Article ID: CMAJOpen-2021-0151

Title: Clinical characteristics, multi-organ dysfunction, and outcomes of patients with COVID-19: a prospective case series

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Reviewer 1
Dr. Nguyen Trieu
Medical researcher, Vietnam

1. The study was well done and straightforward. The evidence obtained in the follow-up of patients with varying degrees of clinical and subclinical levels led to an insight intothe physiology of the patient infected with COVID-19. This has provided documents to prove that the study canprovide a good direction in making treatment regimens and preventing severe disease progression, lowering mortality, lowering complications during and after COVID-19 infection.

   Response: Thank you for your supportive comments!
2. It is necessary to include relevant data extracted from the medical history because this is statistically significant, which will help guide theoutline of the treatment protocol forCOVID-19 infection.

   Response: We agree with the Reviewer and have reported various relevant datarelated to participants' medical history as this is critical to understanding the population and the multi-organ nature of the disease. We welcome any suggestions on further key variables to incorporate based on availability.

Reviewer 2
Michelle Policarpio
Public Health Ontario, vaccine preventable diseases

1. **Page 2, Abstract: Suggest including the data collection period inthe methods section. Note as well that the abstract may have to be updated based on the responses to succeeding items.**

   Response: Thank you for pointing this out. We have now amended the Abstract on page 2, lines 21-23 to say the following: "*We conducted a prospective case series of adult patients (aged 18 years and older) with COVID-19 admitted to oneof two hospitals in London, Canada between March 17 and June 18, 2020, during the first wave of the pandemic.*"

   Page 4, Introduction, Lines 3-37:Introduction provides accurate background and good explanation on the importance of this study. Considerrevising 'will be well-suited' in line 28to 'may potentially'. While this data isvaluable, there are other factors to consider when formulating healthcarepolicies and strategies.

   Response: Thank you for your comment. As you have suggested, we have nowreplaced the phrase '*will be well-suited*' to '*may potentially*' on page 4, line 28.

2. **Page 4, Study design, Line 46: Consider revising from prospective observational study to descriptive study or case series if the intention is to describe rather than test hypothesis. Based on the objective, thepresentation of results, interpretation and conclusion – this seems to be a descriptive study rather than prospective cohort. If the intention is to test hypothesis or determine association between the exposure and outcome of interest, the study would benefit in clarifying the comparison groups/clearly outlining selection of subjects based on exposure status andspecifying the associated outcome of interest.**

3. **Response:** Thank you for this suggestion. We have made the following changesthroughout the manuscript to reflect that this study is a case series:

   Title Page: *"Clinical characteristics, multi-organ dysfunction, and outcomes ofhospitalized patients with COVID-19: A prospective case series".*

   Page 2, lines 21: *"We conducted a prospective case series..."*

   Now Page 5, first line: *"This prospective case series was conducted at two sites inLondon Health Sciences Center (LHSC)..."*

   Page 13, first line: *"In this prospective case series of hospitalized patients withCOVID-19..."*

4. **Page 5, Patient Recruitment and Data Collection, Lines 23-26: Consider outlining which data were collected from which source.**

   Response: We have now added greater detail regarding our data collection process in the Methods section in response to previous comments above. Data sources for each type of data are described in the Supplementary Material. We have revised the statement in the text to ensure that this is clear: *"SupplementaryMaterial Online 1 provides a description of all data elements and sources."*

5. **Page 6, Lines 14-21: Revise to showcomparison between those who remained in a non-ICU location and those transferred later on. Based on the results on page 11 and Tables on pages 23-28, these are the two groupsbeing compared.**

   Response: Thank you for pointing this out. We have now revised to the statementto read as follows (now Page 7, Paragraph 2, Sentence 2): *"In addition, we compared the characteristics of patients who were admitted to and remained in a non-ICU location with patients who were initially admitted to a non-ICU locationbut were subsequently transferred to ICU due to clinical deterioration."*

6. **Page 7, Baseline Characteristics, Lines 2-14: Remove 'th' on the dates and the word 'patients' in line 14 (it ismentioned twice).**

   Response: We have removed 'th' on the dates (now on Page 8) and amended thelast sentence in Paragraph 2 to read as follows: "*Table 1 presents patients' baseline characteristics."*

7. **Page 8, Respiratory Complications, Line 32-33: Insert 'on'after 'was performed'.**

   Response: We have revised the sentence based on your suggestion.

8. **Page 10-11, Secondary infections, Lines 39 in page 10-5 in page 11: These are interesting resultsand good to share! There is limited evidence on the effect of COVID-19 on healthcare-associated infections.**

   Response: Thank you for the supportive comment and we agree about the paucityof data on secondary infections associated with COVID-19 and to address other comments provided, we have now added this as a strength of the study.

9. **Page 15, Limitations, Lines 30- 33: Perhaps you are referring to exposure rather than 'treatment'. One strength is that this study provides valuable information on a new disease(COVID) and provides detailed experience of hospitalized patients from admissions and after discharge, including secondary infections that occur on COVID patients in healthcare settings such as Candida Auris, CDI, etc. One limitation is that conclusion may be difficult to generalize among the patient population. Agree that it may be worthwhile to conduct a larger study involving different hospital types (e.g.,large and small community hospitals) from different locations.**

   Response: To address this and other comments above, we have amended the Limitations sections to encompass this feedback. The Strength and Limitations sections reads as follows: *"Limitations with any*

observational study such as thisone include the inability to draw any conclusions about causality of any specificexposure (e.g., therapy or management strategy) with outcomes. In this study, several assessments were performed on a subgroup of patients who may have differed from those not assessed due to testing and treatment by indication.

Furthermore, our cohort reflects patients at two Ontario hospitals during the firstwave of the COVID-19 pandemic. Larger, multicentre cohort studies are requiredto provide data that are generalizable beyond the location of this study and the first wave of the pandemic. This study has several strengths. We included a cohortof ICU and non-ICU patients across a spectrum of disease severity. Standardized diagnostic microbiologic methods were used to define COVID-19 positivity. Consecutive prospective enrollment reduced selection bias and improved the fidelity of data collection. We also present granular data on the pulmonary andextra-pulmonary manifestations of COVID-19 and secondary infections amongCOVID-19 patients in a healthcare setting. Finally, we provide post-hospital discharge data on the clinical outcomes of patients after hospital discharge.
Finally, this study also provides a detailed experience of patients hospitalized withCOVID-19 starting from hospital admission to beyond hospital discharge."

Reviewer 3

Rahel Zewude
Medicine, The University of British Columbia

This prospective observational study would be of great interest to general practitioners as well as acute care physicians who continue to work on managing survivors of COVID-19 with varying degrees of persisting organ dysfunction/symptomatology. You have clearly and effectively communicated the aim of the article, the study design and findings.

Please see below for section specific feedback and visit the reviewed PDF document for minor grammatical revisions.

Abstract
The abstract succinctly and effectively summarizes the study. See PDF for grammatical revisions.
In the "interpretation" section of the abstract, the authors appear to have drawn the conclusion that COVID-19 is a multisystem disease without evidence of hepatic dysfunction.
Based on observational data of 100 patients, it would be reasonable to draw the conclusion of COVID-19 being a multisystem disease involving neurological, cardiac and thrombotic dysfunction but it would not be reasonable to definitively rule out hepatic dysfunction as a direct or indirect sequelae of COVID-19. As noted later in the article, authors have only used ALT as a surrogate marker of hepatic dysfunction in this cohort and various reports of hepatic dysfunction, albeit indirectly from ischemic hepatitis secondary to shock from severe COVID-19 or from secondary infections such as herpes simplex hepatitis, have been reported. Eg. DOI: 10.1093/cid/ciaa1246

Introduction:
The introduction provides appropriate extent of background information regarding COVID-19
Clinical manifestations and areas of focus in the currently available COVID-19 literature.

Methods:
Study design and setting
The abstract mentions that study patients were admitted to one of two hospitals in London , while the Methods section outlines that the study is conducted in two sites within LHSC and cites two hospitals; Victoria Hospital and University Hospital. Authors need to clarify further and potentially correct the abstract to two hospitals.

STROBE guideline
The article provided a checklist for the STROBE statement and as an observational cohort study it is in full compliance with this guideline.

Patient recruitment and data collection

In this observational study, the study design did not allow for collection of follow up imaging in all patients in the study population. Patients who did not have clinical indications for follow up CT Thoracic or Echocardiogram by December 31, 2020 did not have these variables recorded and alternate markers i.e. outpatient family physician visit etc. were not provided for those who may not have had severe clinical symptoms to warrant outpatient imaging. Therefore it is likely that this design may provide a conservative estimate of the number of patients with cardiac and pulmonary sequelae. Furthermore, as those with follow up CT thoracis and echocardiogram may have had significantly worse cardiac and pulmonary dysfunction as a sequela to prompt this follow up investigations, so the reported severity of these organ dysfunctions may be skewed to those with more severe organ dysfunction as a sequelae.

However, noting that this is a cohort observational study, it is challenging to mitigate these biases, but certainly important to recognize them in the study design to prompt the use of other proxies and equally important to discuss them in the study's limitations.

The chosen baseline characteristics as well as presenting symptoms (table 1 and 2) are reasonably relevant to the outcomes of interest.

Statistical analysis
The descriptive statistic as well as the use of rank-sum test and chi-squared statistic was reasonable in this cohort study.

Authors provided excellent subgroup analysis of patients initially admitted to ICU vs those who were admitted to non-ICU locations but deteriorated and went to ICU later.

The authors selected reasonable predictor values that are grounded on previously available evidence, but also are clinically sound choices for the outcome of interest.

Results

The authors presented their findings with excellent sectioning of multi-system organ dysfunction with respiratory, neurologic, thrombotic, cardiac and hemodynamic as well as renal complications and therapies.

The choice of ALT as surrogate for hepatic dysfunction maybe quite narrow to allow authors to reach their conclusion regarding the absence of hepatic dysfunction (see note in abstract section)

The authors made a great choice in their decision to include secondary infections as these would have influenced the outcomes of multi-organ dysfunction as well.

The characteristics of patients who deteriorated and required a later ICU admission, was adequately described.

Interpretation

While there is currently no strong evidence to support use of anticoagulation, many centres across Canada routinely are using therapeutic anticoagulation for patients hospitalized with COVID-19, so you can incorporate the current pattern of clinical practice here to add weight to your recommendation. Although, further RCTs would be needed to definitively establish the benefit of therapeutic anticoagulation over prophylactic anticoagulation.

Limitations

The authors have appropriately acknowledged that as an observational study they can only make conclusions regarding association of specific treatments and outcomes.
As authors have highlighted the consecutive prospective enrollment of patients into this cohort reduced bias in patient selection.

However, the authors did not acknowledge the limitation in regards to post-hospital discharge data being available only to a limited number of its patient population e.g only 19 CT chest scans and 15 echocardiograms were performed in a study population of 100 patients. It would also be helpful to provide information regarding

how many patients had both CT and echocardiogram performed to give further clarity as to the limitations of a small percentage of the patient population having follow-up investigations. This is a critical limitation of this observational cohort study that needs to be highlighted and well communicated to the readers.
(please see further feedback in the study design section above).

Conclusion
The authors provided concise and reasonable conclusions based on the findings of this observational cohort study.