21-Jan-2021
BMJ-2021-064273
Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study

Dear Mr. Ayoubkhani,

Thank you for sending us your paper, manuscript #BMJ-2021-064273 entitled "Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study", which we have been considering on an expedited, fast track basis. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision. Given that you requested fast track consideration, we expect to receive your revised paper within 1-2 weeks. If you cannot meet this time frame, please communicate directly with the handling editor.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

When you return your revised manuscript, please note that The BMJ requires an ORCID iD for corresponding authors of all research articles. If you do not have an ORCID iD, registration is free and takes a matter of seconds.

Yours sincerely,

Joseph S Ross MD MHS
Associate Editor BMJ
joseph.ross@yale.edu

To submit your resubmission: *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/bmj?URL_MASK=260734af6ae6478f9726832465835ba8

Report from The BMJ’s manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee present for the entire meeting were: Joseph Ross (chair), Gary Collins (statistician), Tim Feeney, John Fletcher, Naz Islam, Elizabeth Loder, David Ludwig, Tiago Villanueva, Wim Weber, Luke Ouma (student observer)

Decision: Revise and Reconsider

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. In your response, please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Next, please also respond to these additional comments by the committee:

Editor's summary:
Observational, retrospective, matched cohort study of patients admitted to NHS hospitals in the UK for COVID-19 (and discharged alive) in order to characterize the epidemiology of post-COVID syndrome (PCS) by quantifying rates of organ-specific impairment following recovery from COVID-19 compared to controls, including how the rate ratio (RR) varies by age, sex, and ethnicity. COVID-19 cases were matched to controls on baseline demographic and clinical characteristics, but there is very little information on the success of matching (Table 1 provides the 48k covid and 239k general population, but doesn't tell us more about the matched group). In addition, after multiple reads I am unsure whether patients were matched to a general population cohort or to a cohort of adults who were hospitailzed. The former does not make for an apples-to-apples comparison to better understand the sequelae of COVID19, since we know only the sickest and most clinically vulnerable are hospitalized (ie, lots of people had COVID and did not require hospitalization).

Adverse events examined were all-cause mortality; hospital readmission for any reason; respiratory disease; major adverse cardiovascular event (MACE, a composite of heart failure [HF], myocardial infarction [MI], stroke, and arrhythmia); diabetes (type 1 or 2); chronic kidney disease (CKD) stages 3-5 (including dialysis and kidney transplant); and chronic liver disease (CLD). Respiratory, MACE, diabetes, CKD and CLD events were identified from diagnoses made in primary care and in hospital (using only primary ICD-10 codes for the latter).

Among nearly 87k individuals (48k in each group, mean age 65, 55% male), covid19 discharges were followed-up for 140 days, controls for 153 days, through end of September 2020. Results text could be written much more clearly, but Table and Figures demonstrate that rates for everything are consistently higher among COIV19 discharges than controls, including all-cause mortality and readmission being 7.7x and 3.5x greater. Rates for some adverse events differed by age, sex and race.

Statistical Editor's comments:
- Very interesting paper but we cannot move forward until the control group is better clarified. The ideal control group would be patients hospitalzed for other pneumonias, viral or bacterial, ideally at approximately the same day and month, in the prior year in order to ensure that COVID was not affecting our understanding of the sequeale of these non-COVID pneumonia patients (because they could not or would not go to their physicians or the hospital during lockdown). So, a control cohort of pneumonia hospitalizations in 2019 compared to COVID hospitalizations in 2020, matched on month and other sociodemographic and clinical characteristics.
- In addition, the revision should clearly report the standardized differences between the two groups so that a reader can assess the success of the matching. Perhaps more advanced propensity matching will be needed.
- More detail on how missing data was handled should be reported. Missing data were handled by creating a ‘missing category’ – this should be avoided as it can lead to biased results (e.g., Groenwold et al CMAJ 2012). I’m also unclear on how this affects the matching – matching on ‘unknown’ seems highly problematic (and we’re not given the characteristics on the matched cohorts). The authors should consider alternative approaches for handling missing data, e.g., multiple imputation.
- Additional explanation on GDPPR would be useful

Other Editor's comments:
- Has the potential to be a very important paper. While they have characterized sequelae for survivors, should mention that many individuals do not survive to discharge. Alternatively, once the matching is done based on hospitalization, the paper would be stronger if it included inpatient mortality as an outcome as well, in addition to sequelae post-discharge (which should remain the focus of the paper).
- Inclusion of covid patients with both codes U07.1 (virus identified) and U07.2 (virus not identified) seems a weakness. Should be better justified, and perhaps sensitivity analyses focused on the subgroup of U07.1 are needed.

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
This is a clear and (as far as I can judge) sound paper on an important topic at a time when UK hospital admissions and deaths from Covid-19 have never been higher. Agree, fast-track is appropriate. I'm not a statistician and the methodology of this kind of research is not my forte, so I will comment more on the context and implications. Note also that during the pandemic I coauthored several papers with Kamlesh Khunti though I am not formally a collaborator on any research (and indeed we've just submitted competing bids for a long covid call). I don't think my links with Kamlesh have skewed my judgement in either direction but am telling you in the interests of full disclosure.

Some suggestions for minor changes follow.

Title: it's a bit jargony and I think the fact that this is a highly skewed sample of people who were *hospitalised* could be made clearer. Suggest "in people who were hospitalised with Covid-19".

I would say more about the fact that most people with long Covid were never admitted to hospital in both the background and discussion. Indeed, my own reading of the literature (especially some of the qualitative literature including but not limited to the papers by my own team) suggests that the pattern of sequelae observed in this hospitalised cohort may be strikingly different from the pattern that is typical of non-hospitalised patients who go on to have problems. In the latter, "brain fog", muscle pain and fatigue seem to dominate (and quite a few have persistent fever) whereas cough and respiratory symptoms seem much less common. However an alternative explanation is that this study didn't find brain fog etc etc because it didn't look for it. Would be good to have a discussion on all that.

Explain GPPDR - what is it, what are its inherent strengths and biases, in what way are controls thus sampled "comparable" to those identified via HES? I'm right at the bottom of the learning curve on these issues and I bet I'm not the only one.

"excluding those who could not be matched to a control". Why couldn't they be matched? How many of them? To what extent might this skew findings and in what direction?

Not possible to involve patients because pandemic. Fair enough but perhaps one of the long covid patient community might like to write a commentary on this? Sharon Taylor writes well, as does Nisreen Alwan. sharontaylor_2000@yahoo.com N.A.Alwan@soton.ac.uk

Nearly 1/3 readmitted; 1/10 died. Shocking but unsurprising. This needs to be flagged in the abstract (which is boring and needs a redraft by the way). The REASONS for readmission need to be urgently surfaced and explored (either in this fast-track paper or in a companion paper). Are patients being discharged precipitously through a policy of "controlling the back door to open the front door"? I am going to paste below an email I received from someone I don't know. Post-discharge follow-up seems terrifyingly slack. GPs don't know what to do. Guidelines/guidance for post-discharge follow-up seem to

either not exist or not get followed. The readmission and death rates revealed in your paper suggest that the email quoted below may be illustrating a wider system problem.

EMAIL SENT TO ME FOLLOWS:
Dear Professor Greenhalgh,
I have your email by following a link on the [regional] post covid guidelines and this took me to a BMJ publication in where I found your email address. I am writing to you in desperation to see whether you can offer advice.

My husband (who is [in his 50s]) has been discharged from [a reputable UK] Hospital after a two week admission (8 days in icu on CPAP with covid pneumonia). He was discharged once his resting sats on air were 88%. He has been offered no follow-up and no pulmonary rehab. He is currently largely remaining in his bed with resting sats of around 88-90 but with even the slightest bodily effort (walking down a flight of stairs or standing to take a shower) these drop to 65%-66%. I don't really understand why he has been discharged without oxygen at home and without any advice or access to rehab. He has lost 12kg - which to my eye seems to be in muscle mass. Since discharge we have seen no improvement. Please could you help us?

I am hoping you will forgive this direct approach. I have had a conversation with a GP but she told me she did not know how to make referrals to pulmonary rehab and her only suggestion was to take my husband back to A&E and he doesn't want to go back - or to a covid assessment hub (a physical impossibility) . The GP also offered a flu jab appointment - I asked if this could happen at home as there is no way he could physically make it safely to a surgery. This appears also not to be possible (leaving me to wonder why a district nurse could not do this).

Thank you for any help or sign-posting you can offer,

Kind regards,

END OF EMAIL

[I have dealt with this query and followed up on it, but I hope you'll agree it's worrying]

Trish Greenhalgh

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Trish Greenhalgh

Job Title: Professor of Primary Care Health Sciences

Institution: University of Oxford, UK

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: OX2 6GG

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 2

Recommendation:

Comments:
Ayoubkhani et al. used the data from national database, incorporating data from General Practice and death registrations data from the Office for National Statistics (ONS) to explore the risk of death, admission to hospital, and other multi-organ dysfunction among COVID-19 patients compared with non-COVID-19 control. The strength included the large sample size, database based on national population in England, and enrollment of non-COVID-19 controls. Some concerns and specific comments are also raised below:

Major concerns:
1. As the controls were matched based on General Practice Extraction Service (GPES) Data for Pandemic Planning and Research (GDPPR) dataset which covers over 56 million individuals in England, the controls are believed to be selected from general population in England. If so, how was the outcome "readmission" defined for controls as "readmission" indicated the controls had admitted to hospital before index date? Was "readmission" actually any admission after index date for controls as they may have not admitted to hospital before then? This needs to be clarified.
2. The authors mentioned individuals with primary diagnosis of COVID-19 were included, with some of them identified by positive laboratory test and others by clinical diagnosis. What is the criterion for clinical diagnosis? The respective proportions of patients of the above two groups should be shown.
3. "The index date was set to date of discharge following the first hospital episode with COVID-19 as the primary diagnosis": How many of the COVID-19 patients included have more than one hospital episode? If there are some of them having more than one, was the reason for the second or even further hospital episode reinfection or not being able to recover when they were discharged for the former hospital episode?
4. One of the inclusion criteria for controls was at least one GDPPR record between one year before the start of the follow-up period and the end-of-study date. Why was one year before chosen? If the information was obtained nearly one year before index date, this would result in misclassification of confounders.
5. For the matched variables, age was categorized into three groups (<50 years, 50-69 years, ≥70 years) as shown in Supplementary Table 1. The matching for age (critically important for outcomes) is quite crude. From Table 1, we can see that the proportions of people with <30 years and 30-49 years among COVID-19 and general population are substantially different. If the two groups are combined together as one group for matching, I am not sure if the mean age of cases and controls can actually be matched. The mean age for COVID-19 cases was 64.5 years, while the age of matched controls was not shown. Furthermore, the matching for other variables such as hypertension and diabetes was based on history but not measured blood pressure and glucose level. The study participants with undiagnosed hypertension and diabetes were classified into the group without history.
6. The case fatality ratio during hospitalization was quite high, not only for ICU patients but also non-ICU patients. According to supplementary Table 3, why was the proportions of death and admission to hospital following discharge even higher among non-ICU patients than ICU patients? Was there any explanation for this? Were the non-ICU patients recovered before they discharged? What is the criteria for hospital discharge? What are the main causes of death after discharge for COVID-19 and controls respectively?

Minor comments:
1. In the statistical analyses section, the calculation of rate ratio was not clearly described including but not limited to the type of statistical models chosen.
2. Table 1 can be attached as supplementary table although it also showed important information. The comparison of baseline characteristics between COVID-19 cases and matched controls are more important to be shown as Table 1 in main manuscript.
3. In Table 2, the result for "respiratory disease (all events)" was also shown as rate per 1,000 person-years. To my understanding, "respiratory disease (all event)" indicates frequency of people with existing respiratory disease which should be prevalence, but incidence rate was shown. This question is the same for Figure 2. For figure 3, was the rate ratio calculated for new-onset events?
4. During pandemic of COVID-19, as the authors have also mentioned in limitations, people without COVID-19 may be more prone to stay at home when encountering with symptoms especially that are tolerable compared with COVID-19 patients. Thus, the proportion or rate of events are more likely to be underestimated for those without COVID-19. The effect of pandemic on admission to hospital and diagnosis of newly onset events may be larger than that we can estimate.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Bin Cao

Job Title: Dr.

Institution: China-Japan Friendship Hospital

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here:

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer's ORCID record, along with the date the record was uploaded; there is no identification of the article's title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes

Reviewer: 3

Recommendation:

Comments:
Thank you for the opportunity to review this manuscript. This is a very nice epidemiologic study that addresses a key knowledge gap in the COVID literature: a quantification of the burden of organ-specific diagnoses experienced after a COVID-19 hospitalization relative to controls matched on demographic and clinical characteristics. The study leverages the Hospital Episode Statistics (HES) Admitted Patient Care (APC) Records for England, which includes data from all hospitalization episodes in England. A highlight of this study is the presentation of overall event rates as well as new-onset cases.

Major comments:

1. Methods, Study Population (page 5): "Candidate controls comprised individuals who: (i) did not meet the COVID-19 inclusion criteria specified above; (ii) had at least one GDPPR record between 1 January 2019 (one year before the start of the follow-up period) and 30 September 2020 (the end-of-study date); and (iii) had not died before 1 January 2020. Each control had the same index date as their matched COVID-19 case." In reading the manuscript the first time, I had presumed that the control group comprised hospitalized patients who did not have COVID, and that the index (i.e. hospital discharge) date was the same for each matched pair. However, it seems that the GDPPR is an outpatient dataset, raising the question of whether these were outpatient controls whose index date was a GP visit.
a. Please clarify whether these were hospitalized controls or outpatient controls.
b. If these were hospitalized controls, please add language to make this explicitly clear in this section of the manuscript, keeping in mind that your international audience is not familiar with the GDPPR.
c. If these were outpatient controls, the readmission outcome would not apply to the control group – the outcome would be hospitalization for the controls and readmission for the cases. Additionally, the use of outpatient controls should be listed as a limitation as the models would not account for the effect of the hospitalization itself on outcomes.

2. Methods, Outcome variables (page 5): "Respiratory, MACE, diabetes, CKD and CLD events were identified from diagnoses made in primary care and in hospital (using only primary ICD-10 codes for the latter), except for the arrhythmia component of MACE for which primary care data were not available."
a. For transparency and reproducibility, please provide the complete list of diagnosis codes used to identify the outcomes in a supplementary table.
b. How did the authors capture arrhythmia if it was not available in the dataset? If it was not captured, this would be a limitation worth mentioning as we know that COVID-19 patients may suffer arrhythmias

due to cardiac involvement and also as a result of certain medications used during the first wave of the pandemic (e.g. hydroxychloroquine causing QT prolongation).
c. For the international reader who may be less familiar with the HES dataset, a reference attesting to the validity and completeness of the primary outcome diagnosis codes in the dataset would be helpful.

3. Discussion (page 9, line 33): "The index event was admission rather than discharge, so the results do not necessarily capture long-term outcomes of COVID-19." Whether Xie et al. used the hospital admission date or discharge date as time zero should not significantly impact their assessment of long-term outcomes; indeed, their Table 4 shows that the median hospital LOS among COVID-19 patients was 6 days (IQR 3-12). Kindly rephase this statement.

4. Supplementary Table 3: This table will be of particular interest to the critical care community, but it seems that "new onset" events are not presented here, as they were in Supplementary Table 2. Would it be possible for the authors to structure this supplementary table in the same way (presenting "all events" and "new onset" events)?

Minor comments:
1. Page 5, line 51: "Arrhythmia" is misspelled.
2. Page 7, line 19: "COVID-19" is misspelled.

Additional Questions:
The BMJ uses compulsory open peer review. Your name and institution will be included with your comments when they are sent to the authors. If the manuscript is accepted, your review, name and institution will be published alongside the article.

If this manuscript is rejected from The BMJ, it may be transferred to another BMJ journal along with your reviewer comments. If the article is selected for publication in another BMJ journal, depending on the editorial policy of the journal your review may also be published. You will be contacted for your permission before this happens.

For more information, please see our peer review terms and conditions.

Please confirm that you understand and consent to the above terms and conditions.: I consent to the publication of this review

Please enter your name: Lauren E. Ferrante, MD, MHS

Job Title: Assistant Professor of Medicine, Section of Pulmonary, Critical Care, and Sleep Medicine

Institution: Yale School of Medicine

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests (please see BMJ policy) please declare them here: Dr. Ferrante is supported by a Paul B. Beeson Emerging Leaders in Aging Career Development Award from the National Institute on Aging (K76 AG057023) and the Yale Claude D. Pepper Older Americans Independence Center (P30 AG021342). She is also mPI of the NIH-funded VALIANT study, a longitudinal assessment of outcomes among older adults hospitalized with COVID (P30 AG021342-18S1).

BMJ are working with ORCID to recognise the importance of the reviewer community. Reviewers are now able to share their activity by connecting their review to their ORCID account to gain recognition for their contributions.

Only the Journal title will be uploaded into the reviewer’s ORCID record, along with the date the record was uploaded; there is no identification of the article’s title or authors. Records are uploaded once a decision (accept, reject, or revision) has been made on the article.

Would you like to be accredited by ORCID for this review?: Yes