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Title: Initial healthcare costs for COVID-19 in British Columbia and Ontario, Canada: an inter-provincial population-based cohort study
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Reviewer 1: Dena Schanzer
Institution: Infectious Disease and Emergency Preparedness Branch, Public Health Agency of Canada

General comments (author response in bold)

In this manuscript, the authors provide estimates of health care costs for COVID-19 using linked health administrative databases. Linked health administrative databases provide a wealth of information at relatively low cost. Understanding the health care costs associated with the COVID-19 pandemic in Canada will be an important component in future policy considerations as we start to learn how to live with this virus as well as for future pandemic planning exercises. Unfortunately, this study has a number of serious limitations that are not fully discussed or were ignored.
We thank the reviewer for their thoughtful comments and insights. We have made a number of changes throughout the manuscript to address their comments. Our replies are below with references to the revised paper.

1) My main concern is the treatment of censored observations, either by death or lost to follow-up, due primarily to the variable follow-up period. The study includes COVID-19 cases identified before June 30, 2020. However, follow-up continued only until July 31, 2020. Hence the follow-up period will range from 1 to 4 months depending on the date of diagnosis. Hence 'mean cost' and 'mean net cost' no longer adequately describe the reported results. 'Mean cost per case for the 30-day period following diagnosis' would be appropriate for the cases, as there would be no health care costs after death. However, costs for the matched controls were only included for the days the matched case was alive. Rather complex, with the baseline estimate potentially open to misinterpretation. Whether the costs for controls after the death of the case should be included will depend on how the estimates are used and how they are described. These details should, at least, be included as a footnote in each table or figure.
For the subsequent periods, it gets even more complicated. For days 31-60, we can see in Table S2 that approximately 20% of the cases were lost to follow-up. This would suggest that the cost per person in scope at the beginning of the period would underestimate the average cost (had a longer follow-up period been used) by approximately 10%. The mental gymnastics required to try to understand these estimates gets rather complex. When periods of observation vary, typically results are presented as units per person time. Better still, why not just include 4 months of follow-up data for each case (and matched control)? Care is still needed in how death is handled. I'd suggest considering reporting both costs per case (and matched control) and costs per person-time. This will account for the impact of death in the most transparent manor [sic].

You will also have to consider how to handle the baseline (costs for the matched controls). In most cases you would want to include the costs for the full period in your baseline estimate, ie, include costs after the death of the matched case. The interpretation of the 'mean net costs' is then the costs per case less expected costs per case for the full period in the hypothetical absence of the disease. The presented results need to be interpreted in consideration of how deaths and lost to follow-up were handled.

We thank the reviewer for these thoughts and comments concerning censoring and deaths in the cases and their controls.

With respect to censoring, the last day of the study observation period was July 31, 2020 and the last diagnosis/index date was June 30, 2020, so nearly all cases were observed for a minimum of one month, unless they moved out of the province or lost MSP/OHIP eligibility. Almost all of the cases who had fewer than 30 days of observation in month 1 died. As the reviewer says 'Mean cost per case for the 30-day period following diagnosis' is appropriate for the cases, because no costs would be incurred after death. Our presentation of costs by health care resource (Table 2) and mean net costs by COVID-19 case characteristics (Figure 3; Table S5), use only the first 30-day period, where we have complete observations. However, in subsequent months, more cases were censored. In consideration of the interpretation of costs for these months, we have added a supplementary figure and table reporting the number and percentage of cases who were censored and died in each 30-day period (Figure S3, and Table S2), and added a paragraph to the Results section (p. 10) reporting censoring rates and average follow-up time. Our estimates of the average costs in those months are lower than they would have been, had the cases been observed for the entire 30 days. We have also expanded our discussion of limitations on pages 15 to 16 (clean version) to describe the impact of censoring on our results.

Two suggestions are provided by the reviewer: 1) present results as units per person time, or 2) just include 4 months of follow-up data for each case and matched control. We had considered reporting the costs per person-day in our original analyses, but we decided that we would stay true to our objective, which was to estimate the health care system costs of care, as observed, and without re-weighting, for cases with COVID-19 in BC and Ontario. When costs are standardized to person-time, such as per person-day, they are more difficult to interpret (cost rates are rarely reported in the literature) and there is a tendency to extrapolate these daily costs to 30-day costs. This is problematic because extrapolation assumes that cases (and matched controls) would have incurred the same costs after death or censoring as they did before. The second suggestion, to include only cases who had 4 months of observation after index date, would discard valuable data from many cases who tested positive within 4 months before July 31, 2020.

In response to the reviewer's questions about how costs were handled after the death of the cases, controls were censored when their case died, so the costs for the matched controls were only included for the days the case was alive. We clarified this in the methods section (under study design and data sources). Following the reviewer's suggestion, we added a footnote under each table and figure that reports costs for the controls or net costs. In addition, we added the number of cases and controls in each 30-day period to the tables and figures reporting costs.

The costs for the cases and their controls were reported in Table S2 in the original manuscript (now Table S3). The primary objective of the study was to estimate individual-level direct medical costs of COVID-19, and thus our main outcome was the costs for the cases. However, recognizing that COVID-19 cases receive health care for non-COVID-19-related health conditions we included matched controls, as in previous studies (for example):

• de Oliveira C, Bremner KE, Liu N, Greenberg ML, Nathan PC, McBride ML, Krahn MD. Costs for childhood and adolescent cancer, 90 days pre-diagnosis and 1 year postdiagnosis: A population-based study in Ontario, Canada. Value Health. 2017 Mar;20(3):345-356. doi: 10.1016

• Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: A longitudinal cohort study. Can J Gastroenterol 2010;24(12):717-726;

• de Oliveira C, Pataky R, Bremner KE, Rangrej J, Chan KKW, Cheung WY, Hoch JS, Peacock S, Krahn MD. Phase-specific and lifetime costs of cancer care in Ontario, Canada. BMC Cancer 2016;16:809.

The matched controls were similar to the COVID-19 cases on the matching variables but did not have a positive COVID-19 test. The net cost (cost for the case minus the mean cost for his or her controls) is therefore an estimate of the cost attributable to COVID-19. We have added a reference that describes the net cost methodology in the "Cost estimation and analysis" section of the Methods:

• Barlow WE, Overview of methods to estimate the medical costs of cancer. Medical Care 2009;47(7 suppl 1):S33-S36.

Our analysis was conducted from the perspective of the individual with COVID-19, and including costs for controls after the case's death would underestimate the actual costs
attributable to COVID-19. The mean costs for the controls would be higher, resulting in net costs that would be lower than those reported in our study.

2) Another major concern I had was with the layout and content of the reported data (tables and figures). I found Table S4 much easier to read/follow, and recommend that it be moved to the main body, as it seems to summarize the main results better. Some of the important features of Table S4 that were not provided in the tables presented in the main body include:

Table S4 (now Table S5) provides net costs for the entire cohort, stratified into different subgroups based on COVID-19 case characteristics. Most of the results reported in Table S5 were reported in the text and in Table 3 and Figure 3. We added information from Table S5 to the second paragraph of the 'Stratified net costs 30 days post-index' section of the Results.

a. In table S4, the highest level of care group was treated as one of many characteristics (rather than separate columns). As no explanation was given for why there was a focus on providing results by highest level of care group only in the main body, the format of Table S4 makes much more sense and appears more complete.

We have added an explanation and justification for the stratified analysis by level of care to the Methods, fifth paragraph of the "Study design and data sources" section in the revised manuscript. We also added level of care to our objective at the end of the Introduction. As reported in the Introduction, the Canadian Institute of Health Information has reported costs for hospitalized patients with COVID-19. One of the unique strengths of our study is that it included COVID-19 cases who

remained in their homes, whether in the community or in long-term care facilities. Also, costs by level of care are useful for models of strategies to reduce severity of illness. Our study showed that if fewer cases required hospitalization, the total health care system costs for COVID-19 would be much lower.

b. Potential comparisons are in adjacent cells so that I can easily see, for example, that costs increase with age until age 80 and can confirm that costs were lower for LTC residents.
These results are presented graphically in Figure 3 and described in the text in the Results, in the section "Stratified net costs 30 days post-index", on page 11 (clean version). We added information on the net costs by residence at index date to the text in that section, in the revised manuscript.

c. An estimate of precision (SE and 95%CI) is included with each estimate of the mean rather than measures of dispersion (median, IQR and SD). By the way, guidelines usually only require one of SE or 95%CI. If you want to report dispersion measures (SD, IQR or median vs mean), I'd suggest moving this information to the supplementary files.
We have added 95% CIs to Tables S3a, S3b, S4a. We have retained the measures of dispersion in Table 2 (SD) in the main paper because they indicate that many of the costs are skewed, with many cases having zero costs and some having very high costs.
As in the original manuscript, all tables with net costs (Table 3, S4b, and S5 in the revised manuscript) included 95% CIs. We removed the standard error from Table S5.

d. I would like to see the costs calculated for the full cohort included (total). This should be your main result. I would also be interested in seeing costs by phase (pre-index, acute and recovery) as we have heard so much about long covid-19.
Thank you for these suggestions. We have added mean costs for the full cohort to Table 2, which reports resource-specific costs in pre-index and month 1 for cases. We also report them in the Results on page 9 (clean version). However, we chose to emphasize the costs stratified by highest location of initial care in the paper as our primary results, because we feel they are essential for providing insights to models of care and decision-making, and reveal considerable heterogeneity in cost. We clarified that costs and resource use are dependent on initial location care as explained in the Methods section on page 6 (clean version). As stated in the Interpretation, total costs to the health care system depend on the number of cases and the mean cost per case. For example, in Figure 2a for BC, we show that the total costs for initial care for all of the cases in the hospital and ICU level of care groups were approximately 9 times the total costs for all cases in the community level of care group, yet the hospitalized cases comprised only 19% of all cases. Figure 2b shows that in Ontario, the corresponding difference in total costs for all cases in the hospital group was just under 6 times the total costs for all cases in the community care group, while the hospitalized cases were only 13% of all cases.
With respect to costs by phase, we report costs for the pre-index month as the reviewer suggests, and month 1 can be considered to be the 3 to 4-week acute phase indicated in clinical studies:
• Ladds E., et al. BMC Health Services Research 2020;20:1144; Greenhalgh T, et al. BMJ 2020; 370:m3026.

Long covid-19 has been defined as symptoms lasting beyond 12 weeks
• Ladds E., et al. BMC Health Services Research 2020;20:1144; Greenhalgh T, et al. BMJ 2020;370:m3026,
However, other definitions propose that late sequelae begin as early as 4 weeks after symptom onset
• Datta SD, et al. JAMA 2020;324(22):2251-2252,
and have multiple manifestations
• Greenhalgh T, et al. BMJ 2020;370:m3026.
We have added a paragraph to the Limitations section of the Interpretation, "administrative data lack sufficient clinical information to determine phases of care for COVID-19. Our observation period covered health care costs attributable to initial COVID-19 care, and did not capture costs arising from long-term symptoms or complications."

e. Given that there were numerous media reports of the large number of deaths that occurred in LTC facilities that were overwhelmed, and that transfers from LTC to hospital were limited, it would seem helpful to report results by highest level of care for LTC and community residents separately. There is also the consideration that patients with dementia are unlikely to receive treatments requiring sedation (ie ventilators), thus also limiting treatment options for many LTC residents. (Some potential research objectives.)
We have added Figure S2 to show the number of cases who resided in LTC at index date and how many were admitted to the hospital for COVID-19 care and how many remained in LTC. Of the 5,152 Ontario cases who were residing in LTC facilities at index date, 87% remained in the LTC level of care group. Corresponding percentages are presented in the manuscript Results, Study cohorts on page 9 (clean version). Here we state that in Ontario, 13.1% of LTC residents were admitted to hospital within 2 weeks after their index date (11.7% with no ICU; 1.4% with ICU). Among the 23,741 cases who resided in the community at index date, 86.5% remained in the community level of care group, and 13.5% were admitted to hospital (9.8% with no ICU; 3.7% with ICU). Thus, LTC and community residents had similar rates of hospitalization but LTC residents were less likely to be admitted to the ICU. Similar results were found for the BC cohort and have been added to the revised paper and are shown in Figure S2.
We have added a sentence about patients with dementia at the end of the first paragraph of the section "Long-term care" in the Interpretation on page 14 (clean version). We thank the reviewer for suggesting a future research objective to consider whether patients with dementia are unlikely to be transferred to hospital, or be admitted to ICU, with or without mechanical ventilation. This would be very interesting to investigate, however this topic is outside of the scope of this current study.

3) Differences in the pre-index costs between cases and matched controls need to be explained. For example, the mean cost for hospitalized cases in the pre-index period was $4,494 and $1,361 for the match controls (Table S2). If controls are appropriately matched to cases, then I would expect their health care needs prior to infection should have been the same (unless they acquired the infection in the hospital). The same for the ICU group.
We have added to the methods section under Cost estimation and analysis, on page 7 (clean version) that the pre-index period was included to capture resource use and costs for investigation of COVID-19 symptoms leading up to the test. This

should clarify that the matched controls and the pre-index period served different roles in the analysis.
The purpose of the matched controls was to provide estimates of the resource use and costs which the cases would have had if they had not been diagnosed with COVID-19. These baseline costs for controls were subtracted from the costs for the cases, within each matched set, to determine the costs attributable to COVID-19. These cases and controls were well-matched as shown in Table 1, with a small standardized difference.
The purpose of the pre-index period was to capture pre-diagnosis work-up, and associated costs. Thus we included the costs for investigation and treatment of symptoms prior to testing and confirmed diagnosis during the pre-index month. The pre-index period was not intended to serve as a baseline or negative control. The reviewer is correct that many cases were in hospital at the time of their positive COVID-19 test. We have added information on the percentage of cases who were in hospital on their Index date to the Results in the last sentence of the first paragraph of "Mean health care costs" in the revised manuscript, on page 9 (clean version). Cases and controls were not matched on being in hospital on Index date.

a. Please note, as discussed above, that the results in Table S3 for days 31 to 120 should either be removed because of the strong downward bias due to the way censored observations were handled, or the methods revised to appropriately handle censored observations.
The cumulative cost estimates in Figure 1 and Table S3 include only cases who were observed for at least one day of the last month. We excluded cases who were censored or who died in previous months from the cumulative costs reported in each month. We have clarified this in the revised Methods section ("Cost estimation and analysis" section on pages 7 to 8 (clean version). We also added footnotes to Figure 1 and Table S4a and S4b that the costs for later 30-day periods are conditional on survival to the start of each period. As described above, we have also added text to the Limitations section on pages 15 to16 (clean version) and page 17 (tracked) describing the bias due to censoring. We have added the number of cases observed in each month to all tables.

CMAJ review questions:

4) Is there a clear research question? I could not identify a specific research question and the methods are not documented sufficiently to make a guess based on the methods. The research question should be specific enough to identity how these costs should be estimated and which costs should be reported.
The objective of the study was to describe direct health care costs for COVID-19 in two Canadian provinces. In the revised manuscript, we have expanded the last paragraph of the Introduction on page 5 (clean version) to explain what costs were not known before this study (the question), and how this study aimed to answer the question:
"Understanding the system-wide costs of health care services for individuals with COVID-19, including those who did not require hospitalization, is essential for economic evaluations of COVID-19 management strategies. Such evidence is crucial to measure the economic burden of COVID-19 illness and inform evidence-based health care planning and decision-making that control the spread and

severity of COVID-19. The objective of this study was to address this gap by estimating the direct health care costs for COVID-19, stratified by the highest level of initial care, in BC and Ontario during its first wave from January to June 2020."

a. Why are costs reported separately based primarily on highest level of care? How does this reporting relate to a research question? Should highest level of care not be considered a characteristic, such as place residence or age?
We have added a paragraph describing the stratification by level of care to the Methods section of the revised manuscript, in the section "Study design and data sources" on page 6 (clean version). We also revised the Introduction on page 5 (clean version) to clearly state our research objective. In the introduction, we state that the although the costs for COVID-19 hospitalizations have been reported by CIHI, our study has the additional advantage of reporting costs for those who were managed at home, whether their home was in the community or in a long-term care facility. The cases who were not hospitalized comprised most of the cases in both provinces during the first wave and continue to do so. Therefore, it is also important from a health care system planning perspective to not only estimate the costs of COVID-19 for hospitalized cases, with or without ICU admission, but also for cases who are managed at the community level who represented the majority of cases. These differing levels of care as used by Public Health Ontario, are responsible for different intensity of health care resource use, and hence guide resource allocation decisions.
We have added the mean costs for the cohort as a whole to Table 2 and to the text as indicated in our reply to comment 2d.

5) The study design should be reviewed.

a. In a retrospective study, subjects are recruited or identified and information is collected about their past. In a prospective study, individuals are followed over time and data about them is collected as their characteristics or circumstances change after recruitment. In this study, cases were identified based on the date of positive covid test and without knowledge of future outcomes, such as health care utilization. Hence, this looks to me like a prospective cohort study rather than a retrospective cohort study. Some explanation on the role of the 'controls' is needed for a cohort study, ie in this study to provide a baseline.
We thank the reviewer for this perspective and have corrected the terminology. Our study is a longitudinal analysis using previously-collected administrative data. We have revised the study description to a historical cohort study with a matched comparison group wherever applicable throughout the manuscript.
In our study, the role of controls is to provide an estimate of the health care costs for individuals who were similar to the COVID-19 cases on the matched variables with the difference of not having a positive COVID-19 test. The net costs (costs for the case minus the mean cost for their controls) were estimates of the costs attributable to COVID-19. We have added several references to the paper under the "Costs" section of the Methods that illustrate the role of controls in costing studies:
• Barlow WE, Overview of methods to estimate the medical costs of cancer. Medical Care 2009;47(7 suppl 1):S33-S36)

• de Oliveira C, Bremner KE, Liu N, et al. Costs for Childhood and Adolescent Cancer, 90 Days Prediagnosis and 1 Year Postdiagnosis: A Population-Based Study in Ontario, Canada. Value Health. 2017;20:345-56.
• de Oliveira C, Pataky R, Bremner KE, et al. Phase-specific and lifetime costs of cancer care in Ontario, Canada. BMC Cancer. 2016;16:809.
• Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: a longitudinal cohort study. Can J Gastroenterol. 2010;24:717-26.

b. The treatment of lost to follow-up likely results in a substantial bias for some results such as for periods of more than 30 days. The easiest solution to correct this is to include at least 120 days of follow-up for each case (and matching controls). Treatment of deaths should also be reviewed. Costs per case (alive at the index date) and costs per person-time could both be reported. Interpretation of costs in light of censoring and the way it was handled should be included in tables, figures (using footnotes), results and the discussion.
Please see our responses to comment 1. We have added footnotes to all tables and figures to explain how costs were estimated. We have added a paragraph to the Limitations in the Interpretation section concerning death and censoring.

c. Controls in this study seem to be used for a baseline measure of health care costs, as are the health care costs for the month before the index date. This should be clarified in the abstract and main body of the document. Results for both cases and controls should be provided in the results section (move tables from supplementary files to main body). Differences in costs between cases and controls for the pre-index period should be examined and discussed, as these differences could suggest poor matching.
We thank the reviewer for this comment. In our study, controls were used to provide estimates of health care costs in the absence of a positive COVID-19 test result. The month before the index date was used to capture costs for the investigation of symptoms before the positive test, and not as a baseline. The controls and the pre-index period are discussed in our replies to comments 3 and 5a. We have also explained the role of the pre-index period in the text as indicated in the replies to comments 3 and 5a. Our matching resulted in balance between cases and controls on observed covariates, as reported in Table 1 and Table S1. We elected to present net COVID-19-attributable costs are the primary outcome of interest in this study. The mean costs for both cases and controls are presented in the supplementary files.

d. Linked health administrative datasets are rich datasets to work with and the investigators should be able a identify an appropriate study design linked to a specific research question. Starting with a consistent follow-up period (for example, report on the health care costs of cases over 4 months post diagnosis), reporting on health care costs for the full cohort (not just by highest level of care), reporting the matched controls as a baseline, and providing results for other categories besides highest level of care (for example baseline, acute period, and recovery periods; place of residence; age; level of co-morbidity) as in Table S4, should provide ideas for specific research questions and a corresponding study design that will address these research questions.
Thank you for this summary of the comments. We have addressed these points above.

6) Methods: Methods are not sufficiently clear and some are not appropriate.

a. The main issue is the treatment of censored observations. If not appropriately handled, censoring can result in significant bias. The potential for risk of bias was not sufficiently considered or discussed.
Thank you for this comment. This point has been addressed in our replies to previous comments.

b. Mean cumulative costs should be removed as the bias introduced by ignoring censoring is largest in the 2,3 and 4-month periods. Options to reduce the bias are available.
We have added an explanation to the Methods in the 'Cost estimation and analysis' section to explain how the cumulative costs were calculated on page 8 (clean version). We present the number and percentage of cases censored in each month in Table S2. The cumulative costs in Table S4 and Figure 1 warrant presentation while acknowledging that the costs may be under-estimations because of administrative censoring. We have added a discussion of censoring to our limitations section, as previously described.

c. The calculation of 'mean net costs' should be described in more detail, and these details should be included as footnotes in tables and figures. I was confused about how the controls were used, and found that Table S4 helped clarify both the 'mean net costs' calculation and the role of the matched controls. Results for both cases and controls should be reported in the main body.
Please see our responses to comments 1 and 5a, above, concerning net costs and the controls.
Table S5 provides net costs for the entire cohort, stratified into different subgroups. Most of the results reported in Table S5 were reported in the text and in Table 3 and Figure 3. We added the remaining information from Table S5 to the second paragraph of the 'Stratified net costs 30 days post-index' section of the Results (page 10-11).
We have selected the tables which focus on the main results that address the study objective for the body of the paper. Table S3 reports the costs for the controls in the Supplementary material.

d. A sub-section on validation should be included. For example, Table S2 includes costs for cases and controls for the pre-index period and they should be similar.
We agree with the reviewer that this was not properly communicated. We have defined the pre-index period in the Methods section (under "Cost estimation and analysis") on page 7 (clean version). Please also see our replies to comments 3 and 5c, above.

e. Comparing cost per person and cost per person-time will also support the readers' understanding of the cost estimates and the potential impact due to options in treating observations censored by death.
Please see our response to comment 1 for a discussion of cost per person-time, and censoring.

f. Expected outcomes that would help aid in understanding the context of the data and risk of bias should be included, for example, proportion of cases hospitalized, average length of stay, distribution of length of stay (or proportions still hospitalized after 1, 2 or 3 months), mortality rates, were not reported.

The proportion of cases hospitalized, with and without ICU, is represented by the level of care groups. All cases who were hospitalized within 14 days after the date of their positive test are in the hospital or ICU level of care group, regardless of their place of residence. Figure S2 illustrates the transitions of cases from their place of residence at index date to their highest level of care location. We also added information on survival and censoring to the revised paper in Table S2 and Figure S3. Please also see our response to comment 2e.

g. What proportion of cases were diagnosed while in hospital? Given the limited access to testing at the time, this may be significant. If high, this would reflect on the potential risk of bias.
We have added information on the number of cases who were in hospital at their index date to the Results on page 9 (clean version). Please also see our reply to comment 2e and 3, above.
Within the first 14 days of their positive test, 13.2% and 10.1% of cases were hospitalized without ICU days, and 5.6% and 3.3% were hospitalized with ICU days (Table 1, Table S1), in BC and Ontario, respectively. The majority of hospitalized cases and ICU cases were male. Among LTC residents at index date, 86% to 87% remained in LTC following their positive COVID-19 test. In BC, 14% of LTC residents were admitted to hospital (2% with ICU), and in Ontario, 13% were admitted to hospital (1.4% with ICU) (Figure S2). In the LTC groups, over 66% of cases were female, with older mean ages and higher mean ADG comorbidity scores[27] than other cases (Table 1).

7) Results: I'd suggest reorganizing the tables so that tables, such as Table S4, that report both the point estimate and 95%CI, or other measure of precision (standard error of the mean) and are easier to read with results likely to be compared in adjacent cells are included in the main body. More detailed tables, and those with measures of dispersion (standard deviation, and interquartile range, or the comparison of mean and median, unless specifically part of the discussion should be moved to supplementary files. I'd also recommend including footnotes for each table and figure to tell readers that additional information is available and direct them to the appropriate supplementary file. Each table should be stand-alone, with the use of footnotes to remind the reader of relevant issues related to the methods used.
Thank you for these suggestions. We have added footnotes to the tables and figures as recommended. We acknowledge that some of the tables in the main body of the paper are cumbersome, which is a result of presenting cost estimates over 5 time periods in two provinces stratified by four groups of highest level of care, but also in line with our study objectives.
Whenever possible, we reorganized the tables to better communicate our study findings.

a. Table 1: In a table assessing the matching of cases and controls, the variable "highest level of care" should be moved from the column to rows and treated as one of the characteristics. Information by highest level of care should be reported for both cases and controls.
Please see our replies to comments 2a, 2d, and 4a above in which we discuss the highest level of care strata. Please see also the revised text in the Cohorts and data section in the Methods, and an additional footnote in Appendix 1f and Figure

S2, that clarify that the highest level of care for COVID-19 was only determined for the cases.

b. Mean cost should be reported for cases and controls. The denominator for the mean cost should be identified (person-time, number of subjects) for each table and figure in either footnotes or the labels.
Table S2 (now Table S3) reported mean costs for cases and controls in the original paper. We have added the number of subjects to all tables and figures, wherever applicable.

c. Mean costs should be provided for the full cohort (rather than just by highest level of care). Mean costs could also be provided for hospitalized patients, prospectively from time of hospitalization (hospitalization costs, including ICU may have some utility for hospital planning).
We have added the mean costs for the entire cohort, as indicated in our reply to comment 2d. We report the mean costs for hospitalization for cases who were hospitalized, with and without ICU days, for the first 30 days after Index date in Table 2, thus capturing the costs of the initial hospitalization for COVID-19. As stated in the Introduction, our study goes beyond the costs reported by CIHI for COVID-19 hospitalization. Our study estimated and reports costs for all publicly-funded health care resources in both the inpatient and outpatient settings.

d. Figure 1: I would like to see the mean cost by month and by phase (pre-index, acute phase, recovery phase). Plotting the cumulative costs is not particularly suitable as variation in monthly costs are only visible for hospital and ICU. Given concerns with bias related to the treatment of censoring, as discussed elsewhere, I'd suggest dropping the cumulative costs.
Please see our replies to comments 3a and 6b, above, in which we explain how the cumulative costs were calculated. Please see the second paragraph of our reply to comment 2d concerning phases.

e. Figure 2: labels or footnotes should address the following questions:

i. Are the ‘controls’ the matched controls, or the pre-index period self-control?
Thank you for requesting this clarification. Throughout the paper, controls are the matched controls, and they are the only controls. As we explained in previous replies to comment 3 and in the revised manuscript, the pre-index period was not a baseline or control period.

ii. Why are the control costs so low for the ICU group? Is this due to the odd treatment of censored observations?
Thank you for noticing this result, which is shown in Table S3. In both provinces, the mean costs for controls for the ICU cases are much lower than the mean costs for the other controls, except for the community controls. This is seen from the pre-index period onwards so it is not due to censoring because there are no deaths or censoring in pre-index and no censoring in the first 30 days. It can be seen from Table 1 and Table S1, that in both provinces, the ICU cases and their matched controls were younger and had lower ADG scores than the hospital controls and the LTC controls. Given the large known effect of age and comorbidity on health care costs, this is the most likely reason for their lower costs. To corroborate this, the mean costs for the controls for the community

cases are the lowest of all 4 control groups and these controls (and cases) are the youngest and have the lowest ADG scores.

iii. Why are the mean costs so different for BC and Ontario?
Thank you for this excellent question. We provide explanation for the differences in mean costs in BC and Ontario in the Interpretation under "Mean costs per patient". One possible explanation for the higher mean costs of hospitalization (with or without ICU) in BC is the relatively higher cost of a standard hospital stay compared with Ontario.
Our teams have conducted interprovincial cost studies for cancer and found differences in the cots of cancer care between Ontario and British Columbia.
• de Oliveira et al. Estimating the cost of cancer care in British Columbia and Ontario: A Canadian inter-provincial comparison. Healthcare Policy 2017;12(3):e95-e108, and
• McBride et al. Comparing childhood cancer costs in two Canadian provinces. Healthcare Policy 2020;15(3): 6–88),
In addition, CIHI reports different costs for COVID-19 hospitalizations across provinces and territories in Canada:
• CIHI. COVID-19 hospitalization and emergency department statistics. 2021; https://www.cihi.ca/en/covid-19-hospitalization-and-emergency-department-statistics.

iv. What is the denominator for the mean? From Table 2, we get mean costs (per hospitalized case?) of $20K and $14K for BC and Ontario respectively. Figure 2 suggests a mean cost of $9M and $65M per case? Reasons for unexpected differences should be investigated further and discussed.
The reviewer is correct that Table 2 shows that the mean costs for hospitalization in the hospital level of care groups are $20,324 in BC and $14,078 in Ontario in the first 30 days after index date. Since all of the cases in the hospital level of care groups were hospitalized, these are indeed the costs for hospitalization per hospitalized case in the first 30 days after index date. Figure 2 is discussed in the paper in the Results section under "Total costs for initial care for all COVID-19 cases". We have added a sentence to clarify that Figure 2 shows the total costs for all cases in each level of care group and their matched controls. We apologize that Figure 2 was incorrectly titled "Mean costs for initial care (pre-index and month 1) for all COVID-19 cases (solid columns) and controls (striped columns) by highest level of care, in a) British Columbia (N = 2,465) and b) Ontario (N = 28,893)". We have corrected the title to indicate that these are <u>total costs for the cohort</u>, not mean costs.
Please note also that Figure 2 includes costs for all resources in the pre-index period and month 1, while the cited costs in Table 2 are for hospitalization in month 1.
We hope that these revisions clarify that Table 2 and Figure 2 are reporting different results.

8) Statements made in the discussion section are interesting and provide some context, though are not related to or supported by the results presented. Some of these statements could possibly be moved to the introduction and used to form more specific research questions.

Thank you for this suggestion. We have made several revisions to the Interpretation section to only discuss statements in relation to our study results.

9) Regarding figures and tables, I have suggested above to provide more information (point estimates with 95%CI in the main body for the main results, include auxiliary results such as average length of stay, and clarifying the labels of the results (for example, include the denominator in the labels) and use of footnotes to remind readers of the methods used, especially related to censoring due to death.
Thank you for reiterating the importance of including 95% CI as an estimate of precision in the tables with mean costs. As we indicated in our response to comment 2c, we have added 95% CIs to Tables S3a, S3b and S4a. In the original manuscript, all tables with net costs (Table 3, S4b, and S5 in the revised manuscript) included 95% CIs.
We have added the number of cases and controls in all tables and figures where feasible, and added footnotes to all table and figures to remind readers of the methods.

10) Limitations: Limitations are not fully addressed. Without a clear definition of the outcome variables reported, it is premature for me to fully comment on limitations. It may be beyond the scope of this study to assess the costs associated with delaying needed but not urgent treatments, but this should be part of a broader discussion on limitations.
We hope that our replies to these comments and revisions to the paper have clarified the outcome variables and methods. We added three limitations to the Limitations section of the Interpretation, namely the issue of censoring such that our costs after month 1 may be underestimates, the difficulty of identifying clinical phases from administrative data, and our 4-month observation period which precluded examination of long-term complication of COVID-19. It is beyond the scope of this study to examine the costs associated with delaying non-urgent non-COVID-19 care.

11) Did you spot any fatal flaws? <i>That is, errors you do not believe the authors could overcome. Please explain clearly.
Describing the study as a retrospective cohort study when it is prospective, is likely the main source of various fatal flaws.
We have clarified in our reply to comment 5a that our study was a historical cohort study, with observation forward in time, and not a retrospective study.

a. The investigators did not handle censored observations appropriately. The irregular follow-up period can be corrected by rerunning the data extraction to include at least 4 months of follow-up for all cases (and baseline controls), or removing the results for the cumulative costs, which will be most strongly biased downward by lost to follow-up due to the short follow-up period. The inconsistent treatment of death will also create biases, though the direction of bias is different than for those lost to follow-up due to the short follow-up period. The investigators could drop the 2-4 month periods, as death is treated inconsistently (zero cost per person during the period of death, while the record is deleted and not included in the denominator in subsequent periods). It would be helpful to the retain cost estimates for these longer periods due to questions about the extent of long-covid. I'd suggest considering reporting costs/index case rather than cost per cases alive at the start of each period, and costs per person-time to better document the impact of death on cost estimates.

Thank you for this excellent summary of the comments concerning censoring and death. We have addressed these comments in our reply to comment 1, as well as in replies to other comments which mentioned them.

b. The precision of the main estimates is not reported in any of main tables. This can be corrected by moving much of the information about the dispersion of individual costs such as the standard deviation, mean vs median and IQR to supplementary files and including 95%CI with each estimate (mostly mean costs) reported in the main body.
Thank you for this suggestion. Please see our replies to comments 2c and 9.

c. The 'controls' are not really controls in the sense of a case/control study, but are used as a baseline estimate of mean health care costs (in the absence of covid-19 infection). It wasn't until I saw Table S2 with costs and number of subjects for both cases and controls that I could conceptualize the study design. Hopefully I got it right in my comments! This can be corrected by a short discussion in the methods section, labelling the controls as baseline controls, and by reporting the results for both cases and the corresponding estimated baseline for each category.
Thank you – as mentioned previously, our controls were a comparison group. We acknowledge that COVID-19 cases received health care for non-COVID-19 health conditions, therefore the matched controls served to estimate the net (COVID-19-attributable) costs. This costing method was utilized in previous studies by members of our study team (mentioned above) and in the health care costs literature.
We have revised the methods section by including separate paragraph on the selection of the controls, with further clarification in Appendix 1b, and citing additional references that utilized controls in costing studies.

d. Highest level of care is just one characteristic, and it is not clear why this is given prominence in the main body. The supplementary tables where highest level of care is treated as just one of the characteristics is much clearer.
Please see our replies to comments 2a, 2d, and 4a for the relevance and rationale of the prominence of highest level of care.

12) The topic should be of interest to *CMAJ* readership. However, it was however difficult to foresee the potential use of the information as presented in the main body. My impression of the main article was that basic data needed to understand the study was missing and I struggled to try to figure out the research objective. Some of the information I was looking for is available in the supplementary files, which should be moved to the main body. Other information, such as length of stay could be added. Given the potentially large volume of output tables, *CMAJ* online may be more appropriate.
Thank you– we have clarified our study objective in the last paragraph of the Introduction. The paragraph reads as follows:
"Understanding the system-wide costs of health care services for individuals with COVID-19, including those who did not require hospitalization, is essential for economic evaluations of COVID-19 management strategies. Such evidence is crucial to measure the economic burden of COVID-19 illness and inform evidence-based health care planning and decision-making that control the spread and severity of COVID-19. The objective of this study was to address this gap by estimating the direct health care costs for COVID-19, stratified by the highest level of initial care, in BC and Ontario during its first wave from January to June 2020."

We also summarize the study in the first paragraph of the Interpretation:
"This historical cohort study with matched comparators provides comprehensive population-based estimates of direct health care costs for COVID-19 cases in four levels of initial care in two Canadian provinces in the first wave of the pandemic. Our study found that costs attributable to COVID-19 vary widely by location of care and remain substantive up to 120 days after index date for cases initially treated in hospital or ICU. The total health care costs were much higher in Ontario than BC due to a higher caseload, while mean costs per COVID-19 case were higher in BC due to differences in location of care and higher unit costs of hospitalization."
As indicated in previous comments, the key results of the study are presented in the tables and figures in the main body of the paper.

Reviewer 2: Jean Yong
Institution: Canadian Partnership Against Cancer

General comments (author response in bold)

Excellent work addressing an important topic that has limited data.
Thank you for this comment.

Questions:

1. Why are the net costs in the pre-index period so high ($966-$3628; Table 3)?
Thank you for this observation. Net costs in the pre-index period represent health care costs associated with presentation and treatment of early symptoms of COVID-19 prior to a positive SARS-CoV-2 test among the cases, including hospitalization and physician visits.
The high net pre-index costs that the reviewer mentions are for cases in the ICU and hospital level of care groups. Table 2 shows resource-specific total (not net) costs for these cases. Hospitalization accounts for 52% to 74% of total costs in the pre-index period for the cases in the hospital and ICU level of care groups. Many of these cases were already in hospital when they were tested, as reported in the revised paper in the Results on page 9 (clean version), hence the relatively high net costs in the pre-index period for the hospitalized cases (with or without ICU)

2. What proportion of patients were still alive at the end of each 30-day period? Curious whether the -ve costs in the LTC group were due to more people dying in the Covid-19 cohort or merely because they had fewer hospital transfers than their controls.
Thank you for this question. The negative costs for the LTC level of care group could not be due to more COVID-19 cases dying than controls because the controls were censored when their case died. Thus, cases and controls were observed for the same number of days in each 30 day period. We have added Table S2, reporting on the number of cases who died and were censored in each 30-day period, as well as the results of a survival analysis (Figure S3).
These report on the cases only because we did not follow the controls for death beyond the death of their case.
By definition, the cases in the LTC level of care group could not be in hospital in the first 14 days after their index date.

3. p13: This section mentioned that BC did a better job than Ontario. How did that relate to the key findings in this study? Do you have any survival data to show that a higher proportion of LTC Covid-19 cases in BC survived, as compared to the Ontario Covid-19 cohort?
Thank you for asking this interesting question. The main finding supporting the comment that BC did a better job at controlling the virus during the first wave is the lower number of cases per capita of population. The BC cohort comprised 0.05% of the BC population while the Ontario cohort comprised 0.2% of the Ontario population. With respect to LTC facilities specifically, 12% of the BC cases were residents of LTC facilities at index date compared with 18% of the Ontario cases. Therefore, our findings suggest that BC did a better job at containing the spread of COVID-19 in the first wave, both in the community and in LTC facilities. We have added the phrase "to contain the spread of infection" to the revised paper on page 12 (clean version).
With respect to survival, however, our study showed that the cases in the LTC level of care groups in BC and Ontario had a similar 30-day survival probabilities (Table S2, Figure S3). Thus, our findings indicate that although residents of LTC facilities in BC were less likely to be infected with COVID-19, those who remained in LTC for 2 weeks after their positive test experienced similar or slightly lower survival. However, we did not examine survival among all LTC residents, including those who were admitted to hospital in the first two weeks after diagnosis. We have added this to the Long-term care section of the Interpretation on pages 15 to 16 (clean version).

Key messages: In addition to higher Covid-19 morbidity and mortality, the overall healthcare costs of Covid-19 were much higher in Ontario than British Columbia ($176 million vs. $22 million) during the first wave Covid-19 pandemic, due to much higher caseloads of Covid-19. This highlights the importance of adequate infection control and public health measures to reduce healthcare costs and the clinical impact of Covid-19.
Thank you for your insight. This key message is further highlighted in the conclusion.
"Reducing both the number and severity of cases is required to mitigate the impact of COVID-19 on health care budgets. Understanding health care costs highlights the importance of adequate infection control and public health measures to reduce healthcare costs and the clinical impact of Covid-19, and plan for recurrent COVID-19 waves."

3. Limitations: Add a statement highlighting that this study included only short-term healthcare costs of Covid-19 cases and did not capture long-term complications of Covid-19.
We agree with the reviewer that our study did not capture long-term costs associated with COVID-19. We added a paragraph to the Limitations (page 17) which reads as follows, "Our observation period covered short-term health care costs attributable to COVID-19 up to 120 days but did not capture long-term complications."