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Title: Organ dysfunction and mortality in hospitalized COVID-19 patients in waves 1 to 3 in British Columbia, Ontario and Quebec: a cohort study

Authors: Terry Lee PHD, Matthew P. Cheng MD, Donald C. Vinh, Todd C. Lee MD, Karen C. Tran MD, Brent W. Winston MD, David Sweet MD, John H. Boyd MD, Keith R. Walley MD, Greg Haljan MD, Allison McGeer MD, Francois Lamontagne MD, Robert Fowler MD, Nataly Farshait MSc, David Maslove MD, Joel Singer PhD, David M. Patrick MD, John C. Marshall MD, Kevin D. Burns MD, Srinivas Murthy MD, Puneet K. Mann MSc, Geraldine Hernandez BSc, Kathryn Donohoe BSc, Genevieve Rocheleau MSc, James A. Russell MD; for ARBs CORONA I

Reviewer 1: Dr. Matthew Weiss

Institution: CHU de Québec-Université Laval
General comments (author response in bold)

General:

This review represents a sub-study of a multi centric observational study on COVID-19 care, focused on the mortality and treatment intensity of patients hospitalized during successive waves of the pandemic. This is a well structured study with a large number of patients enrolled with a sophisticated statistical analysis to allow for risk-adjusted analysis. I personally think the data is important and adds to the ongoing improvement of the care for COVID-19 patients in Canada and globally.

I think the manuscript could be improved for clarity and have included general and specific points below that could result in a more impactful publication.

The interpretation section should have more emphasis on how these findings differ or are consistent with other reports, as well as why they are novel. This should include further discussion of why your methods of risk-factor adjustment were appropriate and yield new insights.

Thank you and we have added as follows to the discussion (p.16):

“Our study aligns with other studies which showed that mortality was lower in wave 2 than wave 1(2-9) and adds novelty by reporting for the first time even further decreases in mortality and organ dysfunction (as reflected by use of respiratory, cardiovascular and renal support therapies) in wave 3. Our methods for risk factor adjustment were appropriate because we adjusted for the major factors associated with increased mortality of COVID-19: age and co-morbidities, baseline systolic blood pressure, and additional potential confounders of organ dysfunction that were different across waves. These adjustments allowed us to tease out the differences in mortality and organ dysfunction across waves while adjusting for risk variables that could have or did differ across waves. The differences between our study and prior studies were that our study was multi-centre, was based in Canada, that we had detailed data regarding use of ventilation, vasopressors and renal replacement therapy over the hospital course and that we had data regarding therapies such as dexamethasone, antibiotics, and anti-viral and anti-fungal agents used while in hospital.”

I am not a statistician, so I cannot formally comment on the statistical analysis. The adjustments seem reasonable, but I would verify that the methods used to adjust DAF (pg 11 line 47) are standard for the that calculation.

The same approach has been used in previous analysis of DAF data (e.g., <https://pubmed.ncbi.nlm.nih.gov/32876695/> and <https://pubmed.ncbi.nlm.nih.gov/33295981/>). Technical details about this method has also been added to Appendix S3.

Intro:

- Consider rewording the first sentence of the introduction.

Thank you and as per the editor comments too we have reworded as follows (p.9):
“The COVID-19 pandemic has five waves in Canada, including the recent omicron-driven wave (as of December 17, 2021(1)).”

- I recommend making the sentence that starts "Studies in different countries..." the first sentence and making the current first sentence the second.

Thank you and we have made that change in that paragraph (p.9).

Methods:

- Pg 10 Line 30: Was there a method to adjudicate if the illness of a COVID + patient was caused by COVID or not?

No there was no adjudication mechanism.

Results

Pg 15 Line 33 - Not sure I would include the paragraph on vaccines since no analysis was possible.

Thank you, we agree and we have removed that paragraph.

Interpretation:

Pg 16 Line 12 - Unsure you need this paragraph, it simply restates the premise of the study from the introduction.

We made changes that refer to page and line number as we are using the PDF of the submission. We have removed that sentence as we interpret the recommendation.

Pg 16 Line 26 - The referencing in this paragraph could be increased to include references to the studies in the later sentences. Also, this paragraph includes several subjective terms (strikingly, remarkable, dramatically, etc.) that distracts from the message. Consider adding that your study demonstrated a correlation between Dexamethasone use and the various therapies in a rewording of the second sentence.

Thank you and we have added references to the later sentences in the paragraph. We have also removed the dramatic terms (strikingly, remarkable, dramatically, etc.). We have also added a sentence as follows about the correlations of dexamethasone use and other therapies as follows (p.16):

“Dexamethasone use correlated with less use of ventilation and vasopressors and was also correlated with increased use of remdesivir in waves two and three.”

Pg 16 Line 49: Consider something like "In several aspects, our findings are consistent with other global reports..." and then "The differences between our and other reports include..."

Thank you and we have added as follows (p.16):

“In several aspects, our findings are consistent with other global reports” as the first sentence of the paragraph.

And we have added as the last sentence of the paragraph:

“The differences between our study and prior studies were that our study was multi-centre, was based in Canada, that we had detailed data regarding use of ventilation, vasopressors and renal replacement therapy over the hospital course and that we had data regarding therapies such as dexamethasone, antibiotics, and anti-viral and anti-fungal agents used while in hospital.

Pg 17 Line 24 and Line 38: Move these paragraphs to limitations.

As suggested, we moved the paragraphs regarding variants of concern and immunity as an additional limitations paragraph (p.18).

Pg 18 Line 15 - While anecdotal, I agree with this and think it should be expanded. For instance, you could mention the multitude of studies that support early weaning, early physiotherapy, reductions in sedation and muscle relaxants and other ICU liberation strategies that decrease mortality and length of stay. Early in the pandemic all of those strategies were ignored in order to decrease transmission to health care workers, very likely to the detriment of the patients. I would say that while speculative, a return to more normal ICU care with increased contact by bedside providers as they became more vaccinated and accustomed to PPE would very plausibly be associated with better outcomes.

Thank you for these suggestions that we have incorporated into the discussion as follows (p.17):

“Starting in wave 2, and prominently in wave 3, health care providers became partially and sometimes fully vaccinated. We note anecdotally that health care providers attended patients at the bedside more frequently when the health care providers perceived that they were safer due to vaccination and availability of adequate PPE. Furthermore, studies later in the pandemic supported early weaning(29, 30), early physiotherapy(31, 32), reductions in sedation and muscle relaxants(33) and other ICU liberation strategies(33) that decrease mortality and length of stay. Early in the pandemic all of those strategies were ignored in order to decrease transmission to health care workers, likely to the detriment of the patients. While speculative, the return to more usual ICU care of critically ill COVID-19 patients that increased direct contact by bedside providers - as the latter became more vaccinated and accustomed to PPE - could plausibly be associated with better outcomes. In addition, improved consistency and organization of COVID-19-specific ward care may have developed with successive waves, contributing to reliable care/interventions and improved patient outcomes(34). Perhaps some of these factors impacted patient outcomes of acute COVID-19.”

The conclusion paragraph should be set off and possibly include a line like "Outcomes improved, possibly related to patient demographics, possibly related to improved COVID specific therapies and return to better baseline ICU care."

Thank you and we have added that to the conclusions as follows (p.18):

“Outcomes improved in wave 3, possibly related to patient demographics, improved COVID specific therapies and return to better baseline ICU care.”

Reviewer 2: Ms. Carmel Montgomery
Institution: University of Alberta
General comments (author response in bold)

Thank you for the opportunity to review this manuscript describing a cohort of COVID-19 hospital admissions in British Columbia, Quebec and Ontario, Canada reporting 28-day mortality, mechanical ventilation, vasopressor and CRRT use compared between waves 1-3. I have a few suggestions for your consideration.

Major comments:

1. Page 11, Line 33. The exclusion of Alberta data could be stated as 'sites that only enrolled patients admitted to ICU' and captured in the exclusion criteria.

Revised as per suggestion (p.11)

2. Page 11, line 33. The Outcomes section would benefit from explanation about why the 14-day calculation period was chosen and why 3 ICU interventions defined organ dysfunction, but ICU admission was not used.

Thank you – please see responses to editor and reviewer # 1.

3. Page 11, line 45. Readers will appreciate a simplified explanation of DAF. Once DAF is defined the remainder of the paragraph could exclude repeated listing of its criteria.

Thank you and we have added the following to the methods of DAF:

“The days alive and free of ventilation, vasopressors and RRT calculation presents use of these therapies while adjusting for deaths in the first 14 days because many patients die within the first 14 days. So, if we only reported duration of ventilation in a ventilated patient who died on day 2, the short duration of ventilation is biased by the early death.”

4. Page 13, Line 13. The authors excluded patients with missing data at the individual level but retained data from the province where recruitment appeared to stop after the first wave. This may present bias in the analysis comparing waves 2 and 3 to wave 1. A sensitivity analysis including only data from provinces with complete data throughout the 3 waves would be a useful addition to this study.

To minimize the bias, we have statistically accounted for the imbalance in provincial contribution across waves in our study by adjusting for site effects in the regression analysis. Please also see point 38 from the editor.

Only BC has consistently contributed data throughout the three waves and our main conclusion was in fact unchanged when we restricted our analyses to BC data. In particular, the adjusted 28-day mortality remained significant for wave 3 vs 1 (OR: 0.33, p=0.014) and wave 3 vs 2 (OR: 0.47, p=0.049). The significance of the results for use of ventilation (wave 3 vs 1: OR=0.31, p<0.001; wave 2 vs 1: OR=0.22, p<0.001), vasopressors (wave 3 vs 1: OR=0.38, p<0.001; wave 2 vs 1: OR=0.32, p<0.001) or renal replacement therapy (wave 3 vs 1: OR=0.18, p=0.045) were also unchanged compared to full analysis.

5. Page 17, line 22. Improved consistency and organization of COVID-specific ward care may have developed with successive waves, contributing to reliable care/interventions and improved patient outcomes (PMID: 32493744).

We have added to the above paragraph on improved care of the critically ill the following sentence on improved ward care (p.17).

“In addition, improved consistency and organization of COVID-19-specific ward care may have developed with successive waves, contributing to reliable care/interventions and improved patient outcomes(34)”

6. Page 24, line 11 indicates proportion of patients admitted to ICU and line 29 reports hospital LOS among survivors. Reporting ICU and hospital LOS among survivors and decedents would be of interest to the reader.

These have been added to Table 2.

7. Page 24, line 12-19. ICU is likely the only service offering invasive mechanical ventilation, RRT and vasopressors. The denominator for each of the ICU interventions should be patients admitted to ICU.

Thank you for the suggestion but we are not sure we should do this because in our study, our perspective and our interest are in the use of these therapies (ventilation, vasopressors, RRT) for the entire population as a whole. For example, if the RRT rate in ICU is constant over waves, but the ICU admission rate decreases over waves, then using ICU admitted patients as the denominator for use of RRT will not detect its decrease across the population as a whole due to the constancy of RRT in ICU, i.e. society has fewer RRT costs, but that could be missed if we use ICU as the denominator.

However, to address this reviewers' concerns and suggestion, we have added this new calculation to Table 2.