PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparative-effectiveness research of COVID-19 treatment: A rapid scoping review
AUTHORS	Pham, Ba; Rios, Patricia; Radhakrishnan, Amruta; Darvesh, Nazia; Antony, Jesmin; Williams, Chantal; Ramkissoon, Naveeta; Cormack, Gordon; Grossman, Maura; Kampman, Melissa; Patel, Milan; Yazdi, Fatemeh; Robson, Reid; Ghassemi, Marco; Macdonald, Erin; Warren, Rachel; Muller, Matthew; Straus, Sharon; Tricco, Andrea

VERSION 1 – REVIEW

REVIEWER	Akoriyea, Samuel Ghana Health Service, Institutional Care
REVIEW RETURNED	18-Oct-2020

GENERAL COMMENTS	This is a good scoping review with just minor revision as per the review. Good work.

REVIEWER	O'Malley, Megan University of Michigan Michigan Medicine, Division of Hospital Medicine, Department of Internal Medicine
REVIEW RETURNED	22-Oct-2020

GENERAL COMMENTS	Objective: The objective of the manuscript is not clearly defined in the abstract. Is the intent of this research to provide details on a faster method to synthesize research results? If so, the discussion would need to provide more details on future implementation and replication of the stated methods. Or is the goal to bring together smaller threads of literature into a synthesized format to better understand treatment for COVID-19? In this case the authors do not provide information if the studies included have been included in other review articles. This would clarify if this manuscript is providing repetitive information. At this point, a review providing only evidence from May 21 is out of date, so a timeline of start date to end date is really needed to understand the helpfulness of this methodology in quickly synthesizing information.

REVIEWER	Pimentel, Juan McGill University, Department of Family Medicine
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	I thank the editors for the opportunity to review this manuscript. Although the topic is highly relevant and the review is well designed, there are some concerns that I share below.

	Major comments - As for any study on COVID-19, this report has been rapidly exceeded by the tumultuous increase of literature on this topic. I suggest an update of the search and results. - The authors state that “to our knowledge, there is no other published review examining more than one type of potential COVID-19 treatment.” (lines 339 and 340). However, there is at least one such review. The authors should demonstrate what their paper adds to the living systematic review and meta-analysis published by Siemieniuk et al entitled Drug treatments for covid-19: living systematic review and network meta-analysis (BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980). Inability to demonstrate the novelty of the submitted work compromises the relevance of this manuscript. Methods - It is not clear what the difference between a scoping review and a rapid scoping review is. Please clarify. - The protocol that the authors cite (https://osf.io/ypz7x) states that the research question is “What treatments have been studied for SARS, MERS, and COVID-19?” (page 3). However, this is not the question that the scoping review answers. Please clarify the reasons for such deviation from the original protocol and describe additional deviations, if any. - The authors described an integrated knowledge translation approach with knowledge users from Health Canada. It would be good to have a more detailed description of these stakeholders (how many of them, position, background, etc.) and their role in the project. - It is not completely clear what Continuous Active Learning is (line 113). Is it software? Please provide a clear description of this tool so interested readers not familiar with the topic can understand. - Since the authors included observational studies, I believe that this study also assesses effectiveness. Please consider this recommendation and adjust the manuscript, including the title, accordingly. - It is not clear if there were any inclusion or exclusion criteria based on the language of the documents. If only manuscripts in English were considered, please describe this as a limitation of the study. - The authors mention the implementation of an automated search as a strength of the study. In knowledge synthesis studies, the searching/screening process is complex. It is hard to believe that a machine learning algorithm performs better than humans. I see the combination of search and screening strategies as a limitation of the study. - Another potential limitation of the study is the fact that most included articles were obtained from pre-print servers, which usually store non-peer-reviewed manuscripts. - The authors included trial registries, such as clinicaltrials.gov, European Union clinical trial register, Chinese Clinical Trial Registry, and the WHO international clinical trials register. I believe these results should be differentiated in the results section since trial registries provide information that is different from manuscripts with research results. Please clarify. Minor comments: - Please mention the search date (May 21, 2020) in the abstract.

REVIEWER	Pimentel, Juan McGill University, Department of Family Medicine
REVIEW RETURNED	07-Dec-2020

GENERAL COMMENTS	I thank the editors for the opportunity to review this manuscript. Although the topic is highly relevant and the review is well designed, there are some concerns that I share below. Major comments - As for any study on COVID-19, this report has been rapidly exceeded by the tumultuous increase of literature on this topic. I suggest an update of the search and results. - The authors state that “to our knowledge, there is no other published review examining more than one type of potential COVID-19 treatment.” (lines 339 and 340). However, there is at least one such review. The authors should demonstrate what their paper adds to the living systematic review and meta-analysis published by Siemieniuk et al entitled Drug treatments for covid-19: living systematic review and network meta-analysis (BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980). Inability to demonstrate the novelty of the submitted work compromises the relevance of this manuscript. Methods - It is not clear what the difference between a scoping review and a rapid scoping review is. Please clarify. - The protocol that the authors cite (https://osf.io/ypz7x) states that the research question is “What treatments have been studied for SARS, MERS, and COVID-19?” (page 3). However, this is not the question that the scoping review answers. Please clarify the reasons for such deviation from the original protocol and describe additional deviations, if any. - The authors described an integrated knowledge translation approach with knowledge users from Health Canada. It would be good to have a more detailed description of these stakeholders (how many of them, position, background, etc.) and their role in the project. - It is not completely clear what Continuous Active Learning is (line 113). Is it software? Please provide a clear description of this tool so interested readers not familiar with the topic can understand. - Since the authors included observational studies, I believe that this study also assesses effectiveness. Please consider this recommendation and adjust the manuscript, including the title, accordingly. - It is not clear if there were any inclusion or exclusion criteria based on the language of the documents. If only manuscripts in English were considered, please describe this as a limitation of the study. - The authors mention the implementation of an automated search as a strength of the study. In knowledge synthesis studies, the searching/screening process is complex. It is hard to believe that a machine learning algorithm performs better than humans. I see the combination of search and screening strategies as a limitation of the study. - Another potential limitation of the study is the fact that most included articles were obtained from pre-print servers, which usually store non-peer-reviewed manuscripts. - The authors included trial registries, such as clinicaltrials.gov, European Union clinical trial register, Chinese Clinical Trial Registry, and the WHO international clinical trials register. I believe these

	results should be differentiated in the results section since trial registries provide information that is different from manuscripts with research results. Please clarify. Minor comments: - Please mention the search date (May 21, 2020) in the abstract.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Dr. Samuel Akoriyea, Ghana Health Service
Comments to the Author:
This is a good scoping review with just minor revision as per the review. Good work.
Response: Thank you!

Reviewer: 2
Dr. Megan O'Malley, University of Michigan Michigan Medicine

The objective of the manuscript is not clearly defined in the abstract.
Response: The objective was revised. It is “to provide an overview of the characteristics of comparative-effectiveness research of COVID-19 treatment.” This objective is consistent with the recommended use of the review method for scoping review.

Is the intent of this research to provide details on a faster method to synthesize research results? If so, the discussion would need to provide more details on future implementation and replication of the stated methods.
Response: The automation tool for titles/abstracts screening was no longer the emphasis of the revised draft manuscript. It had never been our intention to report in details about the automation tool. We however provided the description, algorithm and performance of the automation tool in the Appendix and mentioned the availability of these details in the manuscript.

Or is the goal to bring together smaller threads of literature into a synthesized format to better understand treatment for COVID-19? In this case the authors do not provide information if the studies included have been included in other review articles. This would clarify if this manuscript is providing repetitive information.
Response:The objective of our scoping review is to provide an overview of the characteristics of comparative-effectiveness research of COVID-19 treatment. We justified why this is needed.
We showed the growth in the number of relevant studies from the previous literature search from inception to mid May 2020 and in the update from mid May 2021 in the Discussion section.
As part of the update, the inclusion criteria now specified the inclusion of evidence syntheses (e.g., systematic reviews, scoping reviews, rapid reviews, and overview of reviews) of Covid-19 treatment. The scoping review we conducted included 303 evidence syntheses. We believe the update results are comprehensive with respect to the state of comparative-effectiveness research from inception to May 2021.

At this point, a review providing only evidence from May 21 is out of date, so a timeline of start date to end date is really needed to understand the helpfulness of this methodology in quickly synthesizing information.
Response: We updated the literature search to May 15, 2021. We provided an overview of the characteristics of a large number of primary studies and evidence syntheses. We identified gaps in the comparative-effectiveness literature and suggested practical implications to future studies.

Reviewer: 3
Dr. Juan Pimentel, McGill University, Universidad Del Rosario
Comments to the Author:
I thank the editors for the opportunity to review this manuscript. Although the topic is highly relevant and the review is well designed, there are some concerns that I share below.

Major comments
- As for any study on COVID-19, this report has been rapidly exceeded by the tumultuous increase of literature on this topic. I suggest an update of the search and results.
Response: We updated the literature search to May 15, 2021. This results in a large number of included primary studies and knowledge syntheses.

- The authors state that “to our knowledge, there is no other published review examining more than one type of potential COVID-19 treatment.” (lines 339 and 340). However, there is at least one such review. The authors should demonstrate what their paper adds to the living systematic review and meta-analysis published by Siemieniuk et al entitled Drug treatments for covid-19: living systematic review and network meta-analysis (BMJ 2020; 370 doi: https://doi.org/10.1136/bmj.m2980). Inability to demonstrate the novelty of the submitted work compromises the relevance of this manuscript.
Response: e have expanded the scope of the update to capture primary studies and evidence synthesis (including systematic reviews, scoping reviews, rapid reviews, meta-analyses and overviews of systematic reviews). We provided an overview of these bodies of literature on comparative-effectiveness research on Covid-19 treatment. We believe the results in our updated manuscript are unique and will contribute to the literature on Covid-19 treatment.

Methods
- It is not clear what the difference between a scoping review and a rapid scoping review is. Please clarify.
Response: The methods for a scoping review are designed to guard against bias that may be introduced in the steps of the conduct of the review, including for example comprehensive searches of multiple databases and sources of literature with limited circulation (e.g., government reports, dissertation), and study selection and data extraction conducted by two reviewers independently, with discrepancies reviewed and resolved through discussion. Simplified methods are used in the conduct of rapid scoping review, to reduce person-hours and timelines. We conducted the rapid scoping review using these simplified methods, such as study selection conducted by single reviewers.

- The protocol that the authors cite (https://osf.io/ypz7x) states that the research question is “What treatments have been studied for SARS, MERS, and COVID-19?” (page 3). However, this is not the question that the scoping review answers. Please clarify the reasons for such deviation from the original protocol and describe additional deviations, if any.
Response: We clarified the minor amendments that occurred to the conduct of the review from the original protocol, both in the Methods and Discussion sections.

- The authors described an integrated knowledge translation approach with knowledge users from Health Canada. It would be good to have a more detailed description of these stakeholders (how many of them, position, background, etc.) and their role in the project.
Response: We have revised the Methods section of the manuscript to include the requested details. Dr. Melissa Kampman works as manager/senior epidemiologist for Health Canada. Mr. Milan Patel is a senior manager, Vaccine Supply and Assurance at Public Health Agency of Canada.

- It is not completely clear what Continuous Active Learning is (line 113). Is it software? Please provide a clear description of this tool so interested readers not familiar with the topic can understand.

Response: We have provided a description of the automation tool and its performance in the Appendix, as well as mentioned the availability of such details in the Methods section of the manuscript.

- Since the authors included observational studies, I believe that this study also assesses effectiveness. Please consider this recommendation and adjust the manuscript, including the title, accordingly.
Response: We have revised the title of the draft manuscript to include the term “comparative effectiveness”

- It is not clear if there were any inclusion or exclusion criteria based on the language of the documents. If only manuscripts in English were considered, please describe this as a limitation of the study.
Response: There is no language restriction and we included studies reported in languages other than English.
We have revised the Methods section to explicitly state that there was no language restriction.

- The authors mention the implementation of an automated search as a strength of the study. In knowledge synthesis studies, the searching/screening process is complex. It is hard to believe that a machine learning algorithm performs better than humans. I see the combination of search and screening strategies as a limitation of the study.
Response: We included details pertaining to the automation tool and its performance in the Appendix. The draft manuscript was revised and no longer put much emphasis on the tool.

- Another potential limitation of the study is the fact that most included articles were obtained from pre-print servers, which usually store non-peer-reviewed manuscripts.
Response: We agreed with the reviewer. We added a limitation about pre-prints.

- The authors included trial registries, such as clinicaltrials.gov, European Union clinical trial register, Chinese Clinical Trial Registry, and the WHO international clinical trials register. I believe these results should be differentiated in the results section since trial registries provide information that is different from manuscripts with research results. Please clarify.
Response: Given the large numbers of included primary studies and relevant knowledge syntheses, we refrained from including study and review protocols in our scoping review.

Minor comments:
- Please mention the search date (May 21, 2020) in the abstract.
Response: We have updated the literature search to May 15, 2021 and described details about the search date in the abstract.

VERSION 2 – REVIEW

REVIEWER	Pimentel, Juan McGill University, Department of Family Medicine
REVIEW RETURNED	15-Feb-2022

GENERAL COMMENTS	I thank the editors for the opportunity to re-review this manuscript. I believe the authors have fully addressed my concerns. My only suggestion is to explain the difference between a scoping review

	and a rapid scoping review in the text of the manuscript. Thanks.

VERSION 2 – AUTHOR RESPONSE

Reviewer #3: Comments to the Author:
I thank the editors for the opportunity to re-review this manuscript. I believe the authors have fully addressed my concerns. My only suggestion is to explain the difference between a scoping review and a rapid scoping review in the text of the manuscript. Thanks.
Author Response:
We have addressed the reviewer's comment on lines 103-104 of the manuscript regarding the difference between rapid scoping review and scoping review: ‘Compared to a scoping review, we used streamlined methods in this rapid scoping review (e.g., single reviewers conducted study selection).’