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Article title: Outcomes and characteristics of patients hospitalized for COVID-19 in British Columbia, Ontario and Quebec, Canada: a cohort study comparing omicron wave patients by vaccination status and comparing patients across waves

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Reviewer 1: Manuel Alberto Guerrero Gutierrez / Instituto Nacional de Cancerología, Critical care, Mexico

I was struck by the exclusion of those from the emergency room, however, seeing that those from the ICU were included, I was able to reassure myself. The confidence interval strengthens the fact of vaccine protection. This is why I believe that the publication should be considered for publication.

RESPONSE: Thank you. We would like to clarify that one of the exclusion criteria was emergency Room visits without hospitalization. So those who required hospitalization after the ER visit were included in the current analysis.

Reviewer 2: Mahalakshmi Kumaran / Alberta Health Services

Major comments

Study design:

a) The authors have used a subset of cases admitted to hospital from a prospective cohort study. There could be selection bias as the trail focused on the cases taking angiotensin II type 1 receptor blockers. Authors haven't explained the proportion of cases in the current study who are already in taking ARBs and potential impact on the study outcomes.

RESPONSE: We would like to clarify that the inclusion criteria for ARBs CORONA I was age>18 with confirmed COVID-19 infection, regardless of angiotensin receptor blockers usage. So we do not see a selection bias problem herein. The method section has been revised as follows for clarity:

"Inclusion criteria for ARBs CORONA I were individuals over 18 years of age (regardless of pre-existing angiotensin receptor blockers usage) with confirmed COVID-19 infection For the current study, we
included all ARBs CORONA I patients expect acute COVID-19 readmissions……"

We now reported the proportion of patients with pre-existing ARBs use in Appendix S1 and Table E4.

"Pre-existing use of angiotensin receptor blockers and angiotensin-converting enzyme inhibitors prior to admission in patients included in the current study were 284/1794 (15.8%) and 332/1794 (18.5%) respectively."

b) **Wave 1-3 did not have any vaccinated cases vs comparator group omicron had about 60% vaccinated case. Vaccination has known to have a positive effect on outcomes. Even tough vaccination has started as early as Dec 2020, author did not include any cases who were vaccinated in the waves 2 and wave 3. Even partial vaccination has slightly better outcome vs unvaccinated.**

RESPONSE: In the ARBs CORONA I study, none of the patients enrolled in waves 2 and 3 had at least 2 vaccine doses (our wave 3 data ended on Apr 14, 2021). Only a small percentage of patients was partially vaccinated in waves 2 and 3 (0.5% and 8.2% respectively; Table E4). We agree that partial vaccination may lead to better outcome than unvaccinated, but our sample size would be too small to examine this.

c) **Then timeline of date of vaccination versus disease onset was not clearly indicated, certain cutoff need to be established. For example, cases who got their second dose, prior to their disease onset. Literature evidence suggests, a minimum of 14 days from the dose 1 & 2 is required for vaccine effectiveness.**

RESPONSE: We only collected data on the first two doses, but not any subsequent booster doses. So, we were not able to determine the time from the last vaccination dose and hospital admission. Please also see our response to editorial comment 8d and 27

2. **Insufficient events per variable (10 events per variable) ration for multiple regression analysis**

a. **Insufficient events in the when comparing wave 3 vs omicron wave in the adjusted logistic regression analysis. Even though firth's method was used to address the sample size issue, outcomes were not rare events, merely sampling issue.**

Based on the Figure 3 and Table 2, the primary finding "28-day mortality was significantly lower in vaccinated (n=242) than unvaccinated hospitalized patients (n=130) (adjusted OR:0.36 [95% CI: 0.15,0.89]);". The unadjusted analysis was not significant (Fig3). However, the adjusted analysis was significant, the author has adjusted in total of 7 variables (age, sex, chronic heart disease, chronic kidney disease, hematologic disease, hypertension, and cancer). However, the total no of events 42 out of 441 cases in omicron wave. Based on standard EPV ratio, author can only adjust up to 4 variables for a meaningful multiple logistic regression analysis.

RESPONSE: We acknowledge that we have insufficient events based on the 10 events per variable rule. However, some recent research has suggested that this rule can be relaxed (e.g., PMID: 17182981). Please also see the response to editorial comment #29. We have now noted this in the limitation section as follows:

"The sample size for the comparison by vaccination status within the Omicron wave was limited and the number of events for some outcomes were low. This may limit statistical power and reliability of the adjusted analysis."

3. **Confounders – effects of treatments and vaccination was not considered while**

comparing the waves vs omicron waves. Access to treatments and vaccination vary due to evolving guidelines throughout the pandemic and was not addressed.

RESPONSE: We did not adjust for difference in treatments and vaccination when comparing waves as these all constituted part of the wave effect. Adjusting for these factors would then take away the wave effect as they were in the causal pathway between wave and the outcomes. We thus only adjusted for patient/baseline characteristics

However, per other reviewers' request, we have now added an additional analysis which was restricted to unvaccinated patients (Figure E2) to account for the large difference in vaccination rate across waves.

Please also see the response to editorial comment #8.

4. **Goals of care – patients' goals of care were not discussed, as it played important role in the treatment regime, average age of cases in the study is about ~70Y.**

RESPONSE: We unfortunately do not have information regarding goals of care.

5. **Potential risk factors: Race/Ethnicity and Socioeconomic factors, lifestyle factors like smoking, obesity are some of the important factors affecting the outcome.**

RESPONSE: Please see the response to editorial comment #22.

Minor comments

Result and discussion sections are not well articulated, and flow is interrupted throughout.

RESPONSE: We have added new comments as per the reviewers' and editor's suggestions throughout and have edited further for clarity and flow.

1. **In method section, more clarity is required regarding the original trial from which the study cohort was assembled.**

RSEPONSE: Please see response to your major comment 1a

2. **In the Table 2 missing p-values for the variable between the unvaccinated vs vaccinated, which would be a useful information for the readers.**

RESPONSE: P values have been added.