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Title: Frequency, persistence, and patient-reported outcomes of neurological and neuropsychiatric symptoms in mild COVID-19: a prospective cohort study
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General comments (author response in bold)

I read your paper with great interest. The study employed a prospective design by virtue of enrolling patients who agreed to take part in a clinical trial of a study drug vs. placebo, and agreed to be in the subsidiary observational cohort of neurological symptoms.
We thank the Reviewer for their comments.

MAJOR
1. The authors argue that the current data on neurological and neuropsychiatric symptoms in patients with mild COVID-19 infection are limited due to retrospective study designs and ascertainment of symptoms using medical records; however, can the authors please speak to the generalizability of their findings? The included participants are a) self-selected individuals who agreed to participate in a clinical trial, b) had to have a positive PCR test, which is not always readily available in the last year, and c) had to have ≥ 1 risk factor from e-table 1?
We agree that points A and C are relevant considerations for the generalizability of our findings, as acknowledged in the Discussion (page 13 paragraph 3):

> **"[…] the sampling of patients from a population who consented to a drug trial seeking to prevent severe COVID-19 might result in selection bias; that being said, our sample was quite diverse in terms of age, sex, race, and comorbidities."**

While we agree that PCR tests were not always readily available this past year, we think the fact that everyone in our cohort had PCR-proven SARS-CoV-2 infection is an important strength of our study, adding to the generalizability of our findings to patients with COVID-19.

2. The sample calculation presented in the statistical analyses was based on simply reporting the frequency of symptoms, and NOT for drawing any of the comparisons, using univariable or multivariable models. What are potential implications to the validity of your findings?
This is of course a typical situation in observational studies (and in clinical trials), as we have to pick a primary outcome of interest to power the study, so this simply means that the other comparisons reported can be considered secondary outcomes (or secondary analyses). We have clarified this in the Statistical Analysis section (page 7 paragraph 4):
"As secondary analyses, we examined the proportions of patients independent for instrumental activities of daily living/(IADLs), and reporting some or extreme problems on each EQ-5D domain. We also evaluated the association of neurological/neuropsychiatric symptoms with these outcomes and with

healthcare utilization. Proportions were compared using Fisher's exact test for univariable analyses and logistic regressions for multivariable analyses. EQ-5D responses were converted to Canadian utilities.[27] Scale scores and utilities were compared using Wilcoxon rank-sum for univariable analyses and quantile regressions for multivariable analyses."

3. In Table 2, a variety of self-reported and administrative-data derived outcomes are described. The comparison is made among those with any symptoms vs. no symptoms. Could the authors describe the time point where the authors determine with/without symptoms? This information is not clearly described in the methods, results, or the legend.

The determination for the presence or absence of symptoms for the analyses presented in Table 2, was at 3 months. We have now made it clear in the title of Table 2:

"Table 2. Neuropsychological test scores, self-reported quality-of-life, and healthcare utilization at 3 months and 1 year after mild COVID-19 for patients with and without neurological/neuropsychiatric symptoms reported at 3 months."

4. Further to #3, if those who had any symptoms (n = 40) are those who had presence of symptoms at the 1-year-mark based on page 9/34 lines 40-41, how do the authors justify presenting the results for both self-reported and administrative-data derived outcomes at 3 months stratified on presence or absence of symptoms at the 1-year-mark? When reporting any outcome, the exposure status should be known for any cohort study.

As noted above, the n=40 in this table comes from determinations made at 3 months and not 1 year. We have further clarified the origin of this number in the footnote of Table 2:

"48 patients reported neurological/neuropsychiatric symptoms at 3 months, when defined strictly, excluding anosmia/dysgeusia, myalgia, and headache; of these, 40 patients had data available for the outcomes presented in this table."

5. The same as #4 applies to the results described in Figure 3. Please clarify and justify if the "any symptoms" category in the "3 months" bar graphs represent any symptoms at 3 months or any symptoms during 1 year follow-up.

Again this is based on the determination at 3 months; we have clarified this point in the Figure legend:

"Figure 3. Quality of Life ratings on the EQ-5D-3L for patients with versus without any strictly defined neurological or neuropsychiatric symptoms (as determined at 3-month assessment) at 3-months and 1-year follow-up after mild COVID-19."

6. Can the authors describe which characteristics were adjusted in multivariable regression analyses? Why were these characteristics included?

As noted in response to the Statistical Reviewer, we have explained this more clearly now in the Methods (page 7 paragraph 3):

"Models examining the presence/persistence of neurological/neuropsychiatric symptoms were adjusted for age, sex, race, body mass index (BMI), and asthma, based on published associations with worse COVID-19 outcomes, as well as prior history of any neurological/psychiatric conditions.[27] EQ-5D responses were converted to Canadian utilities.[28] Scale scores and utilities were compared using Wilcoxon rank-sum for univariable analyses and quantile regressions for

multivariable analyses, adjusted for age, sex, BMI, and prior neuropsychiatric history, but also for years of formal education, given this is strongly associated with neuropsychological outcomes.[29]"
We have added two references to justify our selections:

1. **Kompaniyets L, Pennington AF, Goodman AB, et al. Underlying Medical Conditions and Severe Illness Among 540,667 Adults Hospitalized With COVID-19, March 2020-March 2021. Prev Chronic Dis. 2021;18:E66.**
2. **Heaton RK, Grant I, Mathews C. Differences in neuropsychological test performance associated with age, education and sex. In: Grant I, Adams KM, eds. Neuropsychological assessment in neuropsychiatric disorders. New York: Oxford University Press; 1986:108-20.**

7. Can the authors include the output for multivariable analyses?
Certainly, we have presented relevant results of the multivariable analyses on page 10; these are the findings described with "aOR", for adjusted odds ratio, or "adjusted difference".

8. How were the outcomes operationalized? It seems there are three outcomes: presence of any symptom, presence of persistent symptoms, and presence of symptoms without improvement. Can the author describe why all of them were studied, and why results of only some are reported?
We have now added a supplementary table to explain how these outcomes of presence, persistence, and no improvement were operationalized.
eTable 3. Operationalized definitions for the presence, persistence, and absence of improvement in neurological/neuropsychiatric symptoms in the Alberta Neuro-COVID study.

Symptom-related outcome	Operationalized definition (with example)
Presence of symptoms	**The patient reported ≥1 symptom that emerged with or after their COVID-19 infection at some point prior to the time of assessment.** **E.g. if at their 3-month visit, the patient reported new issues with confusion that emerged two days after onset of their COVID-19 illness, then they would be considered to have had "presence" of symptoms at some point of their illness course.**
Persistence of symptoms	**The patient reported ≥1 symptom that emerged post-COVID-19 and was still present at the time of assessment.** **E.g. if the patient reported new issues with confusion that was still present at the time of their 3-month visit, they would be considered to have "persistent symptoms" at that visit.**
No improvement of symptoms	**The patient reported having no improvement in ≥1 symptom that was present at the time of assessment.**

	E.g. if the patient reported new confusion that was still present at the time of the visit, and said there was no improvement in this symptom since onset post-COVID-19.

As these are our main study outcomes, we have indeed reported the results for all three outcomes on page 9, paragraphs 2-3 (we've added some clarifying text as needed). Specifically, paragraph 2 addresses the "presence of symptoms":
"Among 179 patients with neurological/neuropsychiatric symptom assessments, 139 (77.7%) reported ≥1 symptom at any point using the most inclusive definition; this number declined to 105 (58.7%) when excluding anosmia/dysgeusia, and to 48 (26.8%) when additionally excluding myalgia and headache. The most common symptoms were anosmia/dysgeusia (56.3%), myalgia (42.6%), and headache (41.8%), followed by confusion (25.3%), depression, and insomnia (each 24.1%). The median number of symptoms reported by each symptomatic patient climbed from 2 (IQR:1-3) using the most inclusive definition to 3.5 (IQR:1-6) using the strictest definition. Using the most inclusive definition, symptoms generally began within the first week (first symptom, median onset at 6-days, IQR:4-8; last symptom: 7-days, IQR:5-10; Figure 2). Using the strictest definition, the first symptom generally began on the first day of illness (median 1-day, IQR:1-3), but the last symptom was often delayed (median 47.5-days, IQR:2-180). No concerning neurological diagnoses were made and investigations were rare and unremarkable (further details in eTables 3-4).
This section of paragraph 3 on page 9 addresses the "persistence" of symptoms:
"Symptoms improved for most patients over follow-up. At least one neurological symptom, new compared to pre-infection, persisted at 1-year follow-up for 40 (22.3%) patients; excluding anosmia/dysgeusia, this declined to 38 patients (21.2%), and on further excluding myalgia and headache, to 37 patients (20.9%). These patients reported a median of 4 (IQR:2-7.5) persistent symptoms."
This section of paragraph 3 on page 9 addresses those with "no improvement" of symptoms:
"Regardless of symptom definition, 27 patients (15.1% of all 179 patients who completed symptom reports, 67.5% of those with persistent symptoms) reported no symptom improvement over follow-up. Among those with persistent symptoms, the most common symptoms at 1-year were headache (52.5%), confusion (50%), and insomnia (40%, eFigure 1)."

9. Some adjusted odds ratio described in the results section have values of 21, 22, and 66.2! The 95% confidence limits of these odds ratios are in 100s. Can the authors please justify the inclusion of these odds ratio, and acknowledge the limitations of drawing conclusion based on these results?
Indeed, odds ratios can sometimes be quite remarkably high for strong associations. The relatively wide confidence limits reflect the sample size. The limitations of the sample are acknowledged in the discussion.

10. Were all the analyses described in the results e.g., symptom specific association with cognitive performance, planned a-priori?

The planned primary and secondary analyses are now more clearly indicated in the Statistical Analyses section. The association of individual symptoms with neuropsychological test results should be considered exploratory and we have specifically stated this now (page 7 paragraph 4):
"Exploratory analyses included examining the association of specific symptoms with neuropsychological test results".

11. Further to #10, can the authors please explain why results of only some specific symptoms are reported, when there were over 20+ symptoms studied?
As these were exploratory analyses, only significant results have reported for this section.

12. Can the authors please explain why they report unadjusted estimates in tables, figures, and bar graphs, and draw conclusions to their comparisons based on these results, when they have adjusted estimates and knowing that the classification of those with vs. without symptoms is not random? One would argue that adjusting for premorbid neurological/psychiatric symptoms would be important to account for when reporting some outcomes such physician visits, and quality of life.
We think that it is important to also present the simple unadjusted results in the spirit of transparency and to provide the true observed values which we think will be of interest to readers. However, we agree with the Reviewer that for the functional outcomes, healthcare use, and quality of life results, it is important to adjust for the presence of prior neurological/psychiatric history, so we have presented adjusted estimates as well in the main text of the Results, adjusted for this history as well as age and sex (page 10 paragraph 4):
"As for functional outcomes, whereas 124 of 126 (98.4%) patients were pre-morbidly independent for IADLs, only 21 (77.8%) of 27 patients without improvement in neurological/neuropsychiatric symptoms remained independent at 1-year, versus 98.2% of the rest (p=0.005; aOR adjusted for age/sex/neuro-psychiatric history:0.06, 95%CI:0.01-0.58). Similarly, patients with persistent symptoms were less often independent for IADLs at 1-year (with strictest definition, 83.8% vs 97.8%, p=0.042; aOR:0.11, 95%CI:0.01-0.97). Patients with persistent symptoms had more hospitalizations and family physician visits (Table 2, adjusted-difference: 3.0 additional visits, 95%CI:1.0-5.0). Patients with any/persistent symptoms had worse quality-of-life ratings and utility scores at 3-months and 1-year (Table 2, Figure 3); for example, utilities at 1-year for patients with strictly-defined symptoms were 0.16 points lower than those without (adjusted-difference -0.16, 95%CI -0.25 to -0.06)."

MINOR
13. Page 8/34, statistical analyses: "…what constituted such symptoms – first, endorsement of any checklist symptoms; second, excluding anosmia/dysgeusia, which can be rhinal/oropharyngeal in origin; and third, additionally excluding myalgia and headache, which can commonly accompany viral infections." Is there "second" missing here?
We confirm there is nothing missing; as can be seen above, we say "second, excluding anosmia/dysgeusia, which can be rhinal/oropharyngeal in origin".

14. Page 11/34, discussion: "Furthermore, our findings highlight the long-term neuropsychological, health-economic, and patient reported outcomes following mild

COVID-19, and their modification by neurological/neuropsychiatric symptoms." Can the authors describe what health-economic outcomes were reported?
Quality of life and healthcare utilization are both health economic outcomes, so we have clarified the statement accordingly (page 12 paragraph 5):
"Furthermore, our findings highlight the long-term neuropsychological, health economic (quality-of-life, healthcare use), and patient-reported outcomes following mild COVID-19, and their modification by neurological/neuropsychiatric symptoms."

15. For Figure 3, can the authors please report n and % for those with any symptoms and those with no symptoms, and similarly for the panel F?
We have now indicated the n and % for each component of these figure panels.

16. Could the authors consider commenting on possible biological basis for delayed onset of some symptoms e.g., about 25% patients had agitation after 270 days. Any symptom after 30 days of COVID-19, especially those such as confusion, LOC, depression, and numbness may be unrelated to the COVID-19 infection per se.
We agree with the Reviewer that the biological basis for more delayed symptoms is doubtful and have added the following to the Discussion (page 13 paragraph 2):
"The delayed onset of some symptoms in our cohort (e.g. agitation) beyond 30 days of COVID-19 may be unrelated to the infection itself."

17. The questions listed in e-table 2 mention that the selected symptoms should have not been present in the "months before COVID-19" infection, but there was no timeline given. Can the authors discuss some implications for the way these questions were framed?
We think the framing of the questions was adequate to help the patients understand that the symptoms they were reporting or endorsing should have been new since the time of their infection and not more chronic symptoms. However, as noted by the Reviewer in #16 above, this does mean that the patients could endorse symptoms that begun in a rather delayed fashion compared to the onset of their COVID-19 illness, and we have noted that such symptoms may be unrelated to the infection itself (page 13 paragraph 2).