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Title	Outcomes and clinical practice in COVID-19 patients admitted to ICU in Montreal, Quebec, Canada — a descriptive analysis
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Reviewer 1	Simon Oczkowski
Institution	Division of Critical Care, Department of Medicine, McMaster University, Hamilton, Ont.
General comments (author response in bold)	Thank you for the opportunity to review this interesting manuscript, as the Canadian experience with the COVID-19 pandemic has not been well described to present. I do have some comments and questions which if addressed may improve the manuscript. **We would like to thank you for your appraisal, we believe that your comments were very helpful and educational. We modified our paper substantially to address those comments.** Comment #1-1 Page 5: "Prone positioning was often imitated when the FiO2 was sustained above levels generally considered to be safe." What were these, at least roughly? Was it protocolized or a clinician judgement (clinical judgment is fine, but I cannot tell from the manuscript which it was). **Prone positioning initiated was at the discretion of the treating physician. Generally, this occurs when FiO2 requirement was sustained above 65%. We added the following sentence to clarify this in our manuscript.** **Prone positioning was initiated when the FiO2 requirement was sustained above 65% at the discretion of the treating physician.** Comment #1-2 It's not clear to me why the early vs. late period cutoff date of April 5/6 was chosen. Was there a policy change or demographic shift which led to patients after that point being different somehow? It was stated as an a priori decision, a priori to what (the analysis, data collection etc). As this is one of the major decisions in the analysis, it's important that the reasons for this are clear to the reader. Otherwise any arbitrary date could have been chosen. **We agree that by splitting the cohort in two, this led to a much smaller event rate and there may be significant confounders that are not accounted for. As per reviewers/editors suggestions, we have removed the inferential analysis and associated methods from the paper.** Comment #1-3a Page 6. I question the decision removing patients whose advanced directives excluded intubation. In fact these patients were recorded (8) and included the hospital mortality calculation, which is contrary to the decision to exclude. I prefer the choice which seems to have been done, namely providing analysis for this group separately. Given that many patients with severe COVID-19 are older and may have advance directives precluding intubation, this is an important group to try and understand, even though they will not receive "cool" treatments like intubation, NMB, and ECMO. It would be revealing if we understood what treatments they did receive, and their outcomes (if the data is available) and how

	this differs from the other patients. **As per reviewers/editors suggestions, we have removed the inferential analysis and associated methods from the paper.** **To allow for greater generalizability of our mortality results we feel that including patients who have some limitations in levels of intervention is important and therefore feel we should still include these patients in the overall analysis.** Comment #1-3b Page 6: I wouldn't say "excluded patients who refused intubation" as this carries an implication that the patients are being unreasonable. There are many reasons patients may decline to receive invasive mechanical ventilation-- thus I would use more neutral language. Earlier in the manuscript the term "patients whose advanced directives excluded intubation" which is good. This would also provide some consistency through the paper. **Given that we removed the pre/post analysis, all patients are included in the results.** Comment #1-4 Page 9, line 34-39. I'd stick closer to the data as causality is hard to prove in a study like this. It's not clear that the reduced duration of mechanical ventilation was "allowed" by HFNC or if there were other factors involved which were equally or more important. So as opposed to "we were also able to extubate earlier…" I'd state "Duration of ventilation was shorter in the later period. This may have been due to increased use of HFNC post-extubation, thereby allowing earlier liberation from the ventilator. However, this may also have been due to other differences between the populations, such as the younger age of the later cohort." **Given that we removed the pre/post analysis, we emphasized mainly on the overall practice of intubation and HFNC in our entire cohort.** **HFNC was used for 51 patients (48.1%) including in 29 patients for initial respiratory support, of which 20 never required intubation (68.9%). A total of 29 patients (27.4%) underwent prone positioning; among 13 patients (12.2%) who were initially spontaneously breathing, only 3 patients (2.8%) were subsequently intubated.** Comment #1-5 Page 9, line 43-44 -- the COVID-19 clinical phenotypes are not referenced (presumably the Gattinoni papers?) but should be cited. (Parenthetically it is not clear that these phenotypes are truly distinct from other ARDS presentations, however the concept may very well have influenced decision-making, as is described). **Thank you for picking this up, it was an error not including it. However, given that the pre/post analysis was removed, this part of the discussion was no longer pertinent and was removed from the manuscript.** Comment #1-6 Page 10 lines 15-41. I would update this section. With the publication of RECOVERY it is now clear steroids are helpful in patients with ARDS (as was also suggested in the SSC guidelines) and this may have impacted mortality. There is still no high quality data for Toci so it is fair to say it is speculative as to whether it had an effect.

	We have updated the reference and changed the phrasing to highlight the important role steroids may place: **Indeed, the results of the recently published Recovery trial show that low dose dexamethasone improves mortality in severe COVID-19 and is now considered standard of care.** Comment #1-7 Page 10 lines 45-55. I think this may be an interesting topic. Why was HCQ adopted? Who made the decision to use it widely or incorporate it in protocols despite lack of evidence of safety, and who chose to discontinue it? Was it an ICU-level decision? Inidividual clinicians? As written, it sounds like the decisions came out of the ether (maybe they did?). A description of this may be useful learning points about when and how we should or should not adopt new therapies— that unproven treatments whether cheap (HCQ) or expensive (toci) have had rapid uptake with COVID, while other evidence-based approaches have not. (Fortunately JGH stuck with the evidence-based SSC guidelines and data from Villar et al... many centres have used HCQ but not steroids :(Amazing how EBM process works) **The decision for using HCQ was from the local infectious disease group who came out with our initial COVID guidelines. I have clarified this in the text below.** **At the outset, our local infectious disease guidelines recommended hydroxychloroquine...** Comment #1-8 Figure 3 is ambiguous. It is titled "COVID-19 census" but the legend indicates JGH ICU census— implying the total ICU occupancy. Which is it? It would be nice to show in Figure 3 the proportion of the ICU census which was taken up by COVID patients vs. other patients, as well as indicate the "normal" census level before creating new beds (the text states capacity was increased). In doing so one could see what the census would have been without the additional beds, and how big an impact COVID was vs. other critical illness during the time period. **I see the ambiguity, thank you for the suggestion. We have updated the figure to include JGH COVID ICU census and JGH non-COVID ICU census.** Comment #1-9 Page 11, lines 39-41. I don't know if I'd call it "free, universal healthcare" so much "universal health insurance for hospital and physician services." It is not free nor universal to non-citizens, which is certainly a barrier to care for some populations. I think the point is valid, but it should also not imply that the care is free for all. **Thank you for the comment. We have rephrased the sentence to the following:** **...the publicly funded Canadian health system which strives to minimize financial and other socio-economic barriers to accessing health services.** Comment #1-10 Page 11 lines 53-56. The links between the interventions and outcomes are not speculative, but the causal links between the associations are speculative. **We agree with the suggestion and we added the following statement in our manuscript.** **Given the observational nature of our study, any causal link between our**

	interventions and the observed outcomes is speculative. Comment #1-11 Page 12 lines 17-24. Maybe state "We speculate that provincial and institutional pandemic preparedness…." just to make it clear that there is zero data in this review to support this (you didn't compare to other provinces, other policies etc.) What does come from the analysis is the fact that the ICU was not overwhelmed and remained under census. May be better to state "Our institution increased the number of available ICU beds and staff in advance of the pandemic, and did not go over census, which may have contributed to the lower mortality rate." As well given the RECOVERY data I'd also suggest that the early use of dexamethasone at JGH may have contributed to the lower mortality rate. **We agree with this suggestion and have updated the concluding remarks as follows:** **The ability of our institution to rapidly increase human resources and expand our ICU capacity may be in part responsible for the lower observed mortality. Moreover, our frequent use of corticosteroids for severe COVID-19 may have also contributed to our low mortality.** Comment #1-12 To simplify the tables and facilitate comparisons, it may be easier to have one table for demographics, one table for interventions, and one table for outcomes. Each could have 3 columns: "Total" "Early" and "Late." This would facilitate easier comparisons. As laid out, I had to flip back and forth a bit to compare the total to the two time cohorts. **See editor # 27**
Reviewer 2	Anish Mitra
Institution	Division of Critical Care Medicine, Department of Medicine, Surrey Memorial Hospital, Surrey, BC
General comments (author response in bold)	I would like to commend Yang and colleagues for completing this study while caring for patients during this epidemic. It is important to share Canadian data on outcomes for critically ill patients with COVID-19 and they add to the literature describing the Canadian experience in this pandemic. Please find my comments below: **We would like to thank you for your appraisal, your comments are very thoughtful and helpful. we believe that our paper has improved substantially with your suggestions.** Comment #2-1 I would recommend removing the inferential analysis from this manuscript. While describing the differences in patient characteristics and outcomes early in the pandemic to later in the pandemic is interesting, the inferential analysis has significant limitations. First, multiple comparisons are done without accounting for multiplicity. Second, and more importantly, univariate comparison is done between two populations with different characteristics without accounting for confounding. For example, a significant difference is found in the number of patients who are intubated, but this comparison does not account for the difference in age or P:F ratios between the two populations. These limitations make the analyses uninterpretable. **We agree that these data are hypotheses-generating with risk of**

	confounding. And have removed the inferential analysis and associated methods and discussion from the paper. Comment #2-2 Please update the outcome data from June 5th to present day. **We have updated all outcome data to Aug 4th, 2020.** Comment #2-3 P4L23: Please report hospital mortality in the abstract as it is a more relevant patient-centered outcome than ICU mortality. **We agree with the suggestions and added hospital mortality. Previous ICU case series on COVID-19 reported ICU mortality, therefore, we elected to also report a comparable outcome as well.** **The ICU mortality was 17.0% and hospital mortality was 19.8%** Comment #2-4 P4L23: "We describe the outcomes and patient management of critically ill Canadian patients with COVID-19 at our institution". I recommend removing "Canadian" as it may be interpreted that you are only describing your Canadian patients and not your non-Canadian patients. Unless this is what was done? **We wanted to emphasize that these were critically ill patients in Canada. We agree that it is unclear and removed the word "Canadian".** Comment #2-5 Please report how often intermediate dose thromboprophylaxis was provided. **See response to editor - 7** Comment #2-6 Please report how often patients with VTE had thromboprophylaxis and what dose when prescribed. **See response to editor - 7** Comment #2-7 What were your criteria for admission of COVID-19 patients into the ICU? Did this change through the study period? **Like most other conditions we had no strict admission criteria and admission decisions were left to the treating intensivist. We suggested ICU consultation when patients required more than 5L of nasal prongs or rapid clinical deterioration. We have added this statement to the context discussion.** Comment #2-8 P7L15: Please define "when FiO2 was sustained above levels that are generally considered to be unsafe". **The initiation of prone positioning was at the discretion of the treating physician. Generally, it is when FiO2 requirements was sustained above 65%. We agree that the statement is vague, and we added the following clarification to the manuscript.** **Prone positioning was initiated when the FiO2 requirement was sustained above 65% at the discretion of the treating physician**

	Comment #2-9 P6L17: Please describe when and why prone positioning in non-intubated patients on HFNC was utilized? Was this being done at your institution before the COVID-19 pandemic, or was it initiated after initial reports of success from Italy (eg Marco Garrone)? **See comment for editor - 7** Comment #2-10 P7L24: Was non-invasive ventilation not used due to concerns about nosocomial spread? If so, why was this same restriction not applied to HFNC? **Yes, NIV was not used due to concerns of nosocomial spread. As described in the text, this too as applied to HFNC however as evidence emerged suggesting this practice was safe we began using HFNC.** Comment #2-11 P9L1: Why were SARS positive patients admitted for other reasons excluded? **We wanted to study and report outcomes of COVID-19 pneumonia. SARs-COV-2 patients that were asymptomatic and admitted for other medical-surgical reasons were therefore excluded (eg. Cholecystitis, Hip fracture, CABG).** Comment #2-12 P9L24: Please describe how many of the patients undergoing prone positioning and HFNC failed and required intubation. **We agree with the suggestion and added the following.** **A total of 29 patients (27.4%) underwent prone positioning; among 13 patients (12.2%) who were initially spontaneously breathing, only 3 patients (2.8%) were subsequently intubated.** Comment #2-13 I recommend considering the removal of ICU mortality completely and using hospital mortality. The numbers are very similar and I think the latter is a much more important outcome. **We agree that both numbers are similar and hospital mortality is the most important metric, however, to allow comparison with most other COVID ICU studies, we felt we should also report ICU mortality.** Comment 2-14 P9L20: Did all of the patients who refused intubation have advanced directives declining mechanical ventilation prior to their ICU admission? Or did some have their goals of care changed during their ICU admission? **This is a good question, and indeed some patients had their advanced directives discussed on admission to hospital/ICU and some had pre-existing directives.** Comment #2-15 P10L8: Please describe how thromboembolic events were screened? Protocol or based on clinician judgement? **See response for editor #7** Comment #2-16

	Table 4: Please include SOFA **As per reviewers/editors suggestions, we have removed the inferential analysis and associated methods from the paper. Table 4 has therefore been removed.** Comment #2-17 P11L34: Please reference these phenotypes. Probably worth mentioning that the existence of these phenotypes is debated in the literature. **This section as it related to changes in practice over time have been removed.** Comment #2-18 P11L53 – P12L10: Very important to explicitly describe that the late cohort was younger and had fewer comorbidities. **See response above** Comment #2-19 P12L30: I would recommend removing this very speculative statement inferring corticosteroids and/or tocilizumab impacted duration of mechanical ventilation. **See response above** Comment #2-20 P13L46: I recommend removing this very speculative statement regarding mortality and race. This study is not be powered for such a conclusion. **We agree and have removed this statement.** Comment #2-21 P14L17: Please change the word “significant”, which has a statistical connotation. **We have rephrased the sentence as follows: The mortality of critically ill patients with COVID-19 in our Canadian centre appears to be less than previously described in other countries.** Comment #2-22 Please review references, not all have volume/issue/page numbers. **We have checked and corrected references.** Comment #2-23 P10L30: Typographical error referencing Figure 3 instead of Figure 4. **We apologize for this error and fixed it in the manuscript.** Comment #2-24 Figure 3: Survival analysis should be removed because results confounded by different patient populations and competing risk of death. **After examining the complete updated dataset, we agree with the reviewer and elected to remove survival analysis.** Comment #2-25 Actual Figure 3 is not referenced in the results. **We apologize for this error and fixed it in the manuscript.** Comment #2-26

	Table 1: Why is only one race described? **Black race was signaled out as there were many early publications highlighting disproportionate burden of disease and mortality. To ensure our results are interpretable to other jurisdictions we feel it is important to include.** Comment #2-27 Table 1: Why is symptomatic household contact described? Is this implying that household contact was source of infection or a consequence of patient infection? **Initially we had thought it may be of interest to describe to show the burden of disease in families, however, we agree it doesn't add to the focus of our paper and we have removed it.** Comment #2-28 Table 1: Steroids referenced as a cause of immunosuppression. Were any patients given steroids prior to ICU admission for COVID-19? **This group represented patients with a past medical history of immunocompromised conditions prior to the current admission, that included the use of chronic steroid, chemotherapy, or biologic medication. We added the word "chronic" to clarify this.** Comment #2-29 Table 3: Recommend using same nomenclature for discharge from hospital and ICU. Either include "alive" for both or neither. **We agree with the suggestion and removed the word "alive" from the table.** Comment #2-30 Table 4: Include SOFA score. **See response above**