

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	COVID-19 outcomes among adult patients treated with long-term opioid therapy for chronic non-cancer pain in the United States: a retrospective cohort study
AUTHORS	Tuan, Wen-Jan; Spotts, Hannah; Zgierska, Aleksandra E.; Lennon, Robert P

VERSION 1 – REVIEW

REVIEWER	Just, Johannes Universitätsklinikum Bonn, Institute of General Practice and Family Medicine
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	<p>In this retrospective cohort study using electronic health records, the authors compared outcome parameters of 358,164 individuals diagnosed with COVID-19 in January-December 2020 matched by LTOT status (yes/no).</p> <p>While the study is generally well conducted and interesting, the role of confounding factors needs to be emphasized more clearly as patients who show severe COVID-19 and receive LTOT share more baseline characteristics than the study controlled for (see below).</p> <p>General comments:</p> <p>Background: Throughout the text, the authors seem to use LTOT as a synonym for opioid use disorder or non-medical opioid use. This is in my opinion misleading as, even in the light of the Opioid Pandemic, the majority of patients with LTOT receive opioids with a medical indication for chronic non-cancer pain (CNCP) and do not suffer from opioid use disorder (OUD). This is even truer in European countries, where there are no opioid epidemics. As an example, we currently estimate that 5-9% of patients on LTOT in Germany suffer from significant opioid use disorder. This number may well be higher in the US but it almost certainly is lower than 50%. Therefore the background section needs to be revised in order to reflect more on the group that is being analysed (that is who receives LTOT and why --> CNCP).</p> <p>Discussion: While I agree with the general direction of the discussion, more emphasis needs to be put on possible confounders. As I pointed out, patients on LTOT will either suffer from CNCP or OUD or both. CNCP as well as OUD is associated with multimorbidity and a low socioeconomic status. Both patient characteristics</p>
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	<p>(multimorbidity and low socioeconomic status) are in turn associated with a higher probability of severe COVID-19 cases. As the authors did not control for low socioeconomic status and only partly for multimorbidity, the potential bias has to be pointed out more clearly in the discussion section as well as the Abstract. One example for a possible miss of some multimorbidity defining diseases is the greater concentration of serum creatinine (1.3 vs 1.0, $p < 0.01$) and blood urea nitrogen (18.6 vs 17.1, $p < 0.01$) in the LTOT group (kidney disease which is a risk factor for severe COVID-19 was not controlled for). I would kindly like to ask the authors to elaborate more on these limitations as it will increase the quality of the paper without diminishing the important message that patients on LTOT need extra care and attention within health care systems worldwide.</p>
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REVIEWER	Emary, Peter McMaster University, Health Research Methods, Evidence and Impact
REVIEW RETURNED	08-Sep-2021

GENERAL COMMENTS	<p>Thank you for the opportunity to review this interesting manuscript. In general, it is very well-written and covers a timely topic, as it highlights the negative consequences of the intersection between the opioid crisis and the COVID-19 pandemic. I have several minor suggestions and edits for the authors to consider.</p> <p>Strengths and Limitations, page 3, line 22 – I'd recommend placing the word "to" after the word "found," so this part of the sentence reads as, "found to more likely experience..." Also, please consider shortening the five bullet point statements if and where possible.</p> <p>Abstract, page 4, line 12 – Please add the word "this" before the word "study."</p> <p>Abstract, page 5, line 10 – Please pluralize the word "patient" so it reads as "patients."</p> <p>Introduction, page 6, line 22 – Please drop the "s" from the end of the word "shows", so that it reads as "show."</p> <p>Introduction, page 6, line 52 – Please add the word "of" before the word "hospitalized."</p> <p>Introduction, page 7, line 3 – Please add the word "a" before the word "history."</p> <p>Introduction, page 7, line 35 – At this point in the manuscript, I'd recommend not using the abbreviation "OUD." Instead, I'd recommend either spelling it out in full as "opioid use disorders" or using slightly different terminology here so this part of the sentence reads something like, "...and opioid use disorders, such disorders may be clinically under diagnosed, ..."</p> <p>Methods, page 8, line 24 – I'd recommend changing the words "diagnosed of COVID-19" to "with a diagnosis of COVID-19."</p> <p>Methods, page 9, line 19 – I'd recommend changing the word "inpatients" to "inpatient."</p>
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	<p>Results, page 10, line 13 – In the Methods, the authors state that they extracted data from “48 healthcare organizations” in the TriNetX database. In the Results, they state that data was obtained from “51 healthcare organizations.” Is there a reason for the discrepancy? Please clarify.</p> <p>Results, page 11, line 12 – I’d recommend changing the words “not significant” to “non-significant.”</p> <p>Results, page 11, line 17 – I’d recommend changing the word “It” to “This.”</p> <p>Results, page 11, line 42 – I’d recommend adding the words “to be” between the words “found” and “consistently.”</p> <p>Results, page 11, line 52 – I’d recommend adding the word “as” after the word “reported,” and adding an “s” to the end of the word “counterpart” so it reads as “counterparts.”</p> <p>Results, page 12, line 8 – I’d recommend changing the word “was” to “were,” and adding the words “to have” after the word “found.”</p> <p>Table 2, page 12, line 38 – Please change “Patients” to “patients.”</p> <p>Conclusion, page 16, line 35 – Please change the word “ill” to “illness.” I’d also recommend adding the word “admission” after the words “intensive care.”</p> <p>Conclusion, page 16, line 42 – Please elaborate on what you mean by “personal behavior.” Perhaps, the authors could write something like, “...through personal behavior (e.g., masking, physical distancing, hand-washing) and vaccination...”</p> <p>Figure 1, page 18, line 6 – Please change “Patients” to “patients.”</p> <p>Figure 2, page 19, line 6 – Please change “Patients” to “patients.”</p>
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REVIEWER	Hatzakis, Angelos University of Athens, Athens, Greece, National Retrovirus Reference Center, Department of Hygiene, Epidemiology and Medical Statistics
REVIEW RETURNED	22-Sep-2021

GENERAL COMMENTS	<p>This is an interesting and well-written study using retrospective cohort design and electronic health records in a very large database, covering 68 million patients from participating health care organizations. Propensity score matching was used to control the confounding .</p> <p>Overall the study provided strong evidence that COVID-19 patients on LTOT have increased admissions to hospitals, emergency departments and intensive care units and higher mortality rates. Symptoms and laboratory tests were consistent with the above findings.</p> <p>Minor comments:</p> <ol style="list-style-type: none"> 1. In the limitations section the authors should include the numbering of individual limitations. 2. Fig. 1 , Fig.2 – The legends are not self-explanatory. They should include at least the study date and the control group. 3. The authors should update the references list, especially for very recent publications on a similar research question.
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VERSION 1 – AUTHOR RESPONSE

REVIEWER 1	
While the study is generally well conducted and interesting,	Thank you!
<p>the role of confounding factors needs to be emphasized more clearly as patients who show severe COVID-19 and receive LTOT share more baseline characteristics than the study controlled for (see below).</p> <p>Throughout the text, the authors seem to use LTOT as a synonym for opioid use disorder or non-medical opioid use. This is in my opinion misleading as, even in the light of the Opioid Pandemic, the majority of patients with LTOT receive opioids with a medical indication for chronic non-cancer pain (CNCP) and do not suffer from opioid use disorder (OUD). This is even truer in European countries, where there are no opioid epidemics. As an example, we currently estimate that 5-9% of patients on LTOT in Germany suffer from significant opioid use disorder. This number may well be higher in the US but it almost certainly is lower than 50%. Therefore the background section needs to be revised in order to reflect more on the group that is being analysed (that is who receives LTOT and why --> CNCP).</p>	<p>Your point is well taken. We have revised language throughout the manuscript to make clear that we are discussing LTOT – not OUD; this change can lend confidence that the results may be generalizable outside the US.</p>

<p>While I agree with the general direction of the discussion, more emphasis needs to be put on possible confounders. As I pointed out, patients on LTOT will either suffer from CNCP or OUD or both. CNCP as well as OUD is associated with multimorbidity and a low socioeconomic status. Both patient characteristics (multimorbidity and low socioeconomic status) are in turn associated with a higher probability of severe COVID-19 cases. As the authors did not control for low socioeconomic status and only partly for multimorbidity, the potential bias has to be pointed out more clearly in the discussion section as well as the Abstract. One example for a possible miss of some multimorbidity defining diseases is the greater concentration of serum creatinine (1.3 vs 1.0, $p < 0.01$) and blood urea nitrogen (18.6 vs 17.1, $p < 0.01$) in the LTOT group (kidney disease which is a risk factor for severe COVID-19 was not controlled for).</p> <p>I would kindly like to ask the authors to elaborate more on these limitations as it will increase the quality of the paper without diminishing the important message that patients on LTOT need extra care and attention within health care systems worldwide.</p>	<p>Thank you; these are excellent points. We have expanded our discussion of possible confounders.</p> <p>Further, we have re-analyzed the data, creating a new model, which considers the presence of chronic kidney disease (to address BUN/Cr differences), and socioeconomic status.</p> <p>A benefit of the propensity scoring method used is that it mitigates confounding by age, sex, race/ethnicity, and comorbidities (diabetes, essential hypertension, chronic pulmonary conditions, cardiovascular diseases, mental health disorders.)</p> <p>We have added language describing the limitations of propensity scoring that does not account for unknown/unobservable covariates.</p>
	Thank you for your thoughtful review.
Reviewer 2	
<p>Thank you for the opportunity to review this interesting manuscript. In general, it is very well-written and covers a timely topic, as it highlights the negative consequences of the intersection between the opioid crisis and the COVID-19 pandemic. I have several minor suggestions and edits for the authors to consider.</p>	Thank you.
<p>Strengths and Limitations, page 3, line 22 – I'd recommend placing the word "to" after the word "found," so this part of the sentence reads as, "found to more likely experience..." Also, please consider shortening the five bullet point statements if and where possible.</p> <p>Abstract, page 4, line 12 – Please add the word "this" before the word "study."</p>	We have amended the text and figures according to these suggestions.

Abstract, page 5, line 10 – Please pluralize the word “patient” so it reads as “patients.”

Introduction, page 6, line 22 – Please drop the “s” from the end of the word “shows”, so that it reads as “show.”

Introduction, page 6, line 52 – Please add the word “of” before the word “hospitalized.”

Introduction, page 7, line 3 – Please add the word “a” before the word “history.”

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Methods, page 8, line 24 – I’d recommend changing the words “diagnosed of COVID-19” to “with a diagnosis of COVID-19.”

Methods, page 9, line 19 – I’d recommend changing the word “inpatients” to “inpatient.”

Results, page 10, line 13 – In the Methods, the authors state that they extracted data from “48 healthcare organizations” in the TriNetX database. In the Results, they state that data was obtained from “51 healthcare organizations.” Is there a reason for the discrepancy? Please clarify.

Results, page 11, line 12 – I’d recommend changing the words “not significant” to “non-significant.”

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Results, page 11, line 52 – I’d recommend adding the word “as” after the word “reported,” and adding an “s” to the end of the word “counterpart” so it reads as “counterparts.”

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Table 2, page 12, line 38 – Please change “Patients” to “patients.”

Conclusion, page 16, line 35 – Please change the word “ill” to “illness.” I’d also recommend adding the word “admission” after the words “intensive care.”

Conclusion, page 16, line 42 – Please elaborate on what you mean by “personal behavior.” Perhaps, the authors could write something like, “...through personal behavior (e.g., masking, physical distancing, hand-washing) and vaccination...”

Figure 1, page 18, line 6 – Please change “Patients” to “patients.”

Figure 2, page 19, line 6 – Please change “Patients” to “patients.”

Corrected (51).

	<p>Excellent point – language added.</p>
	<p>Thank you for the detailed critique!</p>
<p>Reviewer 3</p>	
<p>This is an interesting and well-written study using retrospective cohort design and electronic health records in a very large database, covering 68 million patients from participating health care organizations. Propensity score matching was used to control the confounding.</p>	<p>Thank you!</p>

Overall the study provided strong evidence that COVID-19 patients on LTOT have increased admissions to hospitals, emergency departments and intensive care units and higher mortality rates. Symptoms and laboratory tests were consistent with the above findings.	
Minor comments: 1. In the limitations section the authors should include the numbering of individual limitations.	Done!
2. Fig. 1 , Fig.2 – The legends are not self-explanatory. They should include at least the study date and the control group.	We have amended the figure legends for clarity.
3. The authors should update the references list, especially for very recent publications on a similar research question.	We have amended our references to include recent similar research.
	Thank you for your recommendations!

VERSION 2 – REVIEW

REVIEWER	Just, Johannes Universitätsklinikum Bonn, Institute of General Practice and Family Medicine
REVIEW RETURNED	27-Oct-2021
GENERAL COMMENTS	Dear authors, the paper has improved significantly - thank you for your thorough revision and this interesting work.

VERSION 2 – AUTHOR RESPONSE

Dear Mr. Bennet,

Thank you for the opportunity to revise our manuscript, retitled, “COVID-19 outcomes among adult patients treated with long-term opioid therapy for chronic non-cancer pain in the United States: a retrospective cohort study.” To thoroughly address the major revisions requested, I have collaborated with other subject-matter experts (adding two co-authors); together we have performed additional analysis and completed substantial revisions of the text to address all editorial and reviewer critiques and recommendations.

In addition, due to the nature of the TriNetX research database, individuals are added from the total pool regularly, so when analyses are repeated, the curated data we access necessarily changed. This means that in revising and fine-tuning the manuscript, our population and percentages (and thus deductive calculations like odds ratio) have also slightly changed. This does not change the thesis or crux of the paper, but it might change the magnitude of various data. I would like to bring this to your attention to avoid confusion regarding the differences you will see in the text and the various tables.

A detailed description of responses is below, and the tracked/blinded manuscripts are uploaded per instruction. We appreciate the detailed reviews, believe the manuscript is considerably strengthened by addressing them, and look forward to your consideration of the revised manuscript.

Sincerely,

Wen-Jan Tuan, DHA MS MPH

Corresponding author