11-Feb-2021
BMJ-2021-064655 entitled "Increased hazard of mortality in cases compatible with SARS-CoV-2 variant of concern 202012/1 - a matched cohort study"

Dear Dr. Challen,

I write with some good news. We sent your paper for external peer review on a fast track basis and have discussed it at today's manuscript meeting with editors and our consultant statistician in attendance. We would like to proceed with the paper, provided you can revise it to address the comments of reviewers and editors. This is an important and timely paper, so we are hopeful that you will be able to address the comments of reviewers and return this within three business days, i.e. by Tuesday 16 February. At that point our statistician, Professor Rafael Perera, will take a look at the paper. Provided he is satisfied, we would then hope to prepare the proofs and publish it rapidly, ideally with an accompanying editorial and press release. I am hopeful that might occur early in the week of 22 February.

I look forward to reading the revised version of the paper. Please be in touch if you have any concerns. Our manuscript administrator will reach out to collect the ICMJE forms on behalf of each author. Supplying them promptly will help with timely publication.

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.

Thank you very much for entrusting us with your work! I am available for any questions or concerns. I always check email over the weekends, so please do not hesitate to contact me if any problems arise.

Sincerely,

Dr Elizabeth Loder

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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.

Present: Wim Weber (chair); Rafael Perera (statistician); Tiago Villanueva; David Ludwig; Joseph Ross; John Fletcher; Jessica Kimpton; Nazrul Islam; Clara Munro; Elizabeth Loder

* The methods section would benefit from additional information. The selection process of how you arrived at the 109545 matched patients is not very clear and requires additional explanation. (Fig. 1 is very confusing).

* You find an average of 171 deaths out of 54773 patients in the S-gene negative arm of the study compared to 101 out of 54773 in the S-gene positive control arm. With the limited adjustments, we wonder how reliable this figure is. Might you comment? For example, it appears that you were not able to take comorbidities into account in your analysis.

* We discussed how to best put results in context. Although the HR of 1.7 seems alarming, the absolute risks remain low and increased transmissibility might be more worrisome than an increase in mortality with the new variant. Perhaps you could discuss this. Might you allude to the absolute risks here to help readers put results into perspective? The absolute risks are small (0.18% in the S+ group), and that is w/o the <30 yrs fraction. Perhaps these numbers should be in the abstract. Although you've included 109,545 patients, only 272 died.

* Might you also make the point that increased transmissibility might be more worrisome than increases in mortality with this variant? It's the spread that is the main problem with this VOC. A small increase in fatality might be considered "noise" at a population level.

* Can you clarify how you obtained mortality data?

* The literature suggests a case fatality rate of somewhere between 0.8 and 1.2%, depending on hospital capacity. But here in a sample of adults 30 and up, the case fatality rate (within 28 days) appears to be 0.24%, 0.31% in the S-gene negative group and 0.18% in the S-gene positive group. Since you are examining 28 days within testing positive, and it takes anywhere from 5-10 days to present with symptoms, perhaps the followup period is too short? We also don't know whether their disease was more severe with respect to the need for acute care/hospitalization, etc.

* Please reconsider some of the terminology used in the paper. You say this is a matched cohort study but you used incidence density sampling - this is probably not the correct term as it is is used for nested case-control studies. The terms "Cases" and "Controls" are also misused here; these two groups should be labelled as Exposed and Non-exposed groups, respectively.

* There is hardly any detail provided on the outcome ascertainment, censoring, and loss-to-follow-up data. We need to know, since a matched cohort study will prevent confounding (from the matched variables) given there was no (differential) loss-to-follow-up.

* The test eligibility was up to 29th of January. Does it mean that some people were only followed-up for just a few days (or even no follow-up at all)? This can be potentially quite problematic.

* It was also not clear how 50 replicates were handled in the statistical analysis. Does it not artificially inflate the sample size?

* There was a cross-over of the survival curves. Was the proportional hazards assumption violated?

* Please justify the 28-day time frame for the outcome.

* We are not clear how you integrated the multiple replicates and that might need some added explanation (possibly as an Appendix). Similarly, some further explanation of the creation of the replicates might be useful.

* Finally, the mortality rate does appear considerably low compared to current levels (closer to 2% and not 0.2%). This would at least need a discussion. It's unclear how this would have affected your

comparison. There does not seem to be a differential follow-up that would explain this as you are matching by spatio/temporal issues.
If the new strain is more common in those with multiple comorbidities, this could explain it, however, this might in itself be important and would require a note in the limitation section.

* Please better explain, for non-UK readers, what is meant by Pillar 1 and 2 testing and the populations that will be captured by each.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how and where you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Comments:
"Increased hazard of mortality in cases compatible with SARS-CoV-2 variant of concern 202012/1 – a matched cohort study" compares rates of death in people with PCR tests exhibiting S-gene target failure (SGTF) with those without SGTF. The authors found that SGTF cases are significantly more likely to die within 28 days of diagnosis, after controlling for a number of factor. This is an important finding with timely and meaningful public health implications. The analysis is thorough and well-supported.

Questions and recommendations:

The methods section says that participants who were diagnosed as late as January 29th were included in the analysis. Final disposition would not yet be available for most cases diagnosed in January. Can the authors clarify how recently-diagnosed cases were handled in the analysis?

Although Public Health England has reported that SGTF is highly correlated with the B.1.1.7 lineage in the UK, that has not always been the case in the United States [1]. I recommend clarifying the robustness of SGTF as a marker for the VOC in your dataset, to benefit international readers.

"Pillar 2" is UK-specific jargon. I recommend clarifying what constitutes a Pillar 2 test (beyond what is stated on page 4 line 12, which I did not find clarifying) and use a more common term throughout.

The text asserts that the VOC was first detected in the UK in December of 2020. Public Health England situation reports suggest that detection was as early as September [3].

There are a number of grammatically errors that should be fixed before publication.

[1]
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/957504/Variant_of_Concern_VOC_202012_01_Technical_Briefing_5_England.pdf
[2] https://www.helix.com/pages/helix-covid-19-surveillance-dashboard
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Reviewer: 2

Comments:
In this paper, the authors conduct a pair-matched analysis of community testing data and death data to estimate the relative mortality of the SARS-CoV-2 variant of concern in the UK. This is one of several analyses of these data that have been done by research groups, at the request of the government. The pair-matched approach enables the authors to match finely on several covariates, including age, locality, and time. The authors estimate a hazard ratio of 1.7, indicating an increase in mortality associated with this variant.
The question is clearly highly impactful, as it has important public health implications for the UK and the rest of the world. The pair-matched approach is sensible, and allows very fine matching, although at the expense of unmatched cases who then do not contribute to the analysis. The authors comment on this trade-off in the discussion. I provide comments on a few reservations I have. First, the methods are not fully described, and more precision will be needed throughout. Second, the logic of the investigation into sources of bias is not always clear. On the other hand, there are other types of sensitivity analyses or subanalyses not included that would help readers evaluate the robustness of the result. I provide several comments below.

Major comments:
1) The authors do not discuss lags in death reporting and how these may affect recent cases. But it seems likely to impact the results as the analysis includes individuals whose first test was on Jan 29th, 2021, for an analysis written on Jan 31st, 2021. How was censoring defined? This should be explained very precisely as a key study method.
2) The authors describe how they identified 50 sets of matched pairs, to generate a more robust result that integrates more of the available data, but they do not describe how this was accommodated in the modeling, point estimation, and confidence interval estimation. This should be explained precisely.
3) Can the authors explain why CT value would be regarded as a potential source of bias? Given that CT could lie along the causal pathway, it may be more interpretable if the analysis is presented as an effect that is not exclusively explained by CT. But it is worth pointing out that adjusting for N gene CT undermines the matching procedure employed. From Shinozaki paper referenced, "when additional confounders are adjusted in the analyses, such cancellation breaks down and ignoring matching variables results in biased estimates." Similarly, why do the authors not adjust for age in the N gene CT model, where age had been shown in the prior model to help explain hazard.
4) Can the authors explain why they control for age and not the other matched covariates in their model? It seems that these could improve the precision of the model by removing sources of variability in hazard. Did the authors explore more flexible models for age than a single linear term?
5) Table 2. "Hazard rate" should be "Hazard ratio." Figure 4A-C. "Hazard rate" should be "Hazard ratio." Similarly, Figure 4 caption. "Slightly lower estimates of hazard" should be "slightly lower estimates of the hazard ratio." Page 7. "Shows a reduction in the overall hazard of S-gene negativity to 1.4" should be "shows a reduction in the overall hazard ratio of S-gene negativity to 1.4." Page 7. "Figure 4 shows the estimates of hazards related to alternating those assumptions." And so on.
6) Section titled Sensitivity analysis. Inadequate detail is provided to the reader, who may not be familiar with the author's preliminary analysis. I suggest providing the prior estimate for context, an accounting of how much more data were made available, and any changes in definitions.
7) Decreasing the CT threshold increases the number of equivocal cases, but I would encourage the authors to point out that this would preferentially target the S-gene positive cases (making them more equivocal) as these have systematically higher CT. So in that way, it has the potential to induce bias.

8) In terms of assessing biological plausibility of increased severity, it would be helpful to see how this hazard ratio holds up across subgroups. Analyses that examine the robustness of the finding across subgroups would provide greater confidence than some of the sensitivity analyses currently included.

Minor comments:
9) Figure 1 and Text. I assume it is rounding of an average, but people will notice that 54,773*2 != 109,545.
10) Kaplan Meier curve needs a more informative x-axis, e.g. time from first positive test.
11) Table 2. Suggest reporting hazard ratios for age and CT value as 10 unit changes, or including more significant digits. 0.9 (0.9 – 0.9) has a very strange appearance.
12) P6 Line 49. Admission is presumably hospital admission, but please clarify in the text. Hospital admission data are not described in the study methods. Are these linked to the death data?
13) Figure 3A and the associated text. The authors should make it clearer to readers that this analysis is restricted to individuals who ultimately died. How does this analysis handle individuals who died but were not admitted to the hospital?
14) Figure 3A. The authors should clarify what bias this analysis is meant to signal.
15) It is unclear why Figure 3B would signal a source of bias. Instead, as the authors note, it reflects when circulation of the new variant took off, enabling enough pairs to be matched. This seems like this information would be better suited for Table 1, by adding a row for each month, providing a summary of the data.
16) Figure 4D. Pairwise bias not clearly defined.
17) Discussion. I would suggest more cautious language than "VOC-202012/1 infections… lead to an elevated risk of death." Was associated with.
18) The authors completed the STROBE checklist for a case-control study, despite this being a cohort analysis.

Natalie Dean
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