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Assessing COVID-19 Outcomes among Adult Patients with Long-Term Opioid Therapy

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Title

Assessing COVID-19 outcomes among adult patients with long-term opioid therapy

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Strengths and Limitations of the Study

- This is one of the few studies utilizing large-scale EHR-based data and propensity score matching approaches to assess the risk of morbidity and mortality from SARS-CoV-2 infection among individuals on long-term opioid therapy, increasing the generalizability and robustness of the study outcomes.
- Study results will help shape the conversations between providers, patients, and public health personnel related to effective prevention and early treatment protocols for patients on long term opioid therapy to reduce the risk and cost burden.
- Individuals on long-term opioid therapy were found more likely to experience severe complications or deaths after being infected by COVID-19; however, the analysis was unable to determine whether people on long-term opioid therapy were more likely to be infected by COVID-19.
- Some patients could receive COVID-19 tests or treatments at healthcare facilities outside of the research data network. The analysis would not include information from these patients, potentially underestimating the risk of negative health outcomes for the target population.
- Patients on long-term opioid therapy could be prescribed opioid medications at different dosage or frequency levels. The study did not assess associations between the dosage of opioid medications and the severity of COVID-19 illness.

ABSTRACT

Objective

Patients on long-term opioid therapy (LTOT) are known to have compromised immune systems and respiratory function, both of which make them particularly susceptible to the SARS-CoV-2 virus. The objective of study was to assess the risk of developing severe clinical outcomes among COVID-19 patients on LTOT, compared to those without LTOT.

Design and data sources

A retrospective cohort design using electronic health records in the TriNetX research database.

Participants and setting

358,164 individuals diagnosed with COVID-19 in January-December 2020 from 51 U.S. healthcare organizations, including 7,256 in the LTOT cohort and 350,908 in the non-LTOT cohort.

Results

Patients in LTOT were more likely than non-LTOT patients to be admitted to the hospital (RR=1.61), emergency department (ARR=2.04), and intensive care unit (RR=2.86), and have higher 30-day mortality rates (RR=1.74). There was greater use of both vasopressors (RR=3.36), and mechanical ventilation (RR=5.78), suggesting that long-term opioid users were more likely to get severely ill. LTOT patients also showed increased risk (RRs ranging from 1.91 to 4.53) of severe symptoms, such as cough, fever, hypoxemia, dyspnea, thrombocytopenia, and acute respiratory distress syndrome. Mixed findings were found in the laboratory results. Compared to their non-LTOT counterparts, LTOT patients consistently showed lower systolic pressure (127.1 vs 128.2), diastolic blood pressure (75.1 vs 75.8), and lymphocyte counts (23.6 vs 24.9), and

substantial elevation in leukocytes (8.1 vs 7.7), platelets (263.2 vs 257.0), and alkaline phosphatase concentration (95.4 vs 85.6).

Conclusion

COVID-19 patient with LTOT were at significantly higher risk of increased morbidity and healthcare utilization. Interventions to improve compliance with protective measures may improve morbidity and decrease healthcare costs for these patients. Prospective studies are needed to confirm and refine these findings.

INTRODUCTION

The COVID-19 pandemic, resulting from SARS-CoV-2 infection, has rapidly spread across the United States since early 2020. By the end of 2020, there were over 20 million confirmed cases and 344 thousand deaths reported in the nation (1). This unprecedented upheaval has led to deaths from the novel coronavirus, in addition to deaths caused by the effects of protracted economic stagnation and social disruption. Vulnerable populations with mental illness and substance use disorders have been disproportionately affected (2, 3). As the nation focuses on the COVID-19 pandemic, the opioid crisis has continued to have devastating impacts on communities. Recent statistics shows a 38.4% increase in opioid-related deaths from June 2019 to May 2020 (4). Literature suggests that the opioid crisis has been escalated by a lack of access to drug screening and treatments for opioid use disorders due to care disruption by the COVID-19 pandemic (5). Ongoing opioid addiction prevention efforts have been interrupted by social distancing practices and isolation that can contribute to the misuse of prescription or illicit opioids (3,6).

Research shows that opioids can trigger acute respiratory depression (e.g., hypoventilation and hypoxemia) through the activation of opioid receptors in the brainstem that can lead to respiratory arrest, bradycardia, or death (7). Chronic opioid use also increases the risk of immunosuppression and infections, especially for people on long-term opioid medications (8). These individuals are likely to have cardiopulmonary morbidity, longer hospitalization, and greater overall care costs. With severe COVID-19 infection, patients may also present with clinical signs and symptoms of respiratory depression (9, 10). Approximately 10-15% hospitalized patients for COVID-19 progressed to acute respiratory distress syndrome (11, 12).

COVID-19 infection can lead to greater morbidity and mortality for individuals with history of recurrently using or misusing opioids (3, 13).

While the risk of increasing morbidity and mortality from SARS-CoV-2 infection among individuals with certain health conditions has been identified and incorporated into outcome prediction models, the relationship between long-term opioid use and SARS-CoV-2-related morbidity and mortality has not been assessed (14). The likelihood of worsened outcomes in patients with long-term opioid use and COVID-19 infection may be explained by the mechanisms of respiratory depression and immunosuppression (15). As a result, COVID-19 patients with a history of long-term opioid therapy may be expected to have more severe health outcomes, potentially resulting in an increased risk of hospitalization, emergency department admissions, and time in the intensive care unit (16, 17). Critically ill patients with SARS-CoV-2 were also more likely to be treated with mechanical ventilation and vasopressors (18, 19). Given the ongoing opioid endemic, more research is urgently needed to investigate long-term opioid use as a pathway to severe COVID-19. While some studies have assessed COVID-19 outcomes and opioid use disorders, OUD may be clinically under diagnosed, justifying this study's focus on operationalizing long-term opioid therapy. This study aims to assess the risk of developing severe outcomes for COVID-19 patients on long-term opioid therapy, in order to help clinicians develop more effective care guidelines for treating COVID-19 patients and raise awareness about the risks of COVID-19 to vulnerable populations on long-term opioid therapy.

METHODS

Study design and data collection

The study applied a retrospective cohort design using electronic health records (EHRs) from 48 healthcare organizations on the research network of the TriNetX database in the United

States (Cambridge, MA). TriNetX is a federated health research network that provides access to continuously updated, de-identified EHR data (demographics, diagnoses, procedures, medications, laboratory tests, and genomics) of more than 68 million patients from participating healthcare organizations. The TriNetX platform only uses aggregated counts and statistical summaries. All the data queries were performed in the TriNetX online portal managed by the Penn State Clinic and Translational Science Institute. Because there was no protected health information (PHI) data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight.

Cohort description

The study population consisted of adults (age≥18 years) diagnosed of COVID-19 between January 1, 2020 and December 31, 2020, based on the combination of one or more disease indicators, including ICD-10 diagnosis codes and positive laboratory test results. Individuals are considered on long-term opioid therapy (LTOT) when they are prescribed with opioids in 3 or more consecutive months or at least 90 days at outpatient settings (20, 21). COVID-19 patients meeting the LTOT criteria within 12 months before their infection were assigned to the LTOT cohort. Individuals with COVID-19 without LTOT were assigned to the control cohort. The analysis excluded individuals who had cancers (malignant and non-malignant), or living in nursing home, hospice or palliative care facilities.

Outcome indicators

The severity of the COVID-19 infection was assessed through three areas: health service utilization, clinical presentation, and diagnostic testing. The health service utilization measure consisted of binary variables (1=yes, 0=no) indicating whether patients were admitted to emergency department, inpatient hospital, intensive care unit, died within 30 days of

hospitalization, placed on mechanical ventilation, or treated with vasopressor medications after being infected by COVID-19. The clinical presentation measure also comprised of binary variables (1=yes, 0=no) indicating the presence of severe physical signs or medical complication, including cough, fever, acute respiratory distress syndrome (ARDS), hypoxemia, thrombocytopenia, and dyspnea. The diagnostic testing consisted of common biometrics or laboratory tests serving as severity indicators of COVID-19 infection, such as C-reactive protein, serum creatinine, and blood urea nitrogen. These tests have also been used to predict the risk of developing serious illness or deaths in both inpatients and outpatient settings (14, 22).

Data Analysis

A number of patient characteristics were considered potential confounding variables, including age, sex, race/ethnicity, and comorbidities (diabetes, essential hypertension, chronic pulmonary conditions, cardiovascular diseases, mental health disorders). The study applied a 1:1 propensity score matching (PSM) technique to balance the baseline characteristics between the comparison and control cohorts and reduce potential selection bias. The matching method was performed using nearest neighbor algorithms with a caliper width of 0.1 pooled standard deviation. Outcomes were compared in COVID-19 patients on LTOT and COVID-19 patients not on LTOT using logistic regression modeling, based on patient cohorts before and after propensity score matching. Risk ratios were computed and a two-sided alpha of less than 0.05 was defined *a priori* for statistical significance between the two groups. All data queries and statistical analyses were performed on the TriNetX portal. Detailed data information for diagnoses and laboratory tests are provided in the Appendix.

Patients and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study population

A total of 358,164 patients diagnosed with COVID-19 from 51 healthcare organizations met the study criteria, including 7,256 individuals in the LTOT cohort and 350,908 in the non-LTOT cohort. Before propensity score matching, the LTOT cohort had a higher average age and a greater percentage of female, white and black patients (Table 1).

Table 1. Patient demographics and comorbidities, before and after propensity score matching

	Before Propensity Score Matching			After Propensity Score Matching			
Characteristic	Long-term Opioid Therapy (N=7,256)	No Long-term Opioid Therapy (N=350,908)	p-value	Long-term Opioid Therapy (N=7,256)	No Long-term Opioid Therapy (N=7,256)	p-value	Standardized Mean Difference
Age, mean ± SD	51.9±17.3	43.1±17.6	<0.01	51.9±17.3	52.4±17.6	0.09	0.028
Sex							
Female, n (%)	4,438 (61.2)	17,7324 (50.9)	<0.01	4,433 (61.1)	4,447 (61.3)	0.81	0.004
Male, n (%)	2,818 (38.8)	17,0437 (49)	<0.01	2,818 (38.9)	2,804 (38.7)	0.81	0.004
Hispanic or Latino							
Yes, n (%)	1,057 (14.6)	40,793 (11.7)	<0.01	1,057 (14.6)	970 (13.4)	0.05	0.035
No, n (%)	4,602 (63.4)	148,831 (42.8)	<0.01	4,597 (63.4)	4,571 (63)	0.65	0.007
Race							
White, n (%)	4,588 (63.2)	181,737 (52.2)	<0.01	4,585 (63.2)	4,566 (63)	0.74	0.005
Black or African American, n (%)	1,488 (20.5)	50,942 (14.6)	<0.01	1,487 (20.5)	1,570 (21.7)	0.09	0.028
Unknown, n (%)	963 (13.3)	103,697 (29.8)	<0.01	962 (13.3)	913 (12.6)	0.23	0.020
Essential (primary) hypertension, n (%)	3,606 (49.7)	34,330 (9.9)	<0.01	3,601 (49.7)	3,675 (50.7)	0.22	0.020
Chronic lower respiratory diseases, n (%)	1,928 (26.6)	17,583 (5.1)	<0.01	1,923 (26.5)	1,923 (26.5)	0.95	0.010
Diabetes mellitus, n (%)	1,989 (27.4)	15,991 (4.6)	<0.01	1,984 (27.4)	1,924 (26.5)	0.26	0.019
Overweight and obesity, n (%)	2,335 (32.2)	19,108 (5.5)	<0.01	2,330 (32.1)	2,302 (31.7)	0.62	0.008
Ischemic heart diseases, n (%)	1,132 (15.6)	6,472 (1.9)	<0.01	1,127 (15.5)	965 (13.3)	<0.01	0.064
Heart failure, n (%)	848 (11.7)	3,495 (1.0)	<0.01	843 (11.6)	641 (8.8)	<0.01	0.092
Nicotine dependence, n (%)	335 (4.6)	2,762 (0.8)	<0.01	334 (4.6)	357 (4.9)	0.37	0.010
Alcohol related disorders, n (%)	991 (13.7)	8,274 (2.4)	<0.01	986 (13.6)	985 (13.6)	0.98	0.015

There was a greater proportion of males and patients with an unidentified race found in the non-LTOT cohort. Patients in the LTOT cohort consistently had more prevalent comorbidities than their non-LTOT counterpart. Differences in these baseline characteristics were statistically significant between the two cohorts. After propensity score matching, most of these differences became not significant, suggesting the demographic characteristics and comorbid conditions were well-balanced between the LTOT and non-LTOT cohorts. Moreover, absolute standardized differences for all measured baseline characteristics were less than 10%. It further supported that both cohorts had very similar distributions of the observed baseline characteristics and matched samples (23).

Healthcare utilization

In the overall population, COVID-19 patients on LTOT were 3 times ($p<0.01$) more likely to have ED visits and 4.8 times ($p<0.01$) more likely to be hospitalized than individuals without LTOT (see Figure 1). LTOT patients also showed greater likelihoods of receiving intensive care (RR=6.8, $p<0.01$), mechanical ventilation (RR=6.31, $p<0.01$), and vasopressors (RR=10.2, $p<0.01$), compared to their non-LTOT counterparts. After propensity score matching, the adjusted risks of utilizing urgent care resources and extensive life support for LTOT patients were 1.6-5.8 times ($p<0.01$) greater than for non-LTOT patients. The 30-day post-diagnosis mortality rates were found consistently higher in the LTOT cohort, regardless of the PSM adjustment (RR=2.97, $p<0.01$ before PSM; RR=1.74, $p<0.01$ after PSM). Data from before and after propensity score matching can be found in supplemental table 1.

Clinical presentation

In pre-matching analysis, LTOT patients were reported three-fold ($p<0.01$) more likely to have fever and cough than their non-LTOT counterpart (Figure 2). The LTOT cohort also

showed greater risks of developing ARDS (RR=7.05, p<0.01), hypoxemia (RR=6.09, p<0.01), dyspnea (RR=4.56, p<0.01), and thrombocytopenia (RR=7.39, p<0.01). In the post PSM analyses, LTOT patients was consistently found more severe medical complications, compared to non-LTOT patients. The adjusted risk ratios ranged from 1.91 for cough and fever, 1.99 for dyspnea, 2.12 for thrombocytopenia, 2.52 for hypoxemia, to 4.53 for ARDS. All differences were statistically significant at the 0.01 level. Data from before and after propensity score matching can be found in supplemental table 2.

Laboratory tests

Mixed results were found in vital and laboratory tests commonly ordered to assess the severity of COVID-19 in the pre- and post-matching analyses (Table 2). Higher systolic blood pressure (127.1 vs 124.9, p<0.01) was observed among LTOT patients before PSM, while LTOT patients consistently showed lower systolic and diastolic blood pressure than non-LTOT patients after matching (127.1 vs 128.2, p<0.01 for systolic BP; 75.1 vs 75.8, p<0.01 for diastolic BP).

Table 2. Laboratory test results among COVID-19 patients with LTOT compared to COVID-19 Patients without LTOT

	Before Propensity Score Matching			After Propensity Score Matching		
Type	Long-term Opioid Therapy mean±SD (n)	No Long-term Opioid Therapy mean±SD (n)	p-value	Long-term Opioid Therapy mean±SD (n)	No Long-term Opioid Therapy mean±SD (n)	p-value
Systolic blood pressure	127.11±19.91 (4,442)	124.9±18.61 (92,131)	<0.01	127.11±19.91 (4,439)	128.24±18.81 (3,389)	0.01
Diastolic blood pressure	75.11±12.77 (4,648)	74.85±12.18 (93,677)	0.15	75.12±12.77 (4,645)	75.83±12.12 (3,431)	0.01
Leukocytes	8.06±4.77 (4,336)	8.09±31.63 (70,827)	0.95	8.06±4.77 (4,332)	7.65±3.31 (2,482)	<0.01
Lymphocytes	23.55±12.06 (3,421)	25.17±11.77 (62,295)	<0.01	23.55±12.06 (3,417)	24.93±11.43 (2,143)	<0.01
Neutrophils	244.85±1161.63 (2719)	263.25±1200.96 (42918)	0.44	245.29±1162.66 (2714)	228.57±1112.11 (1859)	0.63
Platelets	263.2±98.31 (4363)	263.7±91.51 (70562)	0.73	263.2±98.35 (4358)	257.01±85 (2527)	<0.01
Serum creatinine	1.28±3.4 (4469)	1.02±2.23 (69545)	<0.01	1.28±3.4 (4464)	1.18±3.05 (2844)	0.19
Blood urea nitrogen	18.58±14.33 (3608)	17.09±12.99 (54324)	<0.01	18.58±14.33 (3603)	18.11±13.56 (2501)	0.20
Lactate dehydrogenase	409.48±788.76 (1041)	377.74±517.6 (14802)	0.07	408.51±788.51 (1040)	405.93±552.87 (444)	0.95
Alanine aminotransferase	39.1±208.05 (3866)	43.01±160.16 (58154)	0.15	39.13±208.18 (3861)	30.47±42.52 (2366)	0.05
Aspartate aminotransferase	56.16±736.62 (3859)	44.18±390.27 (56702)	0.09	56.2±737.1 (3854)	31.16±114.74 (2309)	0.11

Alkaline phosphatase	95.42±64.24 (3782)	80.69±50.54 (55580)	<0.01	95.36±64.16 (3777)	85.58±52.22 (2306)	<0.01
Serum ferritin	547.04±1076.62 (1464)	769.47±2694.05 (18833)	<0.01	547.7±1077.2 (1462)	634.17±1642.94 (716)	0.14
Troponin I	0.38±3.69 (690)	0.55±6.87 (5506)	0.53	0.38±3.7 (687)	0.83±9.59 (198)	0.32
C-reactive protein	44.31±65.45 (1670)	37.2±57.57 (22008)	<0.01	44.24±65.45 (1668)	37.19±58.33 (700)	0.01

Measurement unit: leukocytes in 1000/microliter; platelets in number/volume; serum creatinine in mg/dL; C-reactive protein (CRP) in mg/L; lymphocytes, neutrophils in cells/μL; blood urea nitrogen (BUN) in mg/dL; serum ferritin, troponin I in ng/mL; lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) in units/liter

The pre-matching analysis reported that LTOT patients had a 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) and a lower concentration of serum ferritin (547.0 vs 769.5, p<0.01), but differences in these lab results were not significantly different between the two cohorts in the post-matching analysis. Despite no difference found in leukocytes and platelets before PSM, substantial elevation in leukocytes (8.1 vs 7.7, p<0.01) and platelets (263.2 vs 257.0, p<0.01) were observed in LTOT patients after PSM. Moreover, in both the pre- and post-matching analyses, LTOT patients showed lower lymphocyte counts (23.6 vs 25.2, p<0.01 before PSM; 23.6 vs 2.9, p<0.01 after PSM), while they had a greater level of alkaline phosphatase concentration than their non-LTOT counterparts (95.4 vs 90.7, p<0.01 before PSM; 95.4 vs 85.6, p<0.01 after PSM).

DISCUSSION

The COVID-19 pandemic has presented persistent public health challenges, particularly among populations with a history of substance use and mental health conditions. Amidst the pandemic, the crisis of the opioid epidemic has continued to rise and strain healthcare resources, society productivity and general well-being. While the literature has identified the pernicious effects of COVID-19 on many clinical findings and laboratory tests, there has been little knowledge about the outcomes and presentation of COVID-19 among patients on long-term opioid therapy. Given the magnitude of both crises, lack of understanding of the relationship

between COVID-19 and opioid use represents a gap that can disadvantage clinicians when considering prevention and early treatment among individuals in this population.

This study revealed that COVID-19 patients with a history of long-term opioid therapy were more likely to be admitted to the hospital, emergency department, and intensive care unit, and have higher 30-day mortality rates. Additionally, there was greater use of both vasopressors and mechanical ventilation, suggesting that long-term opioid users are more likely to get severely ill from COVID-19**.** This aligns with the existing literature that found the need for respiratory support in the ICU among COVID-19 patients struggling with hypoxemia (24). Previous studies have also shown more hospitalizations, ICU admissions, and death among COVID-19 patients with any form of substance use disorder, with particularly strong associations among patients with opioid use disorders (25, 26, 27**).** The cohort of patients on long term opioid therapy in this study had increased risk of severe symptoms such as cough, fever, hypoxemia, dyspnea, thrombocytopenia, and acute respiratory distress syndrome (ARDS). There is significant overlap between the ways in which the pathophysiology of COVID-19 and the interactions of opioids with their mu-receptors mediate both respiratory damage and immunosuppression (10, 24, 28). As such, opioids decrease cytokine and leukocyte recruitment, compromising the innate and adaptive immune pathways, making individuals more susceptible to infection at the same time as opioid-induced respiratory depression amplifies hypoxemia in COVID-19 (8, 15). While there is conflicting literature on the direct effects of opioids on cardiovascular events such as myocardial infarction, some research has demonstrated how cardiorespiratory co-morbidities play a role in the increased risk of severe outcomes among COVID-19 patients on long term opioid therapy (27, 29).

Several studies have examined the prognostic value of various laboratory tests in the setting of severe COVID-19. Our analysis showed that both systolic and diastolic blood pressure was lower among patients on opioid therapy, though this difference was not clinically significant between the two groups. There were significant differences in leukocytes, lymphocytes, platelets, ALT, alkaline phosphatase, and C-reactive protein in our results after propensity score matching. Previous studies have shown that COVID-19 patients have demonstrated some degree of lymphopenia with or without leukopenia, alterations in neutrophil to lymphocyte ratios, mild decreases in platelets, and elevations in inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate (10, 30). In patients on prescription opioids, research has documented some elevations in C-reactive protein and altered platelet, lymphocyte, and monocyte ratios (31, 32). Elevations in kidney, liver, and other systemic organ lab results may indicate the effects of COVID-19 on causing multi-system organ damage or failure (10, 27).

In summary, COVID -19 patients with a history of long term opioid therapy were more likely to experience respiratory distress, inflammation, and clinical symptoms of a weakening immune response. In addition, they often required higher rates of hospitalization, admission to intensive care units, and use of clinical support measures such as mechanical ventilation. These results suggest that there is a possible increased burden on the healthcare system, with regards to cost and utilization of services, for long term opioid therapy patients without effective prevention or when appropriate treatment is not initiated early in the course of disease. It is important for clinicians to recognize these risks within this patient population as they deal with the ongoing challenges of care in the context of COVID-19.

Limitations

This study has several limitations to note and consider. First, there is a possibility that patients with long term opioid therapy captured in the research network received their COVID-19 diagnosis or testing at facilities outside of the participating networks, and therefore would not have been included in the analysis. We chose to operationalize long-term opioid therapy as mentioned in the Methods section, but there is a possibility that patients with a history of chronic opioid use do not meet this specific definition and therefore were not included. There are several socioeconomic factors that are not available in the database, such as type of insurance, education, and urban or rural residence that could act as confounders in the statistical analysis. However, the propensity score matching was able to construct comparable cohorts in order to best determine the effects of long term opioid therapy on the selected outcomes.

CONCLUSION

The COVID-19 pandemic has created challenges and barriers preventing people from accessing addiction treatments. This study using a national research database demonstrates that COVID-19 patients on long-term opioid therapy are at higher risk of serious ill, hospitalization, and intensive care due to prolonged inflammation, acute respiratory distress, and ineffective immune responses. Efforts to decrease SARS-CoV-2 infection rates in persons on long-term opioid therapy through personal behavior and vaccination are critical to decrease morbidity given these patients' increased risk of cough, fever, ARDS, hypoxemia, dyspnea, and thrombocytopenia on presentation. While prospective studies are needed to confirm and further refine these results, clinicians would be prudent to persistently engage their long-term opioid patients to optimize their compliance with COVID-19 protective behaviors, including vaccination.

Contributors

All authors were involved in revisions, read and approved the final manuscript. WJT contributed to the planning and design of the work, literature review, data analysis, interpretation, and writing the manuscript. HS contributed to literature review, data analysis, interpretation, and writing the manuscript.

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Competing interests

None declared.

Ethic approval

All the data queries were performed in the TriNetX online portal managed by the Penn State Clinic and Translational Science Institute. Because there was no protected health information data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of the study.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

No data are available.

Figure 1. Healthcare utilization among COVID-19 patients with LTOT compared to COVID-19 Patients without LTOT

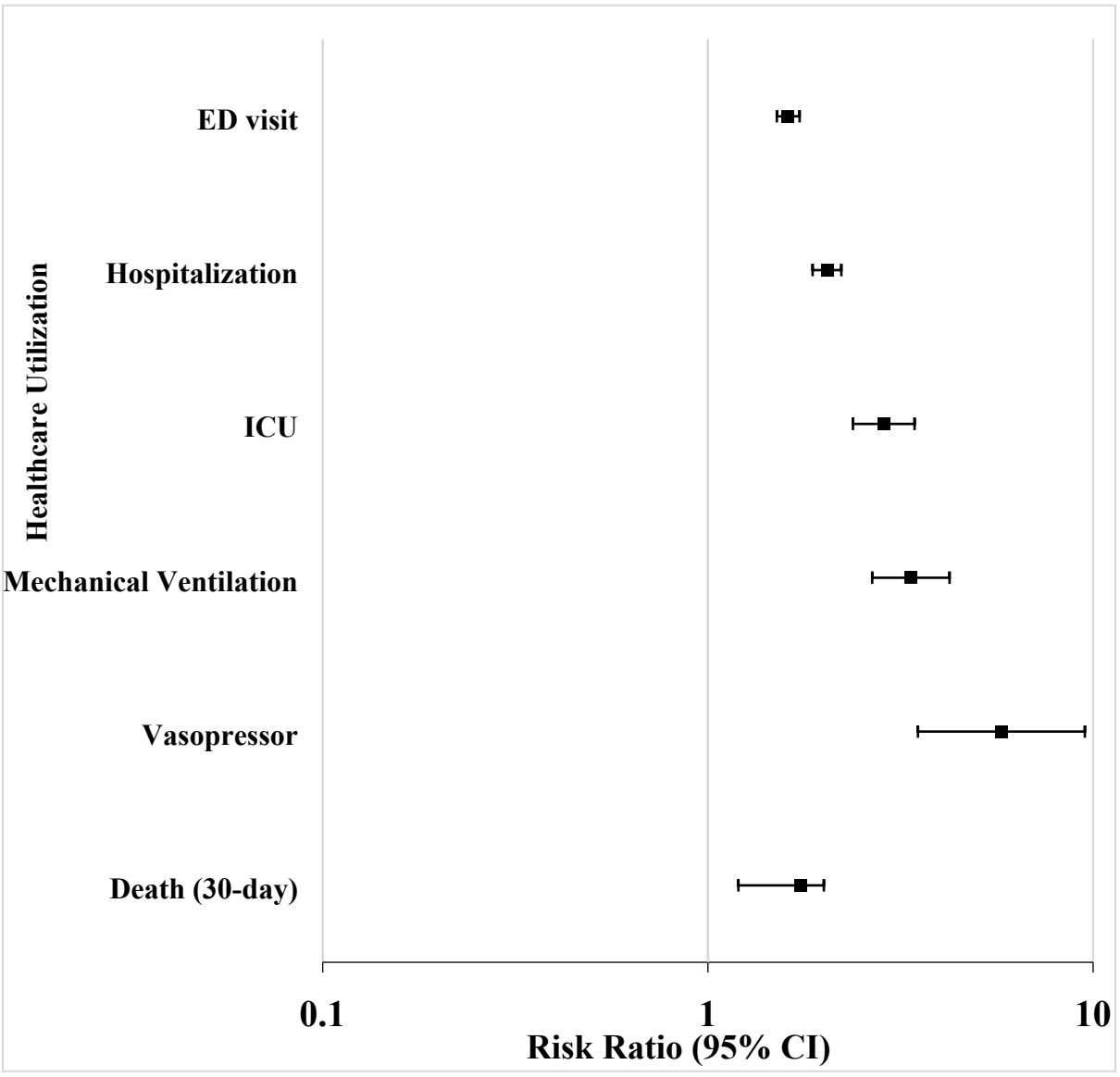
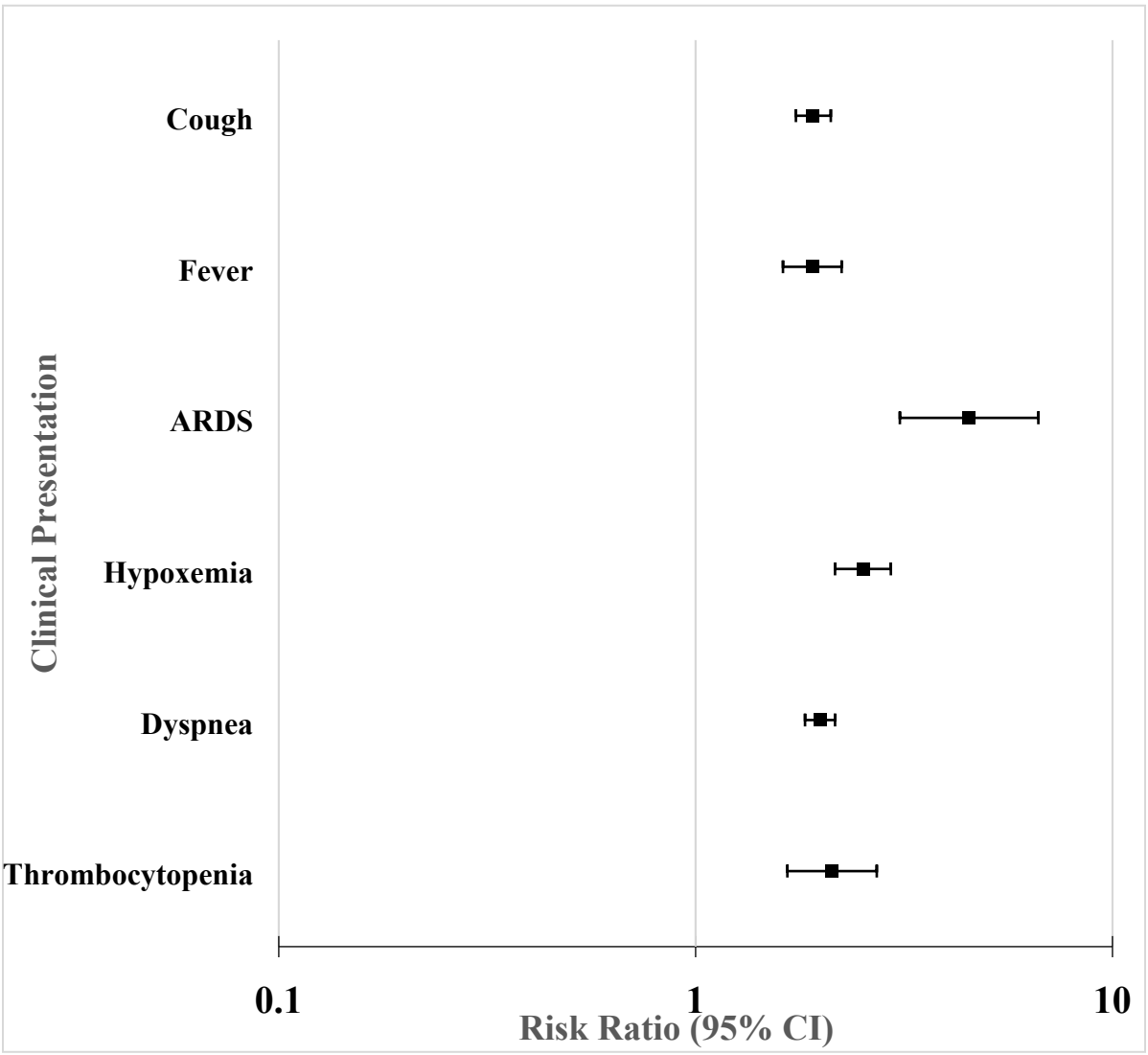


Figure 2. Clinical presentation among COVID-19 patients with LTOT compared to COVID-19 Patients without LTOT



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Supplemental tables

Supplemental Table 1. Healthcare utilization among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

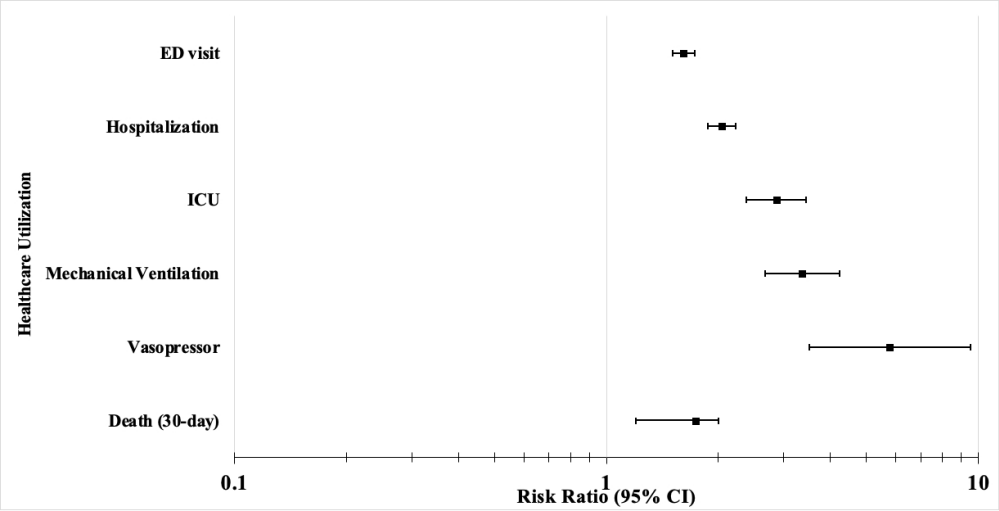
	Before Propensity Score Matching			After Propensity Score Matching		
Utilization	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=350,908), n (%)	Risk Ratio (95% CI)	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=7,256), n (%)	Risk Ratio (95% CI)
ED visit	1,797 (24.77)	28,378 (8.15)	3.04 (2.91,3.17)	1,794 (24.74)	1,112 (15.34)	1.61 (1.51,1.73)
Hospitalization	1,362 (18.77)	13,658 (3.92)	4.78 (4.55,5.03)	1359 (18.74)	667 (9.2)	2.04 (1.87,2.22)
ICU	424 (5.84)	2,975 (0.85)	6.84 (6.19,7.55)	423 (5.83)	148 (2.04)	2.86 (2.38,3.44)
Mechanical Vent	308 (4.24)	2,341 (0.67)	6.31 (5.62,7.09)	306 (4.22)	91 (1.25)	3.36 (2.67,4.24)
Vasopressor	104 (1.43)	488 (0.14)	10.22 (8.28,12.62)	104 (1.43)	18 (0.25)	5.78 (3.51,9.52)
Death (30-day)	257 (3.51)	4,112 (1.18)	2.97 (2.64, 3.38)	257 (3.51)	149 (2.06)	1.74 (1.58, 2.14)

N: total number of patients in the cohort; n: number of patients with the health outcome; 95% CI: 95% confidence intervals

Supplemental Table 2. Clinical presentation among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

	Before Propensity Score Matching			After Propensity Score Matching		
Clinical Presentation	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=350,908), n (%)	Risk Ratio (95% CI)	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=7,256), n (%)	Risk Ratio (95% CI)
Cough	1,083 (14.93)	13,940 (4)	3.73 (3.52,3.95)	1,080 (14.89)	564 (7.78)	1.91 (1.74,2.11)
Fever	415 (5.72)	5,324 (1.53)	3.74 (3.39,4.12)	414 (5.71)	217 (2.99)	1.91 (1.62,2.24)
ARDS	146 (2.01)	994 (0.29)	7.05 (5.93,8.37)	145 (2)	32 (0.44)	4.53 (3.09,6.64)
Hypoxemia	539 (7.43)	4,244 (1.22)	6.09 (5.59,6.64)	537 (7.41)	213 (2.94)	2.52 (2.16,2.94)
Dyspnea	1,435 (19.78)	15,109 (4.34)	4.56 (4.34,4.78)	1,431 (19.74)	720 (9.93)	1.99 (1.83,2.16)
Thrombocytopenia	194 (2.67)	1,260 (0.36)	7.39 (6.36,8.58)	193 (2.66)	91 (1.25)	2.12 (1.66,2.72)

N: total number of patients in the cohort; n: number of patients with the health outcome; 95% CI: 95% confidence intervals



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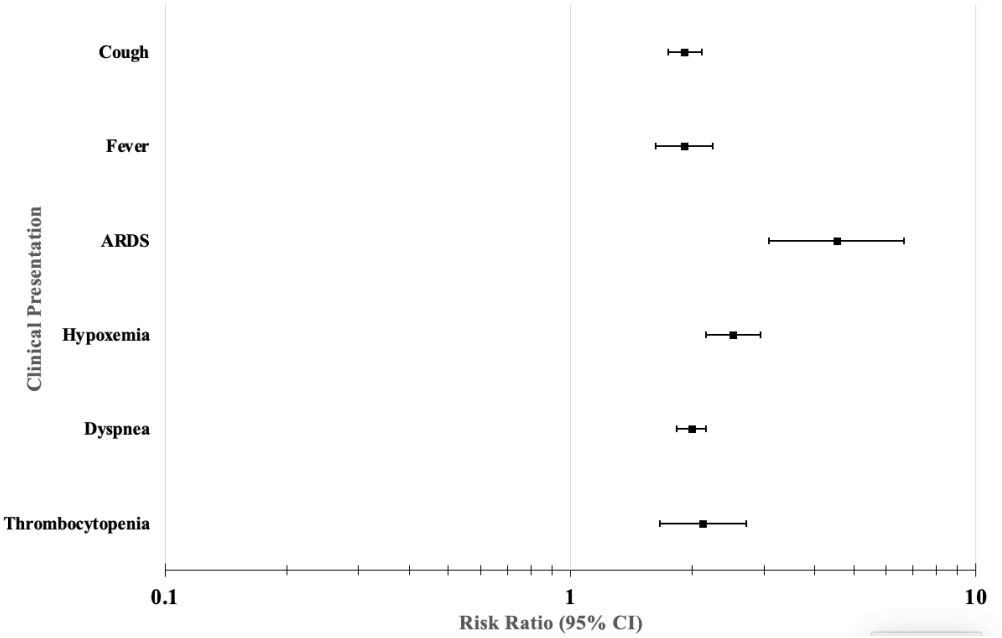

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Supplemental tables

Supplemental Table 1.
Healthcare utilization among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

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Clinical presentation among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

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Clinical Presentation	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=350,908), n (%)	Risk Ratio (95% CI)	Long-term Opioid Therapy (N=7,256), n (%)	No Long-term Opioid Therapy (N=7,256), n (%)	Risk Ratio (95% CI)
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N: total number of patients in the cohort; n: number of patients with the health outcome; 95% CI: 95% confidence intervals

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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

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Title

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

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ABSTRACT

Objective

Patients treated with long-term opioid therapy (LTOT) are known to have compromised immune systems and respiratory function, both of which make them particularly susceptible to the SARS-CoV-2 virus. The objective of this study was to assess the risk of developing severe clinical outcomes among COVID-19 non-cancer patients on LTOT, compared to those without LTOT.

Design and data sources

A retrospective cohort design using electronic health records in the TriNetX research database.

Participants and setting

418,216 adults diagnosed with COVID-19 in January-December 2020 from 51 U.S. healthcare organizations: 9,558 in the LTOT and 408,658 in the control cohort. They did not have cancer diagnoses; only a small proportion might have been treated with opioid maintenance for opioid use disorder.

Results

Patient on LTOT had a higher risk ratio (RR) than control patients to visit an emergency department (RR=2.04, 95% Confidence Interval (CI) 1.93 to 2.16) and be hospitalized (RR=2.91, 95% CI 2.69 to 3.15). Once admitted, LTOT patients were more likely to require intensive care (RR=3.65, 95% CI 3.10 to 4.29), mechanical ventilation (RR=3.47, 95% CI 2.89 to 4.15), and vasopressor support (RR=5.28, 95% CI 3.70 to 7.53), and die within 30 days (RR=1.96, 95% CI 1.67 to 2.30). The LTOT group also showed increased risk (RRs from 2.06 to 3.98, all significant to 95% confidence) of more-severe infection (e.g., cough, dyspnea, fever, hypoxemia, thrombocytopenia, and acute respiratory distress syndrome). Statistically significant differences in several laboratory results and other vital signs appeared clinically negligible.

Conclusion

COVID-19 patients on LTOT were at higher risk of increased morbidity, mortality, and healthcare utilization. Interventions to reduce the need for LTOT and to increase compliance with COVID-19 protective measures may improve outcomes and reduce healthcare cost in this population. Prospective studies need to confirm and refine these findings.

Strengths and Limitations of this Study

- This study utilized large-scale electronic health record (EHR)-based data and propensity score matching to assess the risk of morbidity and mortality from SARS-CoV-2 infection among U.S. adults treated with long-term opioids for chronic non-cancer pain.
- The study findings can help shape the conversations between clinicians, public health personnel, and patients on optimal prevention and early treatment protocols for safer and more effective long-term opioid therapy.
- As a retrospective cohort study, the analysis may be missing data from patients tested or treated for COVID-19 infection outside the research data network, potentially skewing results.
- The study did not assess associations between the dosage of prescribed opioids and the outcomes in patients with COVID-19 illness.

INTRODUCTION

The COVID-19 pandemic, resulting from SARS-CoV-2 infection, has rapidly spread across the United States since early 2020. By the end of 2020, there were over 20 million confirmed cases and 344,000 deaths reported in the U.S.[1] This unprecedented upheaval has led to deaths from the novel coronavirus, in addition to deaths caused by the effects of protracted economic stagnation and social disruption. Vulnerable populations with mental illness or substance use disorders have been disproportionately affected.[2,3] As the nation focuses on the COVID-19 pandemic, the opioid crisis has continued to have devastating impacts on communities. Recent statistics show a 38.4% increase in opioid-related deaths from June 2019 to May 2020,[4] and state-level data have linked stressors of the COVID-19 pandemic to surge in fatal overdoses.[5] Literature suggests the opioid crisis has been escalated by a lack of access to drug screening and treatment for opioid use disorder (OUD) due to care disruption by the COVID-19 pandemic.[6] Ongoing opioid addiction prevention efforts have also been disrupted by social distancing practices and isolation that can contribute to the misuse of prescription or illicit opioids.[3,7] However, studies focused on the opioid crisis in the United States often look only at persons with substance abuse disorders, who have numerous comorbidities with independent COVID-19 risk; little is known about the impact of COVID-19 on people on long-term opioid therapy (LTOT) who do not have such disorders, but may be at increased COVID-19 risk by virtue of their LTOT alone.

Research shows that opioids can trigger acute respiratory depression (e.g., hypoventilation and hypoxemia) through the activation of opioid receptors in the brainstem can lead to respiratory failure or death.[8] Chronic opioid use also increases the risk of immunosuppression and infections, including among people on LTOT.[9] These individuals are

likely to have cardiopulmonary morbidity, longer hospitalization, and greater overall care costs. With severe COVID-19 infection, patients may also present with clinical signs and symptoms of respiratory depression.[10,11] Approximately 10-15% of patients hospitalized for COVID-19 progressed to acute respiratory distress syndrome.[12, 13] While the risk of increasing morbidity and mortality from SARS-CoV-2 infection among individuals with certain health conditions has been identified and incorporated into outcome prediction models, the relationship between LTOT and SARS-CoV-2-related morbidity and mortality has not been assessed.[14] The likelihood of worsened outcomes in patients on LTOT and with COVID-19 may be caused by the mechanisms of respiratory depression and immunosuppression.[15] As a result, this patient population may be expected to have more severe health outcomes, potentially resulting in an increased risk of hospitalization, emergency department admissions, and time in the intensive care unit.[16,17] Critically ill patients with SARS-CoV-2 were also more likely to be treated with mechanical ventilation and vasopressors.[18,19] Although COVID-19 outcomes are known to be worse in persons with opioid and other substance use disorders,[20] such disorders may be clinically under- diagnosed. Further, the vast majority of persons prescribed opioids for chronic pain do not have substance use disorders,[21] yet may still be at risk from their LTOT alone. Hence, research is urgently needed to investigate long-term opioid use in populations beyond those with substance use disorders as a pathway to severe COVID-19.

This study aims to assess the risk of developing severe outcomes among adults with LTOT for chronic non-cancer pain and with COVID-19 infection in the U.S. in order to help clinicians develop more effective care guidelines for patients with COVID-19 and raise awareness about the risks of COVID-19 to vulnerable populations.

METHODS

Study design and data collection

The study applied a retrospective cohort design using electronic health records (EHRs) from 51 healthcare organizations, members of the research network of the TriNetX database in the United States (Cambridge, MA). TriNetX is a federated health research network that provides access to continuously updated, de-identified EHR data (demographics, diagnoses, procedures, medications, laboratory tests, and genomics) of more than 68 million patients from participating healthcare organizations. The TriNetX platform only uses aggregated counts and statistical summaries. All the data queries were performed in the TriNetX online portal managed by the Penn State Clinical and Translational Science Institute. Because there was no protected health information data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight.

Cohort description

The study population consisted of adults (age≥18 years) a diagnosis of COVID-19 between January 1, 2020 and December 31, 2020, based on the combination of one or more disease indicators, including ICD-10 diagnosis codes or positive laboratory test results. Individuals are considered on long-term opioid therapy (LTOT) when they are prescribed with opioids in 3 or more consecutive months or at least 90 days at outpatient settings.[22,23] COVID-19 patients meeting the LTOT criteria within 12 months before their infection were assigned to the LTOT cohort. Individuals with COVID-19 without LTOT in the past 12 months were assigned to the control cohort. The analysis excluded individuals who had cancers, or living in nursing home, hospice or palliative care facilities.

Moreover, this study included various types of opioid analgesics prescribed in outpatient settings, and targeted the population of adults with chronic non-cancer pain. We excluded patients who had cancer diagnoses to limit the impact of opioids prescribed for cancer pain. Although methadone and buprenorphine can be used to treat OUD in addition to chronic pain, methadone prescriptions issued in the outpatient settings are exclusively for pain care; only specialized opioid treatment programs (OTPs) can use methadone for OUD care by dispensing it, thus, this clinical application would not have been captured in our dataset. Buprenorphine can be prescribed for OUD in the outpatient settings for both chronic pain and OUD indications; the research dataset did not allow us to determine the specific indication; we elected to retain those treated with buprenorphine because buprenorphine could have been prescribed to treat chronic pain. In addition, only a small proportion of the study sample was treated with buprenorphine (5.0%), with even smaller proportion (1.6%) having both the OUD diagnosis and being prescribed buprenorphine during the study period.

Outcome indicators

The severity of the COVID-19 infection was assessed through three areas: healthcare utilization, clinical presentation, and diagnostic testing. The healthcare utilization and mortality measures included binary variables (Yes/No) indicating whether patients were admitted to emergency department (ED), inpatient hospital, intensive care unit, placed on mechanical ventilation, treated with vasopressors, or died within 30 days after being infected by COVID-19. Similarly, the clinical presentation measures also indicated the presence/absence (Yes/No) of severe physical signs or medical complication, including cough, fever, acute respiratory distress syndrome (ARDS), hypoxemia, thrombocytopenia, and dyspnea. The diagnostic testing consisted of common biometrics or laboratory tests serving as severity indicators of COVID-19

infection, such as C-reactive protein, serum creatinine, and blood urea nitrogen. These tests have also been used to predict the risk of increased COVID-19-related morbidity and mortality in both inpatient and outpatient settings.[14,24]

Data Analysis

Data in the TriNetX database have been shown referential integrity and be reliable.[25] The coding information of the research data also underwent extensive curation and was mapped to common clinical terminologies to ensure high usability and consistency with the Reporting of studies Conducted using Observational Routinely collected Data (RECORD) guidelines criteria.[26] A number of patient characteristics were considered potential confounding variables, including age, sex, race/ethnicity, and comorbidities (diabetes, essential hypertension, chronic pulmonary conditions, cardiovascular diseases, chronic kidney diseases, mental health disorders). To address potential confounding effects of the socioeconomic status, we included diagnoses, which may indicate increased risk due to socioeconomic and psychosocial circumstances (education and literacy, employment, housing, lack of adequate food or water, or exposure to occupational hazards). The study applied a 1:1 propensity score matching (PSM) technique to balance the baseline characteristics between the comparison and control cohorts, and reduce potential selection bias. The matching method was performed using nearest neighbor algorithms with a caliper width of 0.1 pooled standard deviation. Outcomes were compared in COVID-19 patients on LTOT and COVID-19 patients not on LTOT using logistic regression modeling before and after propensity score matching. Risk ratios (RR), with 95% confidence intervals (95% CI) were computed and a two-sided alpha of less than 0.05 was defined *a priori* for statistical significance between the two groups. All data queries and statistical analyses

were performed using build-in analytics functions on the TriNetX portal. Detailed information for the diagnoses and laboratory tests are provided in supplemental table 1.

Patients and public involvement statement

Neither patients nor the public were involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Study population

A total of 418,216 patients diagnosed with COVID-19 from 51 healthcare organizations met the study eligibility criteria, including 9,558 individuals in the LTOT cohort and 408,658 in the non-LTOT cohort. Before propensity score matching, the LTOT cohort was older, with a greater percentage of female, White and Black patients compared to the control cohort (see table 1).

Table 1. Patient demographics and comorbidities, before and after propensity score matching

	Before propensity score matching			After propensity score matching			
Characteristic	Long-term opioid therapy (N=9,558)	No long-term opioid therapy (N=408,658)	P value	Long-term opioid therapy (N=9,558)	No long-term opioid therapy (N=9,558)	P value	Standardized mean difference
Age, mean ± SD	52.1±17.1	43.1±17.6	<0.001	52.1±17.1	52.7±17.7	0.063	0.033
Sex							
Female, n (%)	5,793 (60.6)	208,267 (51)	<0.001	5,793 (60.6)	5,743 (60.1)	0.460	0.011
Male, n (%)	3,764 (39.4)	199,947 (48.9)	<0.001	3,764 (39.4)	3,804 (39.8)	0.554	0.009
Hispanic or Latino							
Yes, n (%)	1,384 (14.5)	50,634 (12.4)	<0.001	1,384 (14.5)	1,320 (13.8)	0.184	0.019
No, n (%)	6,017 (63)	178,818 (43.8)	<0.001	6,017 (63)	5,995 (62.7)	0.742	0.005
Race							
White, n (%)	5,969 (62.5)	212,907 (52.1)	<0.001	5,969 (62.5)	6,045 (63.2)	0.255	0.016
Black or African American, n (%)	2,200 (23)	62,396 (15.3)	<0.001	2,200 (23)	2,234 (23.4)	0.560	0.008
Unknown, n (%)	1,128 (11.8)	120,420 (29.5)	<0.001	1,128 (11.8)	1,029 (10.8)	0.094	0.033
Essential (primary) hypertension, n (%)	4,816 (50.4)	39,656 (9.7)	<0.001	4,816 (50.4)	4,983 (52.1)	0.166	0.035
Chronic lower respiratory diseases, n (%)	2,425 (25.4)	19,849 (4.9)	<0.001	2,425 (25.4)	2,561 (26.8)	0.250	0.032

Diabetes mellitus, n (%)	2,682 (28.1)	18,589 (4.5)	<0.001	2,682 (28.1)	2,639 (27.6)	0.488	0.010
Overweight and obesity, n (%)	3,089 (32.3)	23,383 (5.7)	<0.001	3,089 (32.3)	3,171 (33.2)	0.206	0.018
Ischemic heart diseases, n (%)	1,575 (16.5)	7,336 (1.8)	<0.001	1,575 (16.5)	1,422 (14.9)	<0.020	0.044
Heart failure, n (%)	1,176 (12.3)	3,865 (0.9)	<0.001	1,176 (12.3)	925 (9.7)	<0.010	0.084
Chronic kidney disease, n (%)	1,448 (15.2)	5,123 (1.3)	<0.001	1,448 (15.2)	1,294 (13.5)	<0.010	0.046
Nicotine dependence, n (%)	1,232 (12.9)	8,937 (2.2)	<0.001	1,232 (12.9)	1,248 (13.1)	0.73	0.005
Alcohol related disorders, n (%)	430 (4.5)	2,848 (0.7)	<0.001	430 (4.5)	426 (4.5)	0.889	0.002
Socioeconomic circumstances, n (%)	469 (4.9)	2,772 (0.7)	<0.001	469 (4.9)	464 (4.9)	0.867	0.002

n, Number of patients; SD, Standard deviation

The LTOT cohort had a greater proportion of males and patients with an unidentified race, and consistently higher prevalence of comorbidities than their non-LTOT counterparts. After propensity score matching, most of these differences became not significant, suggesting the demographic characteristics and comorbid conditions were well-balanced between the LTOT and non-LTOT cohorts. Moreover, absolute standardized differences for all measured baseline characteristics were less than 10%, further confirming that both cohorts had similar distributions of the observed baseline characteristics and matched samples.[27]

Healthcare utilization and mortality

Before the propensity score matching, COVID-19 patients on LTOT were more likely to visit ED (RR=3.80; 95% CI 3.67 to 3.92) and be hospitalized (RR=6.62; 95% CI 6.36 to 6.90) than individuals without LTOT. They also were more likely to receive intensive care (RR=9.03; 95% CI 8.33 to 9.80), mechanical ventilation (RR=7.75; 95% CI 7.07 to 8.50), and vasopressors (RR=10.42; 95% CI 8.90 to 12.20), and were more likely to die within 30 days post-COVID-19 diagnosis (RR=4.04; 95% CI 8.90 to 12.20), compared to their non-LTOT counterparts. After PSM, the adjusted risk of utilizing inpatient care resources or extensive life support remained 2.0-5.3 times higher for patients on LTOT compared to the control cohort (all significant to 95% confidence) (see figure 1). The 30-day post-diagnosis mortality rates were also found to be consistently higher in the LTOT cohort, regardless of the PSM adjustment (RR=1.96; 95% CI

1.67 to 2.30)See supplemental table 2 for details of our results before and after propensity score matching .

Clinical presentation

In pre-matching analysis, patients on LTOT were three times more likely (p<0.01) to have fever and/or cough than their non-LTOT counterparts. The LTOT cohort also showed greater risk of ARDS (RR=3.98; 95% CI 2.91 to 5.44), hypoxemia (RR=2.41; 95% CI 2.10 to 2.76), dyspnea (RR=2.18; 95% CI 2.03 to 2.35), and thrombocytopenia (RR=2.28; 95% CI 1.84 to 2.84). In the post PSM analyses, patients on LTOT were consistently found to have more medical complications compared to non-LTOT patients (see figure 2). The adjusted risk ratios (all significant to 95% confidence) were 2.06 for cough, 2.24 for fever, 2.18 for dyspnea, 2.28 for thrombocytopenia, 2.41 for hypoxemia, and 3.98 for ARDS. See supplemental table 3 for details of our results before and after propensity score matching.

Laboratory tests

Mixed results were found in vital and laboratory tests commonly ordered to assess the severity of COVID-19 in the pre- and post-propensity score matching analyses (see table 2). Higher systolic blood pressure (126.9 vs 124.3, p<0.01) was observed among LTOT patients before PSM, while there were no significant differences in lower systolic (126.7 vs 127.6, p=0.09) and diastolic (74.7 vs 75.1, p=0.12) blood pressure values between LTOT and non-LTOT patients after matching.

Table 2. Laboratory test results among COVID-19 patients with LTOT compared to COVID-19 patients without LTOT

	Before propensity score matching			After propensity score matching		
Type	Long-term opioid therapy mean±SD (n)	No long-term opioid therapy mean±SD (n)	P value	Long-term opioid therapy mean±SD (n)	No long-term opioid therapy mean±SD (n)	P value
Systolic blood pressure	126.92±20.88 (6751)	124.32±18.45 (115578)	<0.001	126.92±20.88 (6745)	127.57±18.97 (4591)	0.092
Diastolic blood pressure	74.72±13.3 (6955)	74.5±12.25 (117093)	0.144	74.72±13.29 (6949)	75.1±12.64 (4635)	0.124
Leukocytes	8.08±5.37 (6249)	8.05±29.6 (81865)	0.935	8.08±5.37 (6245)	7.73±3.46 (3214)	<0.001
Lymphocytes	23.52±12.25 (5244)	25.31±11.73 (73104)	<0.001	23.52±12.25 (5238)	24.79±11.3 (2852)	<0.001
Platelets	259.71±99.28 (6373)	263.86±91.06 (82724)	<0.001	259.76±99.29 (6367)	256.82±84.74 (3300)	0.147
Serum creatinine	1.43±4.19 (6511)	1.01±1.99 (82058)	<0.001	1.43±4.19 (6505)	1.19±1.33 (3715)	<0.001
Blood urea nitrogen	19.42±15.94 (5363)	16.89±12.66 (66174)	<0.001	19.4±15.93 (5357)	18.45±12.87 (3267)	0.004
Lactate dehydrogenase	374.05±680.51 (1800)	369.42±503.9 (17146)	0.721	374.17±680.87 (1798)	318.18±177.96 (628)	0.042
Alanine aminotransferase	40.4±194.16 (5764)	42.75±152.74 (67653)	0.275	40.42±194.26 (5758)	31.49±50.56 (2954)	0.014
Aspartate aminotransferase	51.18±447.66 (5755)	42.48±362.99 (67173)	0.087	51.21±447.89 (5749)	42.39±106.06 (2997)	0.231
Alkaline phosphatase	95.62±62.63 (5677)	80.31±48.37 (66328)	<0.011	95.54±62.55 (5671)	84.65±42.9 (3036)	<0.001
Serum ferritin	613.81±1870.26 (2614)	742.76±2742.34 (22438)	0.019	614.02±1870.59 (2613)	545.99±959.78 (1011)	0.271
Troponin I	0.38±3.32 (1338)	0.72±12.59 (6906)	0.332	0.39±3.33 (1334)	0.25±1.21 (299)	0.494
C-reactive protein	46.33±67.13 (2644)	37.53±56.76 (25138)	<0.001	46.32±67.14 (2642)	38.35±56.43 (906)	<0.001

Measurement unit: leukocytes in 1000/microliter; platelets in 1,000/microliter; serum creatinine in mg/dL; C-reactive protein (CRP) in mg/L; lymphocytes, blood urea nitrogen (BUN) in mg/dL; serum ferritin, troponin I in ng/mL; lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) in units/liter

The pre-matching analysis further showed that the LTOT cohort had a lower concentration of serum ferritin (613.8 vs 742.8, p<0.01) and lower platelet count (259.7 vs 263.9, p<0.01), but differences in these lab results were not significantly different between the two cohorts in the post-matching analysis. Despite no difference found in the leukocyte count and alanine aminotransferase concentration before matching, elevation in leukocytes (8.1 vs 7.7, p<0.01) and alanine aminotransferase (40.4 vs 31.5, p<0.01) were observed in the LTOT cohort after the matching, compared to the control cohort. Moreover, in both the pre- and post-matching analyses, patients on LTOT showed lower lymphocyte counts (23.5 vs 25.3, p<0.01 before matching; 23.5 vs 24.8, p<0.01 after matching), yet greater serum concentrations of creatinine, alkaline phosphatase, and C-relative protein than their non-LTOT counterparts (see table 2).

DISCUSSION

The COVID-19 pandemic has presented persistent public health challenges, particularly among populations with a history of substance use and mental health conditions. Amidst the pandemic, the crisis of the opioid epidemic has continued to rise and strain healthcare resources, society productivity and general well-being.[16,17] Yet, while the literature has identified the pernicious effects of COVID-19 on individuals with OUD,[6,20] little is known about the outcomes and presentation of COVID-19 among patients treated with LTOT for chronic non-cancer pain. Given the magnitude of both crises, lack of understanding of the relationship between COVID-19 and LTOT represents a gap, which can disadvantage clinicians when considering prevention and early treatment among individuals in this population.

This study revealed that COVID-19 patients with a history of long-term opioid therapy were more likely to be admitted to the hospital, emergency department, and intensive care unit, and have higher 30-day mortality rates. Additionally, there was greater use of both vasopressors and mechanical ventilation, suggesting that long-term opioid users are more likely to get severely ill from COVID-19**.** This aligns with the existing literature that found the need for respiratory support in the ICU among COVID-19 patients struggling with hypoxemia.[28] Previous studies have shown more hospitalizations, ICU admissions, and death among COVID-19 patients with any form of substance use disorder, with particularly strong associations among patients with OUD.[20,29,30] Our study demonstrates that patients on LTOT, which was primarily for chronic non-cancer pain, are also at increased risk of severe symptoms such as cough, fever, hypoxemia, dyspnea, thrombocytopenia, and acute respiratory distress syndrome. There is significant overlap between the ways in which the pathophysiology of COVID-19 and the interactions of opioids

with their μ-receptors mediate both respiratory damage and immunosuppression.[10,11,31] As such, opioids can contribute to a decrease in cytokine and leukocyte recruitment, compromising the innate and adaptive immune pathways, potentially making individuals more susceptible to infection at the same time as opioid-induced respiratory depression amplifies hypoxemia in COVID-19.[9,15] While there is conflicting literature on the direct effects of opioids on cardiovascular events such as myocardial infarction, some research has demonstrated how cardiorespiratory co-morbidities play a role in the increased risk of severe outcomes among COVID-19 patients with opioid use disorder.[30,32]

Several studies have also examined the prognostic value of various laboratory tests in the setting of severe COVID-19. There were significant differences in leukocytes, lymphocytes, serum creatinine, blood urea nitrogen, alanine aminotransferase, alkaline phosphatase, and C-reactive protein in our results after propensity score matching. Previous studies have shown that COVID-19 patients have demonstrated some degree of lymphopenia with or without leukopenia, alterations in neutrophil to lymphocyte ratios, mild decreases in platelets, and elevations in inflammatory markers such as C-reactive protein and erythrocyte sedimentation rate.[11,33] In patients on prescription opioids, research has documented some elevations in C-reactive protein and altered platelet, lymphocyte, and monocyte ratios.[34, 35] Elevations in kidney, liver, and other systemic organ lab results may indicate the effects of COVID-19 on causing multi-system organ damage or failure.[11,30] However, the absolute difference between groups for each of the laboratory values is small, with doubtful clinical significance.

Limitations

This study has several limitations to note and consider. First, there is a possibility that patients on LTOT captured in the TriNetX research database received their COVID-19 diagnosis

or laboratory testing at facilities outside of the participating networks, and therefore would not have been included in the analysis. Second, although ideally we would have been able to clearly delineate a population of patients with LTOT prescribed for chronic non-cancer pain, it is possible that patients included in our analysis could have had long-term opioids prescribed for cancer pain or for OUD. Our excursion criteria with cancer diagnoses and preliminary analyses used to estimate the proportion of patients with OUD diagnoses in our sample were designed to mitigate these impacts. Third, we were unable to account for the potential impact of opioid dose, because calculation of the daily morphine-equivalent dose was not possible when using the available TriNetX data. We were also limited in our ability to determine the specific timing of opioid use in relation to the COVID-19 infection; the TriNetX data provided the information on opioid prescriptions issued within a specific timeframe but this may not necessarily correspond to real-life use of opioids by patients; future research should implement a design, which could enable of better evaluation of timing/dose of opioids in relation to outcomes of interest. Fourth, there are several important socioeconomic factors that are not available in the research database, such as type of insurance, education, and urban or rural residence that could act as confounders in the statistical analysis. However, a strength of the large sample size available allowed for robust propensity score matching, which enabled us to construct comparable cohorts in order to best determine the LTOT effects on the selected outcomes and minimize the risk of confounders, increasing the generalizability of results. Lastly, there may be unobserved or unknown confounders present that we did not account for in propensity matching. Future analyses utilizing advanced data mining techniques might be able to better identify currently unidentified yet important confounders.

CONCLUSION

This study leveraged EHR data available through a large national research database and suggested that LTOT is associated with increased risk of severe illness and complications, including death, in adults with COVID-19 infection. This is consistent with anticipated worse outcomes secondary to LTOT causing prolonged inflammation, acute respiratory distress, and ineffective immune responses. Efforts to decrease SARS-CoV-2 infection rates in persons on long-term opioid therapy through personal mitigation behaviors (e.g., masking, physical distancing, handwashing) and vaccination are critical to decrease morbidity. Further research, including prospective studies, is needed to confirm and refine these findings. These results suggest that efforts to decrease SARS-CoV-2 infection rates in persons on LTOT (e.g., through personal mitigation behaviors, such as masking, physical distancing, handwashing, and through vaccination) and considering LTOT as a potential prognosticator for worse outcomes could be critical to decrease morbidity and mortality due to COVID-19 infections, particularly in this clinical population..

Contributors

All authors were involved in revisions, read and approved the final manuscript. WJT contributed to the planning and design of the work, literature review, data analysis, interpretation, and writing the manuscript. HS contributed to literature review, data analysis, interpretation, and writing the manuscript. AEZ and RPL contributed to interpretation and writing the manuscript.

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Competing interests

None declared.

Ethics approval

Formal ethnical approval was not required. All the data queries were performed in the TriNetX online portal managed by the Penn State Clinic and Translational Science Institute. Because there was no protected health information data accessed in the analysis, this research was determined to be exempt from the Institutional Review Board oversight.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

No additional data are available.

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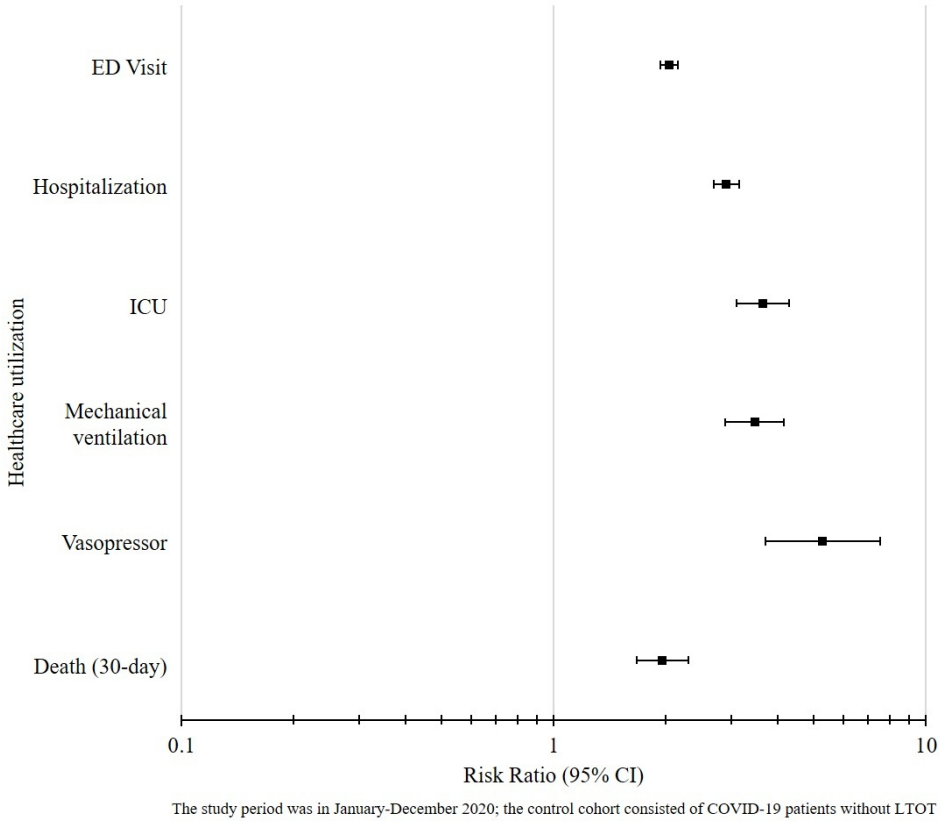

Figure 1. Healthcare utilization among COVID-19 patients with LTOT compared to COVID-19 patients without LTOT

96x81mm (300 x 300 DPI)

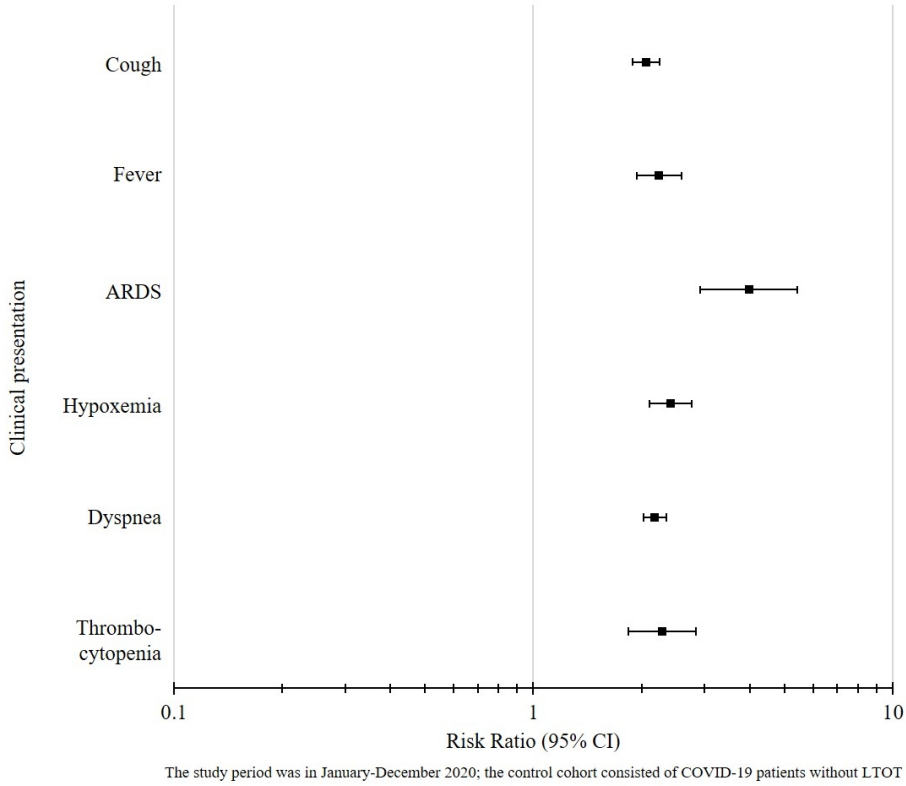

Figure 2. Clinical presentation among COVID-19 patients with LTOT compared to COVID-19 patients without LTOT

100x82mm (300 x 300 DPI)

Supplementary Table 1. Description of coding systems and codes

Coding system	Code	Description
Codes for COVID-19 diagnoses		
ICD-10	U07.1, U07.2	COVID-19 (WHO)
ICD-10	B97.29	Other coronavirus as the cause of diseases classified elsewhere
ICD-10	B34.2	Coronavirus infection, unspecified
ICD-10	J12.81	Pneumonia due to SARS-associated coronavirus
LOINC	94505-5,94506-3,94558-4, 94562-6, 94762-2, 94769-7, 95209-3	SARS-CoV-2 (COVID19) [Presence] in Serum or Plasma by Immunoassay
Comorbidity conditions		
ICD-10	I10	Essential (primary) hypertension
ICD-10	J40-J47	Chronic lower respiratory diseases
ICD-10	E10-E11	Diabetes (type I and type II)
ICD-10	E66	Overweight and obesity
ICD-10	I20-I25	Ischemic health diseases
ICD-10	I50	Heart failure
ICD-10	N18	Chronic kidney disease
ICD-10	F17	Nicotine dependence
ICD-10	F10	Alcohol related disorders
ICD-10	Z55-Z65	Socioeconomic and psychosocial circumstances
Laboratory codes for diagnostic tests		
LOINC	8480-6,76215-3,76534-7,87739-9,87741-5,8459-0,8460-8,8461-6	Systolic blood pressure
LOINC	8462-4,76535-4,87740-7,87736-5,8453-3,8454-1,8455-8,76213-8	Diastolic blood pressure
LOINC	26464-8,49498-9,6690-2,804-5	Leukocytes
LOINC	26478-8,30365-1,736-9,737-7	Lymphocyte count
LOINC	26499-4,751-8,753-4	Neutrophil count
LOINC	26515-7,49497-1,777-3,778-1	Platelets
LOINC	2160-0,38483-4	Serum creatinine
LOINC	3094-0,6299-2	Blood urea nitrogen
LOINC	14804-9,14805-6,2532-0	Lactate dehydrogenase
LOINC	1742-6,1743-4,1744-2,76625-3	Alanine aminotransferase
LOINC	1920-8,30239-8	Aspartate aminotransferase
LOINC	1783-0,6768-6	Alkaline phosphatase
LOINC	20567-4,2276-4,24373-3	Serum ferritin
LOINC	10839-9,42757-5	Troponin I
LOINC	1988-5,30522-7,71426-1	C-reactive protein

Supplementary Table 2. Healthcare utilization among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

	Before propensity score matching			After propensity score matching		
Utilization	Long-term opioid therapy (N=9,558), n (%)	No long-term opioid therapy (N=408,658), n (%)	Risk ratio (95% CI)	Long-term opioid therapy (N=9,558), n (%)	No long-term opioid therapy (N=9,558), n (%)	Risk ratio (95% CI)
ED visit	2,867 (30.0)	32,323 (7.9)	3.80 (3.67,3.92)	2,867 (30.0)	1,404 (14.7)	2.04 (1.93,2.16)
Hospitalization	2,139 (22.4)	13,807 (3.4)	6.62 (6.36,6.90)	2,139 (22.4)	735 (7.7)	2.91 (2.69,3.15)
ICU	664 (7.0)	3,145 (0.8)	9.03 (8.33,9.80)	664 (7.0)	182 (1.9)	3.65 (3.10,4.29)
Mechanical vent	513 (5.4)	2,833 (0.7)	7.75 (7.07,8.50)	513 (5.4)	148 (1.6)	3.47 (2.89,4.15)
Vasopressor	190 (2.0)	779 (0.2)	10.42 (8.9,12.2)	190 (2.0)	36 (0.4)	5.28 (3.70,7.53)
Death (30-day)	425 (4.5)	4,500 (1.1)	4.04 (3.67,4.46)	425 (4.5)	217 (2.3)	1.96 (1.67,2.30)

N: total number of patients in the cohort; n: number of patients with the health outcome; 95% CI: 95% confidence intervals
Mechanical vent: Mechanical ventilation

Supplementary Table 3. Clinical presentation among COVID-19 patients on long-term opioid therapy compared to COVID-19 patients not on long-term opioid therapy

	Before propensity score matching			After propensity score matching		
Clinical Presentation	Long-term opioid therapy (N=9,558), n (%)	No long-term opioid therapy (N=408,658), n (%)	Risk ratio (95% CI)	Long-term opioid therapy (N=9,558), n (%)	No long-term opioid therapy (N=9,558), n (%)	Risk ratio (95% CI)
Cough	1,458 (15.3)	15,350 (3.8)	4.06 (3.87,4.27)	1,458 (15.3)	707 (7.4)	2.06 (1.89,2.25)
Fever	597 (6.2)	5,619 (1.4)	4.54 (4.18,4.93)	597 (6.2)	266 (2.8)	2.24 (1.94,2.58)
ARDS	195 (2.0)	996 (0.2)	8.37 (7.18,9.74)	195 (2.0)	49 (0.5)	3.98 (2.91,5.44)
Hypoxemia	673 (7.0)	4,581 (1.1)	6.28 (5.80,6.79)	673 (7.0)	278 (2.9)	2.41 (2.10,2.76)
Dyspnea	2,043 (21.4)	1,6467 (4.0)	5.31 (5.10,5.54)	2,043 (21.4)	936 (9.8)	2.18 (2.03,2.35)
Thrombocytopenia	265 (2.8)	1,391 (0.3)	8.14 (7.15,9.27)	265 (2.8)	116 (1.2)	2.28 (1.84,2.84)

N: total number of patients in the cohort; n: number of patients with the health outcome; 95% CI: 95% confidence intervals
Mechanical vent: Mechanical ventilation

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found		RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract PP:1, 3 Geographic region: title and abstract Timeframe: abstract PP: 1, 3 Not applicable
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Introduction PP: 6, 7

Objectives	3	State specific objectives, including any pre-specified hypotheses			P: 7
Methods					
Study Design	4	Present key elements of study design early in the paper			P: 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			P: 8
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not	Methods, Cohort Description P: 8 P: 10

		Cross-sectional study - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case		published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.		RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	PP: 9, 10
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of			PP: 9, 10, 11

		assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias			P: 10 (Propensity matching addresses bias from observable covariate differences)
Study size	10	Explain how the study size was arrived at			P: 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why			PP: 9, 10 and Appendix
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss			PP: 10, 11, and Appendix

		to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses			
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P: 8
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data	N/A

				linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram		RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Cohort Description PP: 8, 9
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of			PP: 8, 9

		participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)			
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			Outcome indicators PP: 8, 9
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted			Results PP: 11-14 Supplemental Table 1

		for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses			N/A
Discussion					
Key results	18	Summarise key results with reference to study objectives			PP: 11-14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias		RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they	Strength and Limitations of this study P: 5 Limitations PP: 16, 17

				pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			PP: 15, 16
Generalisability	21	Discuss the generalisability (external validity) of the study results			PP: 16, 17
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based			P: 19
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P: 19

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.