized and long-term symptoms and vaccination.

Response: Thank you for this important comment. We agree that this cohort will be highly valuable for deeper analyses like our recently published paper on long COVID disability (10.1016/j.amjmed.2023.08.009). At the time of submission for this publication, our disability paper was still under review.

VERSION 2 – REVIEW

REVIEWER	Francesca Bai University of Milan, Department of Health Sciences
REVIEW RETURNED	19-Jan-2024

GENERAL COMMENTS	Milan, 19 January 2024 Manuscript title Cohort profile: the Johns Hopkins COVID Long Study (JHCLS), a United States Nationwide Prospective Cohort Study – Manuscript number: BMJOPEN-2023-077742.R1 The authors present the preliminary results of a prospective cohort study including adult patients with and without SARS CoV-2 infection

	who are followed up every 3-6 months. The aim of the study is to investigate the short and long-term outcomes of COVID-19 disease; the sample size, the comparison between patients with history of known SARS CoV-2 infection and patients without SARS CoV-2 infection at baseline and the long follow up are the main strenghts. I think that the manuscript is suitable for publication after minor revisions. Specifically: The authors should better comment that patients self-reported about SARS COV-2 test, thus recall bias could be introduced. The authors find 63% of patients diagnosed with long COVID; this high prevalence could be probably due to a selection bias (patients with persisting symptoms agreed to be followed up, while patients without symptoms didn't accept to complete the survey and be enrolled in the study). They have compared the demographic characteristics of patients who agreed to be followed-up and patients who didn't agree to be followed up. The authors could better comment this in the discussion. The WHO definition is wide and include all possible ongoing symptom; the authors could also analyze the most common clusters of Post COVID-19 condition separately, for example chronic fatigue, chronic pain, respiratory sequalae, brain fog. "Because SARS-CoV-2 tests are not always accessible, eligibility requirements include either a self-reported positive SARS-CoV-2 test or symptoms of COVID-19". Did the authors consider patients with flu-like symptoms or symptoms of upper and lower respiratory tract without performing SARS CoV-2 test as patients with COVID-19? They should better specify this, because without the certainty of SARS CoV-2 infection they could refer to Post Acute Infection Syndromes and not specifically to long COVID. In the study flow chart, please insert also percentages.

VERSION 2 – AUTHOR RESPONSE

Comments for Reviewer 2

Comment 1: The authors should better comment that patients self-reported about SARS COV-2 test, thus recall bias could be introduced.

Response: We appreciate this important comment. We have made the following edits to the Strengths and Limitations section, "The reliance on self-reported clinical data, including self-reported SARS-CoV-2 tests, may result in recall and measurement bias. Although a confirmed SARS-CoV-2 test would be preferable, we recognize that tests were not available to everyone and that restriction to only those with a confirmed test would introduce selection bias."

Comment 2: The authors find 63% of patients diagnosed with long COVID; this high prevalence could be probably due to a selection bias (patients with persisting symptoms agreed to be followed up, while patients without symptoms didn't accept to complete the survey and be enrolled in the study). They have compared the demographic characteristics of patients who agreed to be followed-up and patients who didn't agree to be followed up. The authors could better comment this in the discussion.

Response: Yes, we agree, and have added the following sentences to the Strengths and Limitations section, “The high percentage of participants in our study with long COVID (63%) also likely reflects a selection bias on those willing to participate in COVID-19 research. However, those with and without a history of SARS-CoV-2 infection are similar in their demographic characteristics (Table 1).”

Comment 3: The WHO definition is wide and include all possible ongoing symptom; the authors could also analyze the most common clusters of Post COVID-19 condition separately, for example chronic fatigue, chronic pain, respiratory sequalae, brain fog.

Response: We appreciate this comment; however, it is outside the scope of this cohort profile manuscript.

Comment 4: Did the authors consider patients with flu-like symptoms or symptoms of upper and lower respiratory tract without performing SARS CoV-2 test as patients with COVID-19? They should better specify this, because without the certainty of SARS CoV-2 infection they could refer to Post Acute Infection Syndromes and not specifically to long COVID.

Response: Please see above. We agree that the symptoms of COVID-19 and the flu are similar. However, since we cannot distinguish, we reported them as long COVID per the WHO.

Comment 5: In the study flow chart, please insert also percentages.

Response: Thank you for this suggestion. We have submitted a revised study flow chart with the percentages inserted.