

**Article details: 2021-0055****Title: Outcomes of hospital-acquired COVID-19 in the Canadian first wave epicenter: a retrospective study**

**Authors:** Eve Melançon MD, Marc Brosseau MD, Anthony Bartoli MD Pharm D, Annie-Claude Labbé MD MSc, Christian Lavallée MD MSc, Xavier Marchand-Sénécal MD, Han Ting Wang MD MSc

**Reviewer 1:** Dr. Abdullah Mamun

**Institution:**

General comments (author response in bold)

This is a very important study where authors estimated and compared the mortality among hospital-acquired COVID-19 and nonhospital acquired COVID-19 cases. The findings are very important for the clinicians who deal COVID-19 patients in hospital environment. However, this needs major revision. Authors should mention the study group clearly whenever they presented findings for a specific group.

**We have made the appropriate changes to make our results clearer to the reader.**

Authors did a sensitivity analysis excluding the suspected HA cases. Can this be done for the NHA group as that group also comprised cases from LTCF or living in private elderly residents in a congregate way, and residents living in these facilities are more vulnerable compared to others, which is evident at the beginning of the pandemic.

**We have included here an analysis comparing HA COVID to community cases only for your interest. We did not include this in our paper but we are open to adding it to supplementary if the reviewer team deem the information interesting and pertinent. As expected, the effect of HA status is stronger when LTC patients are excluded from the NHA group.**

**Multivariate logistic regression of factors associated with COVID-19 mortality after excluding all LTC NHA-COVID-19 cases**

Factors	Odds Ratio	95 % Confidence interval
<b>Hospital-acquired COVID-19</b>		
<75 years old	<b>2.90</b>	<b>1.48-5.69</b>
75-84 years old	<b>1.25</b>	<b>0.63-2.47</b>
≥85 years old	<b>0.74</b>	<b>0.40-1.37</b>
<b>Sex</b>		
Female	<b>0.63</b>	<b>0.43-0.92</b>
<b>Solid tumor</b>		
Localized	<b>1.13</b>	<b>0.66-1.92</b>
Metastatic	<b>6.74</b>	<b>3.19-14.2</b>
<b>Hematological malignancy</b>	<b>6.49</b>	<b>2.30-18.3</b>
<b>Moderate to severe chronic renal disease*</b>	<b>2.80</b>	<b>1.61-4.89</b>
<b>Diabetes</b>	<b>1.17</b>	<b>0.79-1.76</b>
<b>COPD</b>	<b>0.99</b>	<b>0.61-1.62</b>
<b>Myocardial infarction</b>	<b>0.99</b>	<b>0.50-1.95</b>

\* Moderate to severe chronic renal disease defined as creatinine > 265 umol/L  
 COPD: COPD: chronic obstructive pulmonary disease

Although the authors performed multivariate logistic regression, they should clearly mention within the table and within the text on what are the variables they adjusted for in the model.

All co-variates are detailed in the Methods section and all co-variates are included in our Table.

Also, is it possible to run this model with adjusting covariates both for HA and NHA group separately to see the association with mortality? Is it possible to adjust the HA/NHA status when the authors did multivariate logistic regression for the overall cohort?

We are not sure we understand your question correctly. We did make a mistake here saying it is multivariate analysis. We performed a multivariable analysis, therefore the co-variates are all included in the model with HA COVID status. As for analyzing the groups separately, here are the data.

Multivariate logistic regression of factors associated with COVID-19 mortality (HA only)

Factors	Odds Ratio	95 % Confidence interval
<b>Age</b>		
<75 years old	1	
75-84 years old	2.70	1.33-5.48
≥85 years old	2.84	1.42-5.69
<b>Sex</b>		
Female	0.61	0.35-1.07
<b>Solid tumor</b>		
Localized	0.79	0.38-1.62
Metastatic	4.87	1.93-12.3
<b>Hematological malignancy</b>	7.15	1.77-28.8
<b>Moderate to severe chronic renal disease*</b>	1.99	0.90-4.43
<b>Diabetes</b>	1.21	0.68-2.18
<b>COPD</b>	0.90	0.46-1.74
<b>Myocardial infarction</b>	0.74	0.25-2.20

Multivariate logistic regression of factors associated with COVID-19 mortality (NHA only)

Factors	Odds Ratio	95 % Confidence interval
<b>Age</b>		
<75 years old	1	
75-84 years old	6.11	3.22-11.6
≥85 years old	11.2	5.90-21.2
<b>Sex</b>		
Female	0.58	0.35-0.95
<b>Solid tumor</b>		

<b>Localized</b>	<b>1.51</b>	<b>0.70-3.26</b>
<b>Metastatic</b>	<b>6.69</b>	<b>1.98-22.7</b>
<b>Hematological malignancy</b>	<b>5.51</b>	<b>1.17-25.9</b>
<b>Moderate to severe chronic renal disease*</b>	<b>4.04</b>	<b>1.94-8.41</b>
<b>Diabetes</b>	<b>1.16</b>	<b>0.68-1.97</b>
<b>COPD</b>	<b>1.16</b>	<b>0.60-2.24</b>
<b>Myocardial infarction</b>	<b>0.90</b>	<b>0.38-2.13</b>

\* Moderate to severe chronic renal disease defined as creatinine > 265 umol/L  
COPD: COPD: chronic obstructive pulmonary disease

Introduction:

1. Authors should mention that these are COVID-19 cases and whether all of these are laboratory confirmed cases or included epidemiologically linked cases (Line 5, 6).

**This information is already included in the “case definition” section of the manuscript. We include only laboratory confirmed cases.**

2. For the reader, it may be helpful to mention that authors are referring to the highest number comparing with other provinces in Canada (Line 9-12, second sentence).

Authors should also mention the population of the province to provide a picture of the population size.

**We have made the suggested changes.**

**See page 5, line 84**

Methods:

1. Authors should define the first wave (i.e. duration) in P2 line 18.

**Since there I no standardized definition and cut-off for the 3 waves in Canada, we decided to define the first wave as the first 2 quarters of 2020 for the purpose of our study. It encompass the first known cases in January 25<sup>th</sup> and ends on June 30<sup>th</sup>. After June 30<sup>th</sup>, we nearly had no hospitalized cases up until September. We have added the time reference in Study design and Setting section.**

2. Authors mentioned in the setting section that most of the COVID-19 patients before March 20<sup>th</sup> were transferred to other hospitals. Considering the study duration in this study, authors must have missed some patients transferred to other hospitals?

**Our center was not designated as COVID-19 reference center prior to march 20<sup>th</sup>. Therefore, COVID-19 patients presenting to our institution were directly transferred from the Emergency Department and were never hospitalized. We do not think we missed any patients prior to this time point.**

3. In the ‘Participants’ section authors may consider mentioning why and how the hospital tracked the COVID-19 patients, was it for all or only hospitalized cases? Authors should specify how the linkage was done (i.e. using unique identifier or so) and what kind of hospital administrative data were linked.

**We agree with the reviewer. We have modified this section to better reflect the tracking system. Also we modified the sentence for data linkage as it wasn’t clear. The linkage was mostly to cross-match IPAC COVID-19 patients list and hospital admission list.**

**“The list of all COVID-19 patients was provided by the hospital Infection Prevention and Control (IPAC) division, which prospectively tracked all SARS-**

**CoV-2 PCR positive inpatients and outpatients in our institution, based on the local laboratory data and other institutions data for patient transfers. The IPAC division include certified infection control practitioners supervised by a medical director. This list was then cross-matched with our hospital administrative dataset to determine which patients were hospitalized.”**

**See page 6, line117**

4. Case definition – What is the definition of uncertain case? Authors mentioned “The Medical Director of IPAC, unaware of each patient’s outcome, reviewed all uncertain cases.” What is the rationale here?

**While most HA Covid cases were easy to classify, some cases needed clinical judgment to determine whether it was really HA Covid. The Medical Director was blinded to patient’s outcome to perform this exercise to mitigate the risk of bias of determining the status based on clinical outcome. We also decided to rephrase the section to remove the ambiguity left with the “uncertain case” formulation. To make it easier to understand, we rephrased it this way in the Case definition section:**

***“Proven HA infections were defined as a positive SARS-CoV-2 PCR >14 days after hospital admission or when an in-hospital epidemiological link was identified with a known COVID-19 positive person by the IPAC division. All final attributions based on epidemiological links were made by the Medical Director of IPAC using best clinical judgement and unaware of each patient's outcome.”***

**See page 7, line 145**

5. Case definition - Was there any advantage of matching HA cases with other published studies? What is the rationale of including cases from long term care facilities within CA cases? Cases from LTCF are a very different group of people; did authors consider comparing this group with other groups in this study?

**While not perfect, matching our data to existing literature allows better comparison between different paper and also might help other researchers interested in this field and compare the different papers. Our study focused on the impacts of hospital-acquired covid-19, as the impact of covid-19 in LTC cases is already well described. Moreover, as stated previously our goal was to explore the impact of covid-19 in a population already affected by a serious acute illness leading to hospitalization, which does not apply to either LTC cases or CCA case. This is why we decided to divide the groups between HA vs NHA. Including more vulnerable LTC cases may bias our results towards the null by including a more vulnerable group in the CCA which may be another explanation why the association between HA-covid was not observed in the older age group. We did perform a comparison between HA COVID and community cases for your interest. Here is the data.**

**Multivariate logistic regression of factors associated with COVID-19 mortality after excluding all LTC NHA-COVID-19 cases**

<b>Factors</b>	<b>Odds Ratio</b>	<b>95 % Confidence interval</b>
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<b>Sex</b>		

<b>Female</b>	<b>0.63</b>	<b>0.43-0.92</b>
<b>Solid tumor</b>		
<b>Localized</b>	<b>1.13</b>	<b>0.66-1.92</b>
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COPD: COPD: chronic obstructive pulmonary disease

6. Statistical methods – Authors mentioned “To evaluate the association between HA-COVID-19 and in-hospital mortality, we performed a multivariate logistic regression with an epidemiological model by including.....”What kind of epidemiological model was used?

**We agree with the reviewer. This is poor wording on our part. We have modified to better describe the analysis performed:**

**“We performed a multivariable logistic regression by including the following pre-specified risk factors for death in COVID patients as co-variates; age, sex, moderate to severe chronic renal disease, solid tumor, hematological malignancy, diabetes, chronic obstructive pulmonary disease (COPD) and myocardial infarction.”**

**See page 10, line 194**

Results

1. Authors may remind the readers about the study duration at the beginning of the results section.

**We have added this precision at the beginning of Results section.**

**“During the three months period, 734 patients were screened for inclusion and 37 were excluded, resulting in 697 hospitalized COVID-19 patients (Figure 1).”**

**See page 11, line 212**

2. P11 , line 47 – It may be informative to report on how many days after discharge these 6 patients became COVID-19 positive.

**We have added the required information.**

**“Out of 139 identified close contact patients associated with sharing a multi-bedded room with a COVID-19 case, 45 (32.4%) became COVID-19 positive during hospitalization, and six had a positive SARS-CoV-2 PCR with an unknown date of symptom onset within 14 days after discharge (3 within 7 days).”**

**See page 11, line 218**

3. Authors should also provide some highlighted findings for the CA and long term cases (i.e. NHA COVID-19 cases).

**We agree with the reviewer there might be interesting differences between CA and LTC patients. Unfortunately, we do not have any more words to spare and also this wasn't the initial objective of our project. We have already provided analysis between community cases and HA covid cases. We are open to share further analysis outside of this project.**

4. While presenting age, authors should clarify what groups they are referring to.  
**We made sure it is more clear throughout the text.**

5. P 11-12: Authors mentioned “HA-COVID-19 patients had a higher prior 5-year history of cancer (localized N=49, 19.3% vs. N=39, 8.8%; metastatic N=27, 10.6% vs. N=15, 3.4%; p=0.001) and COPD (N=59, 23.2% vs. N=66, 14.9%, p=0.006).” They should clarify what is the comparison group and which proportion belongs to which group.  
**We have made the required changes.**

6. P 12, Line 16: “Two patients received tocilizumab and three patients received hydroxychloroquine.” Are all these patients belonged to HA group? Authors should clarify this.

**The tocilizumab were given to HA COVID patients. And the three hydroxychloroquine were given to NHA patients. We have added this to the manuscript.**

7. P 12-13: “There was no increased risk of death older patients (OR, 1.15; 95% CI 0.59 to 2.22; p=0.687 in the 75-84 age group and OR, 0.73; 95% CI 0.40 to 1.32; p=0.30 in the 85 age group).” What is the reference age group here? Is this same for HA/NHA group? Authors should specify the group.

**We have clarified this section.**

**“There was no increased risk of death for older patients (OR, 1.15; 95% CI 0.59 to 2.22; p=0.687 in the 75-84 age group and OR, 0.73; 95% CI 0.40 to 1.32; p=0.30 in the ≥85 age group) compared to patients younger than 75 years old”**

**See page 12, line 251**

Interpretation:

1. P 13: “In the present study, one-third of all hospitalized COVID-19 cases were acquired due to inhospital transmission, with a significant increase in mortality rates.” Authors should mention the comparison group or delete ‘increase’.

**We agree with the reviewer. We have made the suggested changes.**

**“In the present study, one-third of all hospitalized COVID-19 cases were acquired due to in-hospital transmission, with a higher mortality rate among patients younger than 75 years old. “**

**See page 13, line 262**

2. P 14 Line 30: “Our NHA-COVID-19 group provided a good representation of the most severe CA COVID- 19 patients, with 91.2% of the total NHA cases being community acquired and....” This is the first time authors mentioned 91.2% NHA cases were CA. As mentioned before that authors should highlight the NHA cases’ findings in the results section in the first paragraph where they have presented the HA cases findings...

**We agree with the reviewer. We added the information in the Results section.**

3. P 14, Line 37/38: “A cohort study of 252 hospitalized patients with COVID-19 and active cancer, HA-COVID-19 was an independent risk factor of mortality (HR, 2.3; 95% CI 1.3 to 4; p=0.005). Their mortality rate in the HA-COVID-19 group was higher than our results (47% vs. 38%), likely due to their cohort being exclusively cancer patients (22)” Authors should move the reference in the first sentence.

**We have moved the reference.**

4. P 16, line 11: "This was mitigated by excluding secondary cases with a serial interval smaller than 3 days" This needs more clarity to better understand what has been done.

Table 1: The tile says between, it seems incomplete

Table 3 : COPD is repeated

**This refers to the following sentence in the methods section:**

***"COVID-19 acquisition was linked to transmission between patients in the same room only if close contacts developed symptoms (or tested positive if asymptomatic)  $\geq 3$  days after the index patient symptom onset and their first contact, and up to 14 days after their last contact."***

**To bring more clarity, we added the following sentence at the end of the paragraph in the Method section:**

***"A 3-day gap was used since it represents the lower end of the COVID-19 serial interval."***

**See page 9, line 187**

**Reviewer 2:** Dr. Balthasar Hug

**Institution:** Luzerner Kantonsspital

General comments (author response in bold)

General

- Melancon et al present a single center, retrospective cohort study from March 1st to June 30th 2020 of hospitalized patients of age 18 or older with Covid-19 infection. They follow the question, whether patients infected with Covid-19 in-hospital might suffer a different outcome than those infected out-of-hospital. This is an interesting and very timely question and the paper is well written and an interesting read. There remain some minor issues mentioned below that need the attention of the authors.

- Naming unity: the virus is called SARS-CoV-2 in some instances and Covid-19 in others. I would suggest to use one single expression e.g. Covid-19 that is mostly used in the paper and well understood by readers. SARS is often related to the pandemia of 2003 which was a virus of the same family but not the same virus.

**We understand that it might seem odd to use both COVID-19 and SARS-CoV-2 in terms of nomenclature. SARS-CoV-2 refers to the virus causing the disease named COVID-19, like HIV refers to the virus and AIDS to the disease. Hence, we elected not to systematically change all the SARS-CoV-2 denomination to COVID-19. Any time we talk about a diagnostic test looking for the virus or the virus transmission, we decided to keep SARS-CoV-2 in the manuscript. We changed the other SARS-CoV-2 for COVID-19.**

Methods

- This is a retrospective, observational study that provides hypothesis generation but no causal relationships. This needs to be mentioned in the limitations section of the discussion.

**We have added this to our limitations.**

***"First, it is a single-centre retrospective study, therefore limiting the generalizability of our in-hospital COVID-19 transmission data and also not meant to prove causality."***

**See page 15, line 310**

- Collapsing proven and suspected cases (p. 8, lines 48-50) might have altered the outcome of the study. Thank you for expanding in this regard in the limitations section.

**Including more vulnerable LTC cases may bias our results towards the null by including a more vulnerable group in the NHA group. This is hinted at in our interpretations. Also, this strengthens the positive results found in the younger than 75 years patients. We agree this is an interesting aspect, but due to lack of words we opted to talk about more important limitations mentioned by other reviewers and the statistician.**

- The authors mention that they gathered the treatment of patients in their data in RedCap. Treatment with steroids was not different between the groups ( $p=0.27$ ); all the others like tocilizumab and hydroxychloroquine were later proven to be of no or minimal use. Did the authors also gather information about anticoagulation like low molecular weight heparins, NOACS and warfarine? This would be interesting information since we now know more about the hypercoagulability state during Covid-19 infection. And this might have influenced the outcome. Thank you for expanding on this.

**We agree with the reviewer. Anticoagulation seems to be an effective therapy in COVID-19. Unfortunately we did not collect this data since it was not considered a treatment during that time period. Therefore it is impossible for us to expand more on this matter.**

- Please add on p.9, line 21 to "N95 respirator" the word "mask". A respirator might also be a machine.

**We appreciate how taken alone, the word respirator can have multiple meanings and could pose some confusion. However, N95 respirator is the nomenclature used in various public health bodies communications, such as the Public Health Agency of Canada, the US CDC and the WHO. The use of Filtering Facepiece Respirator (FFR) was also considered but was felt to be less commonly used than N95 respirator.**

#### Results

- "Data linkage" on p. 11, line 25: please explain what you linked with what. The word Linkage does not appear in the methods section.

**We agree with the reviewer this isn't clear and we have modified both the Methods and Results section:**

**"The list of all COVID-19 patients was provided by the hospital Infection Prevention and Control (IPAC) division, which prospectively tracked all SARS-CoV-2 PCR positive inpatients and outpatients in our institution, based on the local laboratory data and other institutions data for patient transfers. The IPAC division include certified infection control practitioners supervised by a medical director. This list was then cross-matched with our hospital administrative dataset to determine which patients were hospitalized. "**

**See page 6, line 117**

- P. 11, line 50: "The median age was 75 years...". Please add "of all patients", so the reader knows that this is not about a subgroup.

**We have made the suggested modification.**

**"The median age was 75 years old [IQR 62-85] for the full cohort"**

**See page 11, line 225**

#### Discussion

- Limitations section: see above re retrospective design in the methods section  
**This was addressed as suggested.**