Published in final edited form as:

Psychiatr Serv. 2021 May 01; 72(5): 578–581. doi:10.1176/appi.ps.202000534.

The Impact of Substance Use Disorder on COVID-19 Outcomes

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Abstract

Objective: The goal of this study was to examine the impact of **substance use disorder** on the risk of hospitalization, complications, and mortality in adult patients diagnosed with COVID-19

Methods: We conducted a propensity score (PS) matched double cohort study using data from the TriNetX Research Network database to identify 54,529 adult COVID-19 patients (≥18 years) diagnosed between February 20, 2020 and June 30, 2020.

Results: Our primary analysis—PS matched on demographic characteristics, diabetes, and obesity—showed that substance use disorder was associated with an increased risk of hospitalization (OR=1.84; 95% CI=1.69, 2.01), ventilator use (OR=1.45; 95% CI=1.22, 1.72) and mortality (OR=1.30; 95% CI=1.09, 1.56).

Conclusions: Our findings suggest that COVID-19 patients with substance use disorders are at increased risk for adverse outcomes. The attenuation of ORs in the final model suggests that the observed risks may be partially mediated by drug-related respiratory and cardiovascular disease.

Keywords

Substance Use Disorder; COVID-19

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to rapidly spread worldwide. As health care systems across the globe battle this pandemic, identifying patients at high risk of COVID-19 and associated complications has become critically important. Persons with substance use disorder are likely to be at increased risk of contracting SARS-CoV-2, due to their higher rates of homelessness, overcrowded living conditions, incarceration, and poor access to health care.[1] In addition, given the virus's impact on the respiratory, cardiovascular, and immune systems—which can be impaired by opioids, tobacco and other substances of abuse— persons with substance use disorders are at increased risk of COVID-19 complications, including acute respiratory distress syndrome (ARDS), renal failure and death.[1,2]

Persons with substance use disorders may be particularly vulnerable to the adverse respiratory effects of COVID-19, especially those using drugs that damage the lungs and

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impair the respiratory system, such as opioids, benzodiazepines, methamphetamines, and alcohol.[1,2] Likewise, substance use disorders have long been linked with immunosuppression. There is ample evidence that opioids, alcohol, methamphetamines, smoking, and vaping all have strong immunosuppressive effects, resulting in greater susceptibility to infection, more severe and longer lasting illnesses, and lower levels of protective antibodies in the blood.[3,4] In addition, some substance use disorders— such as tobacco smoking, cocaine and alcohol use disorder—are associated with adverse cardiovascular effects, including, hypertension, ischemia, venous thromboembolism, and brain hemorrhage.[5,6]

Given the range of pathways through which substance use disorders can adversely affect COVID-19 progression, understanding the impact of substance use disorders in such patients holds relevance to clinicians and public health planners as they seek clinical and policy approaches to this epidemic. The primary goal of this study was to examine the impact of substance use disorders on the risks of hospitalization, complications and mortality in adult patients diagnosed with COVID-19.

Methods

Data for this study were obtained from the TriNetX Research Network platform, a global federated network of electronic medical record (EMR) data from 35 health care organizations representing hospitals, primary care clinics, and specialty treatment providers designed to facilitate research related to COVID-19. Health care organizations contributing EMR data to the TriNetX platform are typically large academic health centers and their affiliates. TriNetX provides access to continuously updated, de-identified aggregate EMR data including demographics, diagnoses, procedures, medications, laboratory values, and genomics. At the time of the current study, the network included data from approximately 54,167,797 patients from 35 health systems across the US. The TriNetX platform is described in detail elsewhere.[7] The analyses of these data were conducted from June 17, 2020 through July 31, 2020. This study was reviewed and approved by the University of Texas Medical Branch IRB.

We queried the TriNetx Research Network to select adult patients (age ≥18) diagnosed with COVID-19 infection in the database between February 20, 2020 and **June 30**, 2020. Patients were identified as COVID-19 positive if they had a billable code for COVID-19 (ICD-10 codes: B34.2, B97.29, J12.81, U07.1, U07.2) or a positive SARS-CoV-2 laboratory test result (LOINC codes: 94500–6, 94315–9, 94309–2, 94533–7, 94534–5, 94559–2). Patients were excluded if they did not have at least one health care visit in the 12 months before COVID-19 diagnosis. We excluded patients with diagnosis codes of other specified viral infection (ICD-9 code: 079.89) or suspected exposure to other biologic agents (ICD-10 code: Z03.818) during the same timeframe.

A diagnosis of substance use disorder in the 12 months prior to COVID-19 diagnosis, was determined using algorithms, based on ICD-10-CM codes, defined in the Centers for Medicare and Medicaid Services (CMS) chronic conditions disease warehouse (CCDW).[8] We examined demographic characteristics (age, sex, race, ethnicity) and the following

comorbid conditions that have been linked to adverse outcomes in COVID-19 patients: diabetes (ICD-10-CM= E08-E13), hypertension (ICD-10-CM=I10), COPD (ICD-10-CM=J44), ischemic heart disease (ICD-10-CM=I20-I25), obesity (ICD-10-CM=E65-E68), and cerebrovascular disease (ICD-10-CM=I60-I69). Mortality and hospitalization were assessed directly from the EMR data. Mechanical ventilation was defined using the following CPT codes: 39.65, 31500, 5A1935Z, 5A1945Z, 5A1955Z, 1015098, 0BH17EZ, 0BH13EZ, 0BH18EZ, 1022227. All three outcomes were assessed using a follow-up time of 21 days from the COVID-19 diagnosis date.

Descriptive statistics were presented as frequencies with percentages for categorical variables and as mean ± standard deviation for continuous measures. Baseline characteristics were compared using a Pearson Chi-square tests for categorical variables and an independent-samples T-tests for continuous variables. To account for differences in baseline characteristic between the groups, 2 propensity score-matching (PSM) models were developed using logistic regression to derive well matched groups for comparative outcomes analysis. Variables included in the PS matched models included age, race, ethnicity and 5 comorbidities (diabetes, obesity, hypertension, COPD, ischemic heart disease and cerebrovascular diseases). Given that many substances use of abuse increase the risk for chronic respiratory and cardiovascular diseases,[1,2,5,6] we determined that 4 of the comorbidities under study (hypertension, COPD, ischemic heart disease, and cerebrovascular disease) were possible mechanistic pathways between substance use disorder and adverse COVID-19 outcomes. We therefore excluded these 4 conditions from the primary PS matched models. All statistical analyses were conducted on the TriNetX platform, which utilizes a combination of JAVA™, R,21 and Python™ programming languages.

Results

Table 1 presents demographic and clinical characteristics in the PS matched substance use disorder and non-substance use disorder COVID-19 cohorts. A total of 54,529 COVID-19 positive patients identified in the US TriNetx database; of those, 5,562 (10.2%) had a substance use disorder (supplement table). Males, blacks, Hispanics, and persons with diabetes, hypertension, COPD, ischemic heart disease, obesity, and cerebrovascular disease were over-represented in the substance use disorders subgroup. Both PS matched cohorts achieved strong balance on all matched variables.

Three outcomes—hospitalization, ventilator use and mortality—within 21 days of COVID-19 diagnosis were examined in SUD versus non-substance use disorder cohorts. First, in the unmatched analysis (supplement table), substance use disorder was associated with an increased risk of hospitalization (32.5% vs.17.4%, OR=2.29, 95% CI=2.16, 2.44), ventilator use (6.0% vs. 3.1%, OR=2.02; 95% CI=1.79, 2.28) and mortality (4.9% vs. 2.8%, OR=1.81 95% CI=1.58, 2.07). In the PS cohort that was matched on demographic characteristics, diabetes, and obesity, substance use disorder was associated with an increased risk of: hospitalization (32.5% vs. 20.7%, OR=1.84; 95% CI=1.69, 2.01); ventilator use (6. 0% vs 4.2%, OR=1.45; 95% CI=1. 22, 1.72), and mortality (4.9% vs 3.8%, OR= 1.30; 95% CI=1.08, 1.56). The final PS matched cohort included 4 additional

comorbidities—hypertension, COPD, ischemic heart disease, cerebrovascular disease—that were potentially mechanistic pathways between substance use disorder and adverse outcomes. This model showed that substance use disorder was still associated with an increased risk of hospitalization (30.9% vs 22.6%, OR=1.53; 95% CI=1.40, 1.65), ventilator use (5. 4% vs 4.3%, OR=1.28; 95% CI=1.07, 1.52), but not with mortality (4.7% vs 4.2%, OR=1.00; 95% CI= 0.84, 1.19).

Discussion

In this double cohort study of 11,124 adults diagnosed with COVID-19, we found that—after propensity score matching on demographic characteristics, diabetes and obesity—substance use disorder was associated with increased hospitalization, ventilator use, and mortality. When hypertension, COPD, ischemic heart disease, and cerebrovascular disease—possible mediators between substance use disorder and COVID-19 adverse outcomes--were added to the matching algorithm, the increased risks for hospitalization and ventilator use persisted, but the mortality risk was attenuated. Overall, our findings were consistent with a broad literature that has reported adverse effects of substance use disorder on the respiratory, cardiovascular, and immune systems.[1–3,9] The attenuation of risks, particularly mortality, in the final model—after matching on respiratory and cardiovascular diseases—suggests that the increased risks experienced by patients with substance use disorder may be driven, at least in part, by drug-related respiratory and cardiovascular disease. [1–3,9–13]

Hypertension, COPD, ischemic heart disease, and cerebrovascular disease all represent important mechanistic pathways between substance use disorder and COVID-19 adverse outcomes. For example, smoking of tobacco and cannabis and vaping damage lung tissue, cause inflammation, diminish lungs' capacity to respond to infection, and increase angiotensin-converting enzyme 2 (ACE2) receptor density, all of which can exacerbate respiratory disease caused by SARS-CoV-2.[1,211] Likewise, prolonged alcohol exposure is linked to impaired mucociliary clearance and lung function while methamphetamine use is linked to non-cardiac pulmonary edema, ARDS, alveolar hemorrhage, pneumonia and pneumoconiosis.[10,11] In addition, cocaine, methamphetamines, alcohol, tobacco and opioids are reported to have adverse effects on the cardiovascular system, including hypertension, ischemia, VTE and brain hemorrhage.[5,12,14]

Substance use disorders can also increase the risk of adverse COVID-19 outcomes by way of immunosuppression.[3] For example, opioids exert various suppressive effects on both the innate and adaptive immune systems, especially among long-term users (≥90 days in a year). Largely by binding to the μ receptor and modulating various downstream cellular signaling pathways, opioids impair the recruitment and function of virtually all immune cells such as macrophages, NK cells, granulocytes, and B and T lymphocytes.[3] Methamphetamines are also reported to increase immune dysregulation, particularly in the lungs.[15] Similarly, chronic alcohol exposure interferes will all aspects of the adaptive immune response—including both cell mediated and immune responses—which increase the susceptibility of persons with AUD to viral and bacterial infections.

The results of our study may have been influenced by several limitations. First, the diseases and medical conditions examined in this study were based on ICD-10-CM codes. Such codes are not always accurate or complete. Second, the TriNetX platform does not represent the general US population, but rather only those people who receive clinical care within the 35 health care organizations in the network. Third, reliance on EHR data precluded assessment of a number of potential confounding factors such as region and markers of adverse socioeconomic disadvantages, such as neighborhood density, occupational exposure hazards, access to care, access to timely COVID testing, and quality of care for preexisting non-COVID chronic conditions. Despite these limitations, this study has a number of strengths including a large sample from 35 health systems covering all major regions of the US and a rigorous propensity score matching based analysis.

Conclusions

Our findings suggest that COVID-19 patients with substance use disorder have an increased risk of adverse outcomes. The attenuation of the mortality risk in the final model may reflect an important mediating role of drug-related respiratory and cardiovascular disease. More longitudinal research is needed to further understand the relationship between short and long-term use of various substances of abuse, the interactions of the substances with COVID-19 related medications, and the pathways for COVID-19 complications. Continued research on this important topic will inform clinicians, health system leaders, and policy makers on delivery of care for the growing number of Americans living with substance use disorders who are at high-risk for COVID-19 and other infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Research Support: T32HS02613301 (Agency for Healthcare Research and Quality)

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Highlights

- Persons with substance use disorders may be particularly vulnerable to the adverse respiratory effects of COVID-19, especially those using drugs that impair the cardiovascular and respiratory systems.
- This double cohort study of 11,124 adults diagnosed with COVID-19, reports that— after propensity score matching on demographic characteristics, diabetes and obesity—substance use disorder was associated with increased hospitalization, ventilator use, and mortality.
- The reduction of risks, particularly mortality—after additionally matching on hypertension, COPD, ischemic heart disease and cerebrovascular diseases—suggests that observed risks may be mediated, at least in part, by drug-related respiratory and cardiovascular diseases.

TABLE 1.

Characteristics and Outcomes in Unmatched and Propensity Score Matched COVID-19 Cohorts, with and without Substance Use Disorder

Characteristics	Matched on demographics, obesity and diabetes					Matched on demographics and comorbidities[b]				
	No Substance Use Disorder N =5,562		Substance Use Disorder N = 5,562		*P*[a]	No Substance Use Disorder N = 5,450		Substance Use Disorder N = 5,450		*P*[a]
	N	%	N	%		N	%	N	%	
Age (mean, SD)	54.0	17.2	54.0	17.2	.953	54.4	17.8	53.8	17.3	09
Gender					.790					.134
Female	2,609	46.9	2,623	47.2		2514	46.1	2,592	47.6	
Male	2,952	53.1	2,938	52.8		2934	53.8	2,857	52.4	
Race					.805					.129
White	3,145	56.5	3,116	56.0		3168	58.1	3,063	56.2	
Black	1,729	31.1	1,728	31.1		1633	30.0	1671	30.7	
Asian	64	1.2	72	1.3		61	1.1	72	1.3	
Unknown/ Other	624	11.2	646	11.6		588	10.8	644	11.6	
Ethnicity					.973					.660
Hispanic	623	11.2	629	11.3		631	11.6	626	11.5	
Not Hispanic	3,576	64.3	3,565	64.1		3497	64.2	3,461	63.5	
Unknown	1,363	24.5	1,368	24.6		1322	24.3	1,363	25.0	
Comorbidities										
Diabetes	1,649	29.7	1,675	30.1	.590	1642	30.1	1,587	29.1	0.25
Hypertension	2,360	42.4	3,089	55.5	<.0001	3045	55.9	2,977	54.6	0.19
COPD	307	5.5	1,085	19.5	<.0001	906	16.6	971	17.8	0.10
Ischemic heart dis	722	12.3	1,383	24.9	<.0001	1276	23.4	1,280	23.5	0.93
Obesity	1,849	33.2	1,864	33.5	.763	1778	32.6	1,806	33.1	0.57
Cerebrovasc dis	447	8.0	851	15.3	<.0001	741	13.6	795	14.6	0.14
Outcomes (3 weeks)										
	N	**%**	**N**	**%**	**OR 95% CI**	**N**	**%**	**N**	**%**	**OR 95% CI**

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Characteristics	Matched on demographics, obesity and diabetes						Matched on demographics and comorbidities[b]					
	No Substance Use Disorder N =5,562		Substance Use Disorder N = 5,562		*p*[a]		No Substance Use Disorder N = 5,450		Substance Use Disorder N = 5,450		*p*[a]	
	N	%	N	%			N	%	N	%		
Hospitalization	1152	20.71	1808	32.51	1.84	1.69, 2.01	1,231	22.59	1,682	30.86	1.53	1.40, 1.65
Ventilator use	235	4.23	334	6.01	1.45	1.22, 1.72	233	4.28	294	5.40	1.28	1.07, 1.52
Death	210	3.78	270	4.85	1.30	1.08, 1.56	256	4.70	257	4.72	1.00	0.84, 1.20

[a]Baseline characteristics were compared using a Pearson chi-square test for categorical variables and an independent-samples t-test for continuous variables.

[b]Diabetes, obesity, hypertension, COPD, ischemic heart disease and cerebrovascular disease