Impact of Cannabis Use, Substance Use Disorders, and Psychiatric Diagnoses on COVID-19 Outcomes: A Retrospective Cohort Study

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ABSTRACT

Objective: While psychiatric disorders have been recognized as a risk factor for COVID-19 outcomes, the impact of substance use disorders (SUD) on COVID-19 outcomes has not, to date, been examined in a systematic manner. We examined the association between SUD (cannabis, cocaine, alcohol, opioid, benzodiazepine) as well as psychiatric diagnoses (schizophrenia, mood disorders, anxiety disorders) and COVID-19 outcomes in a large, retrospective cohort study.

Methods: COVID-19–positive patients admitted to a large health care system in the US between January and December 2020 were included in this study. SUD and psychiatric diagnoses were identified from urine toxicology reports and ICD-10 diagnosis codes in the electronic medical record, respectively. Multivariable logistic regression was performed controlling for potential confounders such as age, race, sex, smoking status, and medical comorbidities. COVID-19–relevant outcomes included mortality, need for intensive care unit (ICU) admission, need for ventilatory support, length of hospitalization, and number of hospitalizations.

Results: Among COVID-19 patients (N = 6,291), those with SUD were more likely to require ICU admission (adjusted odds ratio [AOR] = 1.46, P = .003) and ventilatory support (AOR = 1.49, P = .01). The association between SUD and ICU admission was driven by alcohol use disorder (AUD), whereas that between SUD and ventilatory support was driven by both AUD and opioid use disorder (OUD). Patients with SUD were more likely to have a longer mean maximum length of hospitalization (11.32 vs 8.62 days, P < .0001) and a greater mean number of hospital admissions in 2020 (2.96 vs 2.33, P < .0001). These associations were significant for cannabis use disorder, AUD, OUD, and benzodiazepine use disorder. The association with greater number of admissions was also significant for cocaine use disorder. Patients with psychiatric diagnoses were also more likely to have a greater maximum length of hospitalization (11.93 vs 8.39 days, P < .0001) and hospital admissions (2.72 vs 2.31, P < .0001). These associations were significant for schizophrenia, mood disorders, anxiety disorders, and anxiety disorders.

Conclusions: COVID-19 patients with SUD had greater likelihood of requiring critical interventions, such as ICU admission and ventilatory support. SUD and psychiatric diagnoses were also associated with a longer duration of hospitalization and greater number of hospital admissions. These findings identify COVID-19 patients with SUD and psychiatric comorbidities as a high-risk group.
Impact of SUD on COVID-19 Outcomes

The coronavirus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 virus, has resulted in unprecedented morbidity and mortality. As of November 2021, there have been more than 250 million cases and 5.1 million deaths worldwide, with over 47 million cases and 783,000 deaths in the United States alone.1 Despite the development of vaccines, the COVID-19 pandemic continues to overwhelm several nations due to difficulties in vaccine rollouts and the emergence of the more virulent variants, such as the delta variant.

Identifying risk factors that predispose individuals to negative COVID-19 outcomes is important to ensure that vaccine efforts and medical attention are appropriately directed, especially in resource-poor settings. The Centers for Disease Control and Prevention (CDC) has employed a risk stratification approach using age > 65 years, body mass index (BMI) > 30, and the presence of chronic lung and heart disease to guide vaccine efforts in the US. In addition, recent literature has begun to explore the association between prior psychiatric diagnoses and health outcomes in COVID-19 patients.2–9 Multiple studies have found evidence for an increased association between mortality related to COVID-19 and psychiatric disorders, including schizophrenia, bipolar disorder, and depressive disorders.2–9 There is also some evidence for increased rates of COVID-19 infection among patients with schizophrenia.3 However, there is only preliminary evidence for the association between psychiatric disorders and other COVID-19–related health outcomes, such as length of hospitalization and need for critical in-hospital interventions, such as ventilatory support or intensive care unit (ICU) admission.10

While several studies have looked at the association between psychiatric diagnoses and COVID-19 outcomes, the association between substance use disorders (SUD) and COVID-19 outcomes has been less systematically studied. Preliminary evidence suggests that patients with SUD, especially opioid use disorder (OUD) and alcohol use disorder (AUD), are at an increased risk of COVID-19–related mortality and hospitalization.11–13 One study14 proposed that opioid-induced respiratory depression may explain the increased risk of more severe health outcomes in COVID-19 patients with OUD. There are fewer data on the impact of SUD, such as cocaine or cannabis use disorders, on other COVID-19–related health outcomes, such as need for ICU admission or ventilatory support.

Elucidating the relationship between psychiatric disorders, SUD, and COVID-19 health outcomes is a crucial endeavor to expand the list of risk factors and to guide vaccine rollout efforts. Understanding this interaction is also essential for directing appropriate medical attention to patient populations that may be predisposed to more severe COVID-19 infections. The aim of the current study was to examine the association between SUD, psychiatric diagnosis, and COVID-19–related clinical outcomes, adjusting for demographic factors, smoking status, and medical comorbidities.

**METHODS**

**Database Description**

We conducted a retrospective cohort study of all COVID-19–positive patients admitted to the Yale New Haven Health (YNHH) system, a large health care system in New Haven, Connecticut, between January and December 2020. Data were extracted from electronic health records (ie, EPIC EHR Software, Epic Systems Corporation) with the help of the Yale Center for Clinical Investigations (YCCI) Joint Data Analytics Team (JDAT). The study was approved for exemption of review and waiver of consent by the institutional review board of Yale University. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

**Study Population**

The cohort consisted of 6,291 COVID-19–positive patients admitted to the YNHH system from January to December 2020. The exposure variables of interest were psychiatric diagnosis (including schizophrenia, mood disorders, and anxiety disorders) and SUD (including AUD, OUD, benzodiazepine use disorder, cannabis use disorder, and cocaine use disorder). Psychiatric and substance use disorder diagnoses were identified from urinalysis results and ICD-10 diagnosis codes in each patient’s problem list on EPIC. The outcome variables of interest determined a priori were mortality, ICU admission, length of ICU admission, need for ventilatory support, number of days on ventilatory support, number of hospital admissions from January to December 2020, and maximum length of hospitalization.

**Clinical Points**

- COVID-19 patients with substance use disorders (SUD) have a greater likelihood of requiring critical interventions, such as intensive care unit admission and ventilatory support.
- Comorbid SUD and psychiatric diagnoses were associated with a longer duration of hospitalization and greater number of hospital admissions. Hence, COVID-19 patients with comorbid SUD and psychiatric diagnoses should be considered a high-risk group.


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The following analyses were performed: (1) we examined whether there was an increased risk of mortality, ICU admission, and need for ventilatory support among COVID-19–positive patients with any SUD or psychiatric diagnosis; (2) we examined whether COVID-19–positive patients with any SUD or psychiatric diagnosis who required an ICU admission or ventilatory support had a longer duration of ICU admission or ventilatory support; and (3) we examined whether COVID-19–positive patients with any SUD or psychiatric diagnosis had a greater number of hospital admissions and longer maximum length of hospitalization.

Statistical Analysis
All analyses were controlled for age, sex, race, smoking status, and medical comorbidities measured by the Charlson Comorbidity Index (CCI) derived from ICD-10 diagnosis codes. We performed a multivariable logistic regression analysis to assess the adjusted odds ratio (AOR), 95% confidence interval (CI), and P value for the following categorical outcome variables: mortality, ICU admission, and need for ventilatory support. We performed a 1-way analysis of variance (ANOVA) test to determine the adjusted geometric mean, 95% CI, and P value for the following continuous outcome variables: length of ICU admission, days on ventilatory support, number of hospital admissions, and maximum length of hospitalization. All outcomes were assessed for normality prior to analysis using normal probability plots and Kolmogorov test statistics. When outcome variables were not normally distributed, log transformation was performed. All analyses were conducted using SAS, version 9.4 (SAS Institute, Inc).

RESULTS

Patient Characteristics
The total study population comprised 6,291 patients (48% male and 52% female) with a mean ± SD age of 62 ± 19 years. The rate of mortality in this cohort was 13%. The rates of ICU admission and need for ventilatory support were 28% and 12%, respectively. Among those requiring an ICU admission and ventilatory support, the mean ± SD duration was 9 ± 11 days and 11 ± 14 days, respectively. The mean ± SD maximum length of hospitalization was 11 ± 12 days, and the mean ± SD number of hospital admissions was 1 ± 1. Further details of the study demographics are listed in Table 1.

Associations Between COVID-19 Outcomes and SUD
Mortality among COVID-19 patients with any SUD was not significantly different from that among those without SUD (AOR = 1.04 [95% CI, 0.68–1.61], P = .85). However, COVID-19 patients with any SUD had a greater risk of requiring an ICU admission (AOR = 1.46 [95% CI, 1.13–1.87], P = .003) and ventilatory support (AOR = 1.49 [95% CI, 1.09–2.03] P = .01) during hospitalization than those without SUD. Among patients with any SUD, only those with AUD had a significantly greater risk of requiring ICU admission (AOR = 1.53 [95% CI, 1.14–2.06], P = .005), while there was a significantly greater risk of requiring ventilatory support among both AUD (AOR = 1.47 [95% CI, 1.02–2.12], P = .04) and OUD (AOR = 1.86 [95% CI, 1.05–3.32], P = .03) patients (Table 2). Although COVID-19 patients with any SUD were more likely to require an ICU admission and ventilatory support, among those requiring these interventions, there was no significant association between SUD and either length of ICU admission (P = .74) or days on ventilatory support (P = .82).

However, COVID-19 patients with SUD had a significantly longer mean (95% CI) maximum length of hospitalization than those without SUD when adjusted for age, sex, race, smoking status, and CCI score (11.32 [10.40–12.33] vs
8.62 [8.44–8.81] days, \( P < .0001 \). Among those with SUD, there was a significant association between maximum length of hospitalization and the following subcategories of SUD: AUD (11.05 [9.98–12.24] vs 8.67 [8.49–8.86] days, \( P < .0001 \)), OUD (12.47 [10.47–14.85] vs 8.71 [8.53–8.90] days, \( P < .0001 \)), benzodiazepine use disorder (15.92 [11.91–21.28] vs 8.73 [8.55–8.92] days, \( P < .0001 \)), and cannabis use disorder (13.99 [10.18–19.25] vs 8.74 [8.55–8.93] days, \( P = .004 \)) (Figure 1A). COVID-19 patients with SUD also had significantly more mean (95% CI) hospital admissions in 2020 than those without SUD after adjustment for age, sex, race, smoking status, and CCI score (2.96 [2.87–3.06] vs 2.34 [2.23–2.36], \( P < .0001 \)), OUD (3.22 [3.01–3.45] vs 2.35 [2.33–2.37], \( P < .0001 \)), benzodiazepine use disorder (3.24 [2.90–3.62] vs 2.35 [2.34–2.37], \( P < .0001 \)), cannabis use disorder (3.46 [3.06–3.92] vs 2.35 [2.33–2.37], \( P < .0001 \)), and cocaine use disorder (2.90 [2.67–3.15] vs 2.35 [2.33–2.37], \( P < .0001 \)) (Figure 1B).

### Table 3. Risk Associations Between COVID-19 Outcomes and Psychiatric Diagnosis

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>AOR (95% CI)</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric diagnosis</td>
<td>Mortality</td>
<td>0.86 (0.66–1.12)</td>
<td>.25</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>ICU admission</td>
<td>0.97 (0.81–1.15)</td>
<td>.71</td>
</tr>
<tr>
<td>Psychiatric diagnosis</td>
<td>Ventilatory support</td>
<td>0.81 (0.63–1.05)</td>
<td>.10</td>
</tr>
</tbody>
</table>

Abbreviations: AOR = adjusted odds ratio, ICU = intensive care unit.
Associations Between COVID-19 Outcomes and Psychiatric Diagnosis

There was no significant difference in the risk of mortality (AOR = 0.86 [95% CI, 0.66–1.12], P = .25), ICU admission (AOR = 0.97 [95% CI, 0.81–1.15], P = .71), and ventilatory support (AOR = 0.81 [95% CI, 0.63–1.05], P = .10) between COVID-19 patients with any psychiatric diagnosis (schizophrenia, mood disorders, or anxiety disorders) and those without a psychiatric diagnosis (Table 3). Among patients who required an ICU admission or ventilatory support, the length of ICU admission (P = .32) and days on ventilatory support (P = .25) were not significantly different between those with a psychiatric diagnosis and those without one.

However, after adjustment for age, sex, race, smoking status, and CCI score, COVID-19 patients with any psychiatric diagnosis had a significantly longer mean (95% CI) maximum length of hospitalization than those without a psychiatric diagnosis (11.93 [11.29–12.60] vs 8.39 [8.20–8.58] days, P < .0001). Among patients with a psychiatric diagnosis, those with schizophrenia (15.56 [13.90–17.42] vs 8.62 [8.43–8.80] days, P < .0001), anxiety disorders (12.21 [11.23–13.28] vs 8.60 [8.41–8.79] days, P < .0001), and mood disorders (11.63 [10.85–12.47] vs 8.55 [8.37–8.74] days, P < .0001) had a significantly longer maximum length of hospitalization (Figure 2A). COVID-19 patients with a psychiatric diagnosis also had a greater mean (95% CI) number of hospital admissions in 2020 than those without a psychiatric diagnosis when adjusted for age, sex, race, smoking status, and CCI score (2.72 [2.67–2.78] vs 2.31 [2.29–2.33], P < .0001). This association was significant for those with schizophrenia (2.81 [2.69–2.94] vs 2.35 [2.29–2.33], P < .0001).
outcomes,17,18 including ventilator use,12 ICU admission, 11 have shown an increased risk of adverse COVID-19 comorbidities. Surprisingly, neither psychiatric diagnosis nor AUD, benzodiazepine use disorder, cocaine use disorder, and cannabis use disorder. The associations were also significant for most or all of the subcategories of SUD, including OUD and AUD. However, patients with any SUD did not have a significantly longer duration of ICU admission or ventilatory support. Unlike patients with any SUD, those with any psychiatric diagnosis were not at greater risk of requiring ICU admission or ventilatory support. We also found that patients with any SUD or any psychiatric diagnosis had a significantly longer maximum length of hospitalization and number of hospital admissions. These associations were significant for most or all of the subcategories of SUD, including OUD, AUD, benzodiazepine use disorder, cocaine use disorder, and cannabis use disorder. The associations were also significant for all subcategories of psychiatric disorders, including schizophrenia, mood disorders, and anxiety disorders. Surprisingly, neither psychiatric diagnosis nor SUD was associated with a greater risk of mortality in COVID-19–positive patients after adjustment for medical comorbidities.

Although one observational study with a small sample size16 suggests a low incidence of severe COVID-19 infections in patients with SUD, our study results are consistent with most studies in the literature that have shown an increased risk of adverse COVID-19 outcomes,17,18 including ventilator use,12 ICU admission,11 and hospitalization11 in COVID-19 patients with SUD. We also found that among the categories of SUD, OUD and AUD were significantly associated with a greater risk of requiring critical interventions, such as ICU admission and ventilatory support. This result is consistent with a previous study in the literature that showed OUD and AUD were associated with the worst COVID-19 outcomes among the subcategories of SUD.13 The association between OUD and increased risk of ventilatory support may be due to opioid-induced respiratory depression that has been suggested as a plausible biological mechanism for the increased risk of hypoxemia in COVID-19 patients with OUD.14 Another analysis found that among COVID-19–positive patients, those with AUD and cocaine use disorder were associated with increased risk of hospitalization.11 Similarly, our results suggest an increased risk of negative COVID-19 outcomes, specifically increased hospital admissions and longer duration of hospitalization, in patients with prior psychiatric diagnoses, such as schizophrenia, mood disorders, and anxiety disorders. These results are consistent with several other studies that have found an increased risk of adverse health outcomes in patients with prior psychiatric diagnoses, especially schizophrenia, bipolar disorder, and other mood disorders.5,9,19,20 Notably, our results suggest that even patients with an anxiety disorder had longer lengths of hospitalization and more hospital admissions, an association that was not found in other studies.7,19

Unlike other studies in the literature,3,4,12,13,21,22 our study did not find an increased risk of mortality in patients with either a psychiatric diagnosis or any SUD when adjusting for demographic variables and medical comorbidities. There may be many reasons for this finding, albeit speculative. First, it is possible that prior reports of increased mortality in patients with schizophrenia have sensitized the health system to the fact that this population is at high risk, and thus resulted in more intensive care for these patients. This possibility may explain the finding of longer duration of hospitalization and greater number of hospitalizations in this population in our dataset. Secondly, it is possible that the finding of increased mortality in patients with psychiatric diagnosis and SUD is mediated by increased medical comorbidity. Since we used CCI score as a covariate in our analysis, we were unable to detect group differences.

The main limitation of our study is that we focused on all-cause mortality and not COVID-19–specific mortality during the year of 2020. Our findings did not show an association between either psychiatric diagnosis or SUD and mortality in COVID-19 patients admitted to YNHH in 2020. However, this does not necessarily preclude the possibility that patients with a psychiatric diagnosis or SUD had an increased risk of mortality specifically attributable to COVID-19–related complications. Another limitation of our study was that we included all patients who tested positive for COVID-19 during one of their admissions to YNHH. It is possible that some of these patients were asymptomatic during their time of admission and were in the hospital for health concerns unrelated to COVID-19. This possibility limits our ability to make a direct conclusion about an association between patients with active COVID-19 infection and either psychiatric diagnosis or SUD. Furthermore, patients admitted to YNHH mainly come from the Greater New Haven area, a demographic that has a higher percentage of people who identify as African American (33.6% vs 13.4%) or Latino (30.8% vs 18.5%) than the average US population as well as a higher percentage of people in poverty defined by the US Census Bureau (25.2% vs 11.4%).23 Thus, the generalizability of our study results to other subpopulations in the US may be limited.

However, one major strength of our study is that we controlled for medical comorbidities in a systematic way using the CCI, which has become a well-established way of objectively controlling for the effect of medical comorbidities in patients.15 In addition, unlike previous studies, we controlled for the smoking status of patients, which minimizes a large confounding factor when studying COVID-19 outcomes.
While our study results show a significant association between SUD and psychiatric diagnoses and COVID-19 outcomes, it is important to note that these results came from a 2020 patient population, before the introduction of COVID-19 vaccines. Recent studies suggest that vaccine hesitancy may be greater among people with psychiatric diagnoses and SUD.24–26 One study24 reveals a higher prevalence of vaccine hesitancy across several psychiatric diagnoses, including major depressive disorder, bipolar disorder, generalized anxiety disorder, attention-deficit/hyperactivity disorder, and SUD. Those with SUD and nicotine use disorder/tobacco dependence had a higher prevalence of vaccine hesitancy after adjusting for potential sociodemographic confounders. Future studies should focus on assessing the effect of vaccination status on the association between SUD and psychiatric diagnoses with COVID-19 outcomes, especially as vaccination efforts across the nation ramp up. Another question that remains unanswered is whether neuropsychiatric symptoms are causally linked to COVID-19 infection and whether these symptoms persist—ie, the so-called “long COVID syndrome” or “post–COVID-19 syndrome”27—or whether SUD and psychiatric comorbidity are risk factors for the syndrome. Longitudinal studies with detailed phenotyping will be required to answer these questions.

In summary, our retrospective cohort study found that COVID-19 patients admitted to YNHH from January to December 2020 had an increased length of hospitalization and number of hospital admissions if they had comorbid psychiatric diagnoses, such as schizophrenia, mood disorders, or anxiety disorders, or any SUD when controlling for age, sex, race, smoking status, and medical comorbidities using the CCI score. We also showed that patients with SUD were more likely to require critical interventions, such as ICU admission and ventilatory support. Together, these findings suggest that patients with comorbid psychiatric diagnoses and SUD are more at risk of developing serious complications of COVID-19 infections and are also more likely to have prolonged hospitalizations. Thus, it is important that we make more of an effort to identify these patients early on in their COVID-19 course to avoid more serious complications. Our findings suggest that perhaps COVID-19 patients with comorbid psychiatric diagnoses and SUD may be falling through the cracks in terms of medical management when earlier interventions might have prevented them from having worse health outcomes. As the COVID-19 vaccination efforts ramp up, it would be prudent to prioritize those patients with psychiatric diagnoses and SUD, who may otherwise be susceptible to prolonged and more severe courses of COVID-19 infection.28 Our findings are hence relevant to psychiatrists in enabling them to advocate for patients with psychiatric disorders and SUD and to help them navigate a complex health system to obtain vaccination and early treatment. The findings also have significance for public health policy makers. Of note, “medical cannabis” dispensaries were allowed to stay open as “essential businesses” during the COVID-19 pandemic.29 Our results raise concern regarding this policy since those with comorbid cannabis use disorder were more likely to have higher number of hospitalizations and longer duration of hospitalizations.

REFERENCES

15. King JT Jr, Yoon JS, Rentsch CT, et al.
1. Which of the following substance use disorders is associated with a requirement for higher-level interventions, such as ICU admission and ventilatory support, for COVID-19 infection?
   a. Benzodiazepine use disorder
   b. Alcohol use disorder
   c. Cocaine use disorder
   d. Cannabis use disorder

2. A 45-year-old man with a psychiatric history of schizophrenia and opioid use disorder presents to his primary care provider for routine follow-up. He is hesitant to receive the COVID-19 vaccine. In addition to providing education about the vaccine, which of the following should the primary care provider inform the patient about?
   a. Having schizophrenia puts you at a higher risk of dying from COVID-19.
   b. Your history of opioid use disorder puts you at a greater risk of being infected by COVID-19.
   c. Your psychiatric history and substance use disorder put you at a greater risk of more severe COVID-19 outcomes, such as longer hospitalization.
   d. You have the same risk of severe COVID-19 outcomes as any other 45-year-old individual without major medical comorbidities.

3. Cannabis use disorder is associated with a longer length of hospitalization and greater number of hospital admissions in COVID-19 patients when controlling for age, sex, race, smoking history, and medical comorbidities.
   a. True
   b. False