

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk factors for severity of COVID-19: a rapid review to inform vaccine prioritization in Canada
AUTHORS	Wingert, Aireen; Pillay, Jennifer; Gates, Michelle; Guitard, Samantha; Rahman, Sholeh; Beck, Andrew; Vandermeer, Ben; Hartling, Lisa

VERSION 1 – REVIEW

REVIEWER	Osborne, Vicki Drug Safety Research Unit
REVIEW RETURNED	25-Sep-2020

GENERAL COMMENTS	<p>This is a well-written and interesting rapid review of high importance given the current COVID-19 pandemic. I have a couple of comments for the authors consideration:</p> <p>Introduction page 5, line 40: Please give examples of the “PROGRESS And Other Factors” at first mention in the introduction. I found these later in the methods but I think its clearer to include when first mentioned.</p> <p>Strengths and limitations, page 19: could the authors comment on the limitation of conducting the rapid method vs the traditional SR method? Also, how frequently would you recommend updating this review, given the acknowledgement that evidence should continue to be reviewed.</p>
-------------------------	--

REVIEWER	Nordberg, Per Karolinska Institute, Dept. of Cardiology, Centre for Reuscitation Science
REVIEW RETURNED	19-Oct-2020

GENERAL COMMENTS	<p>Thanks for giving me the opportunity to review this manuscript. The authors have the overall aim to identify high-risk groups that should be prioritized for vaccination in Canada and to assess the magnitude of this risk factors and severe outcomes.</p> <p>Although that I read the manuscript with great interest, there are several limitations that needs to be addressed. First, the form of “rapid review” was unknown for me and is not clearly defined. That only one of the authors was involved in the selection of studies seems to be integrated in this definition. At the same time this one of the limitations of the study.</p> <p>The manuscript would benefit from having a more generic, global approach to this issue with vaccination than only the task from</p>
-------------------------	---

	<p>NACI. Especially as you include studies from many parts of the world and not only North America.</p> <p>It is difficult to find definitions of the study population you would like to address. Is severe Covid19 defined as need for hospitalization, need for intensive care or need for mechanical ventilation at the intensive care. I think this review would benefit from defining your target population better, which you might find from the NACI instructions.</p> <p>How you used comparators is for me unclear. Did the comparators include patients admitted but without the prespecified potential risk factors? Or did you also include patients that were not admitted? In summary I think the review has the potential to improve if you define you population and comparators better, determine how you define severe Covid19 and use a more generic approach when discussing your findings.</p>
--	--

REVIEWER	Rod, J. Queensland University of Technology
REVIEW RETURNED	18-Nov-2020

GENERAL COMMENTS	<p>The document has two aims:</p> <ul style="list-style-type: none"> - Provide a rapid evidence synthesis of risk factors for COVID-19 severity for the Canadian context. - Quantify the quality of the evidence for the risk factors <p>The author's justification for the research is that knowledge of these factors might help in the equitable and efficient allocation of a vaccine among high-risk populations.</p> <p>The study generally followed the published protocol in PROSPERO. The arguments were presented logically, and the summary tables provide highly relevant information based on the aims of the review.</p> <p>I found of particular importance that disease severity was not evaluated using a composite index of severe-fatal disease and that an effort was made to provide the associations of different risk factors with the full length of the natural history of the COVID-19 disease.</p> <p>Given the academic merit of the presented work, the following general comments are intended to assist authors in achieving publication.</p> <ul style="list-style-type: none"> - The methodological trade-off or a rapid review, vs a more in-depth analysis needs a little more justification. - The limitations section should consider the above-mentioned trade-off, especially considering that risk of bias assessments was conducted at the study level, while the aim was to provide an evidence quality analysis at the individual risk factor- severe outcome level. - It would be interesting to know the author's opinion on which of the severe disease outcomes should be prioritized when targeting a particular group. Based on the presented data in Table 2. Hospitalization seems to have (i) a higher magnitude of associations and (ii) higher confidence in the magnitude of
-------------------------	--

associations. I think this is important for the decision-making of policymakers and should be briefly discussed in the discussion.

- I think it is important to highlight the granularity of the analysis along the continuum of the natural history of the disease as a strength of the used methodology. To the best of my knowledge, there is only one existing review that has separated outcomes, yet it was only focused on sex and gender as risk factors (Gebhard, Regitz-Zagrosek, Neuhauser, Morgan, & Klein, 2020). Most other reviews of the risk factors for COVID-19 disease severity had focused either on mortality or a composite outcome of severe-critical-fatal disease (Drager, Pio-Abreu, Lopes, & Bortolotto, 2020; Leung, 2020; Rod, Oviedo-Trespalacios, & Cortes-Ramirez, 2020; Singh & Khunti, 2020; Wolff, Nee, Hickey, & Marscholke, 2020; Zheng et al., 2020). The recommendation of analyzing risk factors by detailed outcomes along the natural history of the COVID-19 disease was specifically emphasized by our review (Rod et al., 2020).

More detailed comments.

Page 6

Line 15 –

Perhaps specify to what stakeholders the sentence is referring to. The consensus is among the medical community, the scientific community, government, international organizations?. In Canada, OECD members?

Line 21

Reference or example to support the unprecedented pace.

Line 21

“Once a successful COVID-19 vaccine candidate becomes”. The words COVID-19 and candidate could be removed from the sentence as the whole paragraph is referring to COVID-19 vaccine candidates.

Line 19 – 28

There are opportunities for easing the readability by reducing the times the word vaccine(s) and COVID-19 is used within the paragraph.

Line 24 -25.

Given that the eventual vaccine is still under development and subsequent approval is needed. I would not necessarily think it is “urgent” to plan for its efficient use. As this is the rationale that supports the paper, I would say it is perhaps, “of high relevance to policymakers” or “of high priority to policymakers”

Page 7

Lines 3-5

I agree with the suggestion that COVID-19 vaccines have become a global priority and the importance of the presented research is highlighting that particular groups should be offered the vaccines as a priority based on risk factors for disease severity. However, I think there is a need to increase the robustness of the rationale for a “rapid review”. Currently, in the text, there is only one line suggesting that vaccine development is occurring at “an unprecedented pace”. I would suggest including literature and examples of the COVID-19 vaccine timelines to convey more accurately the feeling of urgency.

Page 9

Synthesis section:

Lines 27 to 28

It will be useful to direct the reader to supplementary material 5 for a more detailed overview of the findings.

The certainty of the evidence section:

The document presents an evaluation of risk of biases (RoB) at the study level focusing on three types of biases. Nevertheless, the focus is on the certainty of the evidence of risk factors – outcomes associations. This implies that the external validity of the overall quality appraisal conducted at the studies decreases at the outcome level, and it is a very important component for upgrading and downgrading the certainty of evidence based on the GRADE approach.

The potential benefit of the rapid review somewhat justifies the trade-off between (i) not using a RoB assessment at the outcome level vs the magnitude that a conducted RoB could affect the certainty of evidence evaluations. Nevertheless, it is important for the reader and future researchers to know about this limitation, given that this is important information for decision making and a potential rationale for conducting a more in-depth analysis in the future.

Page 9

Lines 38 – 43

“Among the factors identified as increasing risk of severe outcomes, age seemed to be the most influential; adults older than 60 years may have at least 5 times increased odds of hospitalization and mortality from COVID-19 compared to those aged less than 45 years. This increased risk appears to magnify at least to some degree even for those older than 60 years, with those aged over 80 years having double the mortality risk of those aged 65-69 years”.

There is a valid implied representational overlap of risk and odds as being association tools in epidemiological studies. However, risk is often more associated with probability than odds. Given that probability and odds convey different mathematical information, it

	<p>might be prudent to refer to “Among the factors that increase the chance of severe outcomes”, “this increased association appears” and “double the magnitude of association of those”. The interpretations of odds as risk (with risk mostly understood as probability within the quantitative perspective of risk) might repeat in other sections within the document. Using the term association for the description of both probability and odds could also increase the consistency in relation to the research question proposed in the protocol in PROSPERO.</p> <p>Page 20</p> <p>Lines 43 to 56 seems to be more relevant for the limitation section.</p> <p>Cited references:</p> <p>Drager, L. F., Pio-Abreu, A., Lopes, R. D., & Bortolotto, L. A. (2020). Is Hypertension a Real Risk Factor for Poor Prognosis in the COVID-19 Pandemic? <i>Curr Hypertens Rep</i>, 22(6), 43. doi:10.1007/s11906-020-01057-x</p> <p>Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H. K., Morgan, R., & Klein, S. L. (2020). Impact of sex and gender on COVID-19 outcomes in Europe. <i>Biol Sex Differ</i>, 11(1), 29. doi:10.1186/s13293-020-00304-9</p> <p>Leung, C. (2020). Risk factors for predicting mortality in elderly patients with COVID-19: A review of clinical data in China. <i>Mechanisms of Ageing and Development</i>, 188, 111255. doi:https://doi.org/10.1016/j.mad.2020.111255</p> <p>Rod, J. E., Oviedo-Trespalacios, O., & Cortes-Ramirez, J. (2020). A brief-review of the risk factors for covid-19 severity. <i>Rev Saude Publica</i>, 54, 60. doi:10.11606/s1518-8787.2020054002481</p> <p>Singh, A. K., & Khunti, K. (2020). Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review. <i>Diabetes Res Clin Pract</i>, 165, 108266. doi:10.1016/j.diabres.2020.108266</p> <p>Wolff, D., Nee, S., Hickey, N. S., & Marschollek, M. (2020). Risk factors for Covid-19 severity and fatality: a structured literature review. <i>Infection</i>, 1-14. doi:10.1007/s15010-020-01509-1</p> <p>Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., Peng, J., . . . Tang, W. (2020). Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. <i>J Infect</i>, 81(2), e16-e25. doi:10.1016/j.jinf.2020.04.021</p>
--	--

VERSION 1 – AUTHOR RESPONSE

Authors’ Responses to Reviewers’ Comments

Reviewers’ Comment	Authors’ Response	Reference
Reviewer 1		
This is a well-written and interesting rapid review of high importance given the current COVID-19 pandemic.	Thank you for your review and comments.	Not applicable (NA).
I have a couple of comments for the authors consideration: Introduction page 5, line 40: Please give examples of the “PROGRESS And Other	Thank you for pointing this out. We have included some examples of the P ² ROGRESS factors, as revised:	Introduction

<p>Factors” at first mention in the introduction. I found these later in the methods but I think its clearer to include when first mentioned.</p>	<p>“The resulting “P²ROGRESS And Other Factors” framework includes a range of biological and social factors that likely contribute to inequities in health outcomes across population groups (e.g., pre-existing disease/condition, place/state of residence, race/ethnicity/culture/language, occupation, gender identity/sex)...”</p>	
<p>Strengths and limitations, page 19: could the authors comment on the limitation of conducting the rapid method vs the traditional SR method?</p> <p>Also, how frequently would you recommend updating this review, given the acknowledgement that evidence should continue to be reviewed.</p>	<p>Given the restrictions in resources and a short timeframe, our review was guided by rapid review methodology rather than conventional resource-intensive systematic review processes.</p> <p>We have expanded on the limitations of the rapid review vs. conventional systematic review methodology in the Strengths and Limitations of the Review, at the end of the Discussion.</p> <p>Given that evidence in this area is emerging rapidly, it would be prudent to update the review before recommendations are finalized.</p>	<p>Strengths and Limitations of the Review</p>
<p>Reviewer 2</p>		
<p>Thanks for giving me the opportunity to review this manuscript. The authors have the overall aim to identify high-risk groups that should be prioritized for vaccination in Canada and to assess the magnitude of this risk factors and severe outcomes.</p>	<p>Thank you for your review and comments.</p>	<p>NA</p>
<p>Although that I read the manuscript with great interest, there are several limitations that needs to be addressed. First, the form of “rapid review” was unknown for me and is not clearly defined. That only one of the authors was involved in the selection of studies seems to be integrated in this definition. At the same time this one of the limitations of the study.</p>	<p>Thank you for raising this.</p> <p>We have outlined the rapid review methodology and expanded on the limitations of the approach undertaken, when compared to conventional systematic review methods, in the Methods and at the end of the Discussion section. Many rapid reviews do not include quality or certainty assessments, so this is a relative strength of our work versus several other rapid reviews being conducted on this topic.</p> <p>Note to Editor: We have added a paragraph at the beginning of the Methods providing background information on rapid reviews. Please review and determine if this is necessary apart from what we provided that follow in the Methods and the Strengths and Limitations sections.</p>	<p>Methods; Strengths and Limitations of the Review</p>
<p>The manuscript would benefit from having a more generic, global approach to this issue with vaccination than only the task from NACI.</p>	<p>Thank you for your comment.</p>	<p>NA</p>

<p>Especially as you include studies from many parts of the world and not only North America.</p>	<p>We have followed the journal editor’s suggestion to highlight the objective of our work for the Canadian context.</p> <p>We included studies from OECD countries that would be similar to Canada (i.e., high-income and near-universal/universal healthcare), such that evidence from these countries could be considered most applicable to our population and healthcare system.</p>	
<p>It is difficult to find definitions of the study population you would like to address. Is severe Covid19 defined as need for hospitalization, need for intensive care or need for mechanical ventilation at the intensive care. I think this review would benefit from defining your target population better, which you might find from the NACI instructions.</p>	<p>We outlined the study populations of interest in the Methods:</p> <p>“Eligible source populations, in order of priority, were people (a) from a general/community sample, (b) with COVID-19 confirmed (by laboratory testing or epidemiologic linkage), and (c) hospitalized with COVID-19. Although potentially of interest, studies only including people with a risk factor of interest were not included.”</p> <p>We have revised the manuscript to clarify our use of “severe COVID-19” within the context of the broad range of outcomes:</p> <p>“We refer to this range of outcomes as “severe COVID-19” or “severity of COVID-19” throughout the review, though distinct from the composite outcome of “severe disease”. Each of these outcomes are applicable to at least one of the abovementioned eligible populations.”</p> <p>We have also commented that we did not include studies where the entire population had severe disease (e.g., ICU settings).</p>	<p>Eligibility Criteria</p>
<p>How you used comparators is for me unclear. Did the comparators include patients admitted but without the prespecified potential risk factors? Or did you also include patients that were not admitted?</p>	<p>Thank you for raising this.</p> <p>We included comparators of patients from same source population, but without the risk factors. For example, when including a sample from the general population/community for a particular risk factor, an eligible comparator group would also be from a community sample, but without the risk factor.</p> <p>We have revised the Methods to clarify this:</p> <p>“Eligible comparators were those within the same source population (e.g., all hospitalized, as described above) that did not have the P²ROGRESS And Other Factor, or experienced a</p>	<p>Eligibility Criteria</p>

	P ² ROGRESS And Other Factor to a different degree (e.g., older vs. younger).”	
In summary I think the review has the potential to improve if you define you population and comparators better, determine how you define severe Covid19 and use a more generic approach when discussing your findings.	Thank you. Please see above responses.	NA
Reviewer 3		
<p>The document has two aims:</p> <ul style="list-style-type: none"> - Provide a rapid evidence synthesis of risk factors for COVID-19 severity for the Canadian context. - Quantify the quality of the evidence for the risk factors <p>The author's justification for the research is that knowledge of these factors might help in the equitable and efficient allocation of a vaccine among high-risk populations.</p> <p>The study generally followed the published protocol in PROSPERO. The arguments were presented logically, and the summary tables provide highly relevant information based on the aims of the review.</p> <p>I found of particular importance that disease severity was not evaluated using a composite index of severe-fatal disease and that an effort was made to provide the associations of different risk factors with the full length of the natural history of the COVID-19 disease.</p> <p>Given the academic merit of the presented work, the following general comments are intended to assist authors in achieving publication.</p>	Thank you for your review and comments.	NA
The methodological trade-off or a rapid review, vs a more in-depth analysis needs a little more justification.	<p>Rapid reviews typically streamline conventional standard review processes. To ensure methodological rigour, we conducted pilot testing with more than one reviewer at each step; once a high level of agreement was achieved, a single reviewer proceeded with completing the step. We also involved reviewers with extensive experience conducting systematic reviews, as another means of ensuring methodological rigour.</p> <p>We have outlined our rapid review approach in the Methods, and discussed the trade-offs in the Limitations section at the end of the Discussion.</p>	Strengths and Limitations of the Review

<p>The limitations section should consider the above-mentioned trade-off, especially considering that risk of bias assessments was conducted at the study level, while the aim was to provide an evidence quality analysis at the individual risk factor- severe outcome level.</p>	<p>We have discussed the trade-offs in the rapid review approach we undertook, in the Strengths and Limitations section. We have also added discussion of the limitations of the risk of bias appraisals. Many rapid reviews do not conduct any assessment of risk of bias or certainty so this is a relative strength of our approach.</p>	<p>Strengths and Limitations of the Review</p>
<p>It would be interesting to know the author's opinion on which of the severe disease outcomes should be prioritized when targeting a particular group. Based on the presented data in Table 2. Hospitalization seems to have (i) a higher magnitude of associations and (ii) higher confidence in the magnitude of associations. I think this is important for the decision-making of policymakers and should be briefly discussed in the discussion.</p>	<p>The current review provides evidence that there is high confidence hospitalization appears to have a higher magnitude of association for people with specific risk factors, in particular, pre-existing conditions (obesity class III, heart failure, diabetes, chronic kidney disease [community sample or with COVID-19], dementia [community sample]), older age (>45 years vs. younger), male gender, Black race/ethnicity (community sample or with COVID-19), homelessness, and low income ($\leq 25^{\text{th}}$ vs. $> 50^{\text{th}}$ percentile).</p> <p>It is outside the purview of the current work to make direct statements regarding implications of the findings on policy decisions, which may consider a multitude of other factors (e.g., resources, feasibility) beyond the evidence we synthesized. We have presented the findings of the review in the Results and Discussion, which will inform decision-making by stakeholders while taking into account local contextual factors.</p>	<p>Table 2; Results, paragraph 1; Discussion, paragraph 1</p>
<p>I think it is important to highlight the granularity of the analysis along the continuum of the natural history of the disease as a strength of the used methodology. To the best of my knowledge, there is only one existing review that has separated outcomes, yet it was only focused on sex and gender as risk factors (Gebhard, Regitz-Zagrosek, Neuhauser, Morgan, & Klein, 2020). Most other reviews of the risk factors for COVID-19 disease severity had focused either on mortality or a composite outcome of severe-critical-fatal disease (Drager, Pio-Abreu, Lopes, & Bortolotto, 2020; Leung, 2020; Rod, Oviedo-Trespalacios, & Cortes-Ramirez, 2020; Singh & Khunti, 2020; Wolff, Nee, Hickey, & Marschollek, 2020; Zheng et al., 2020). The recommendation of analyzing risk factors by detailed outcomes along the natural history of the COVID-19 disease was specifically emphasized by our review (Rod et al., 2020).</p>	<p>Thank you for your comment. We have highlighted this as a methodological strength of the review in the strengths and limitations box and at the end of the Discussion.</p>	<p>Strengths and limitations box; Strengths and Limitations of the Review</p>
<p>More detailed comments. Page 6</p>	<p>We have removed this sentence as it was applicable at the time, but seems outdated as there</p>	<p>Introduction</p>

<p>Line 15 –</p> <p>Perhaps specify to what stakeholders the sentence is referring to. The consensus is among the medical community, the scientific community, government, international organizations?. In Canada, OECD members?</p>	<p>appears to be identification of/consensus on some populations that are at increased risk of severe outcomes from COVID-19.</p>	
<p>Line 21</p> <p>Reference or example to support the unprecedented pace.</p>	<p>We have included citations to support the pace of vaccine development, as follows:</p> <p>“Vaccine development has been progressing at an unprecedented pace;[7-10]...”</p> <p>[7] Health Canada. Statement on UK’s authorization of its first COVID-19 vaccine, manufactured by Pfizer/BioNTech. 2020. https://www.canada.ca/en/health-canada/news/2020/12/statement-on-uks-authorization-of-its-first-covid-19-vaccine-manufactured-by-pfizerbiontech.html</p> <p>[8] Health Canada. Vaccines and treatments for COVID-19: Progress. 2020. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/prevention-risks/covid-19-vaccine-treatment.html</p> <p>[9] World Health Organization. Draft landscape of COVID-19 candidate vaccines. 2020. https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines</p> <p>[10] Thanh Le T, Andreadakis Z, Kumar A, Gómez Román R, Tollefsen S, Saville M, et al. The COVID-19 vaccine development landscape. <i>Nature reviews drug discovery</i>. 2020;19(5):305-6.</p>	<p>Introduction</p>
<p>Line 21</p> <p>“Once a successful COVID-19 vaccine candidate becomes”. The words COVID-19 and candidate could be removed from the sentence as the whole paragraph is referring to COVID-19 vaccine candidates.</p>	<p>We have removed “COVID-19” and “candidate” for redundancy in this sentence.</p>	<p>Introduction</p>
<p>Line 19 – 28</p> <p>There are opportunities for easing the readability by reducing the times the word vaccine(s) and COVID-19 is used within the paragraph.</p>	<p>We have removed redundant words in this paragraph.</p>	<p>Introduction</p>

<p>Line 24 -25.</p> <p>Given that the eventual vaccine is still under development and subsequent approval is needed. I would not necessarily think it is “urgent” to plan for its efficient use. As this is the rationale that supports the paper, I would say it is perhaps, “of high relevance to policymakers” or “of high priority to policymakers”</p>	<p>We have revised this sentence, as suggested:</p> <p>“Therefore, it is of high priority to policymakers to plan for the efficient, effective and equitable allocation of vaccines...”</p>	<p>Introduction</p>
<p>Page 7 Lines 3-5</p> <p>I agree with the suggestion that COVID-19 vaccines have become a global priority and the importance of the presented research is highlighting that particular groups should be offered the vaccines as a priority based on risk factors for disease severity. However, I think there is a need to increase the robustness of the rationale for a “rapid review”. Currently, in the text, there is only one line suggesting that vaccine development is occurring at “an unprecedented pace”. I would suggest including literature and examples of the COVID-19 vaccine timelines to convey more accurately the feeling of urgency.</p>	<p>As per above comment and response, we have included citations to illustrate the COVID-19 vaccine timelines in the following sentence:</p> <p>“Vaccine development has been progressing at an unprecedented pace;[7-10]...”</p>	<p>Introduction</p>
<p>Page 9, Synthesis section: Lines 27 to 28</p> <p>It will be useful to direct the reader to supplementary material 5 for a more detailed overview of the findings.</p>	<p>Thank you for your comment and suggestions.</p> <p>The Synthesis section is intended to outline our methods, keeping the actual findings to the Results.</p> <p>In the beginning of the Results section, we have revised the sentence to direct the reader to detailed results:</p> <p>“Table 2 shows a summary of findings for associations between each reported risk factor and outcomes of interest; detailed data are in the Supplemental File (Supplement 5).”</p>	<p>Results, Associations Between Risk Factors and Outcomes</p>
<p>The certainty of the evidence section:</p> <p>The document presents an evaluation of risk of biases (RoB) at the study level focusing on three types of biases. Nevertheless, the focus is on the certainty of the evidence of risk factors – outcomes associations. This implies that the external validity of the overall quality appraisal conducted at the studies decreases</p>	<p>We have outlined the limitations of this approach at the end of the Discussion section.</p>	<p>Strengths and Limitations of the Review</p>

<p>at the outcome level, and it is a very important component for upgrading and downgrading the certainty of evidence based on the GRADE approach.</p> <p>The potential benefit of the rapid review somewhat justifies the trade-off between (i) not using a RoB assessment at the outcome level vs the magnitude that a conducted RoB could affect the certainty of evidence evaluations. Nevertheless, it is important for the reader and future researchers to know about this limitation, given that this is important information for decision making and a potential rationale for conducting a more in-depth analysis in the future.</p>		
<p>Page 9 Lines 38 – 43</p> <p>“Among the factors identified as increasing risk of severe outcomes, age seemed to be the most influential; adults older than 60 years may have at least 5 times increased odds of hospitalization and mortality from COVID-19 compared to those aged less than 45 years. This increased risk appears to magnify at least to some degree even for those older than 60 years, with those aged over 80 years having double the mortality risk of those aged 65-69 years”.</p> <p>There is a valid implied representational overlap of risk and odds as being association tools in epidemiological studies. However, risk is often more associated with probability than odds. Given that probability and odds convey different mathematical information, it might be prudent to refer to “Among the factors that increase the chance of severe outcomes”, “this increased association appears” and “double the magnitude of association of those”. The interpretations of odds as risk (with risk mostly understood as probability within the quantitative perspective of risk) might repeat in other sections within the document. Using the term association for the description of both probability and odds could also increase the consistency in relation to the research question proposed in the protocol in PROSPERO.</p>	<p>Thank you for your comment and insights.</p> <p>As suggested, we have replaced “odds” and “risk” with “increased association” (or similar) throughout the manuscript to more accurately present the data and for ease of interpretation, and consistency, for example:</p> <p>“Among the factors that increase the chance of severe outcomes, age seemed to be the most influential; adults older than 60 years may have at least 5 times the magnitude of association with hospitalization and mortality...”</p>	<p>Results; throughout manuscript</p>

<p>Page 20 Lines 43 to 56 seems to be more relevant for the limitation section.</p>	<p>Thank you. We have moved these lines from the beginning of the Discussion (summarizing the evidence) to the Limitations of the Evidence section that follows.</p>	<p>Limitations of the Evidence</p>
<p>Cited references:</p> <p>Drager, L. F., Pio-Abreu, A., Lopes, R. D., & Bortolotto, L. A. (2020). Is Hypertension a Real Risk Factor for Poor Prognosis in the COVID-19 Pandemic? <i>Curr Hypertens Rep</i>, 22(6), 43. doi:10.1007/s11906-020-01057-x</p> <p>Gebhard, C., Regitz-Zagrosek, V., Neuhauser, H. K., Morgan, R., & Klein, S. L. (2020). Impact of sex and gender on COVID-19 outcomes in Europe. <i>Biol Sex Differ</i>, 11(1), 29. doi:10.1186/s13293-020-00304-9</p> <p>Leung, C. (2020). Risk factors for predicting mortality in elderly patients with COVID-19: A review of clinical data in China. <i>Mechanisms of Ageing and Development</i>, 188, 111255. doi:https://doi.org/10.1016/j.mad.2020.111255</p> <p>Rod, J. E., Oviedo-Trespalacios, O., & Cortes-Ramirez, J. (2020). A brief-review of the risk factors for covid-19 severity. <i>Rev Saude Publica</i>, 54, 60. doi:10.11606/s1518-8787.2020054002481</p> <p>Singh, A. K., & Khunti, K. (2020). Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: A narrative review. <i>Diabetes Res Clin Pract</i>, 165, 108266. doi:10.1016/j.diabres.2020.108266</p> <p>Wolff, D., Nee, S., Hickey, N. S., & Marschollek, M. (2020). Risk factors for Covid-19 severity and fatality: a structured literature review. <i>Infection</i>, 1-14. doi:10.1007/s15010-020-01509-1</p> <p>Zheng, Z., Peng, F., Xu, B., Zhao, J., Liu, H., Peng, J., . . . Tang, W. (2020). Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. <i>J Infect</i>, 81(2), e16-e25. doi:10.1016/j.jinf.2020.04.021</p>	<p>Thank you for providing these citations for reference.</p>	<p>NA</p>

VERSION 2 – REVIEW

REVIEWER	Rod, J. Queensland University of Technology
REVIEW RETURNED	31-Dec-2020
GENERAL COMMENTS	I think the authors have addressed a common point between the reviewers by presenting more information about the need for a

	rapid review and the limitations associated with this method. They have also addressed all my other comments well.
--	--