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Substance use disorders and COVID-19: An analysis of nation-wide Veterans Health Administration electronic health records

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ABSTRACT

Background: Substance use disorders (SUD) elevate the risk for COVID-19 hospitalization, but studies are inconsistent on the relationship of SUD to COVID-19 mortality.
Methods: Veterans Health Administration (VHA) patients treated in 2019 and evaluated in 2020 for COVID-19 (n=5,556,315), of whom 62,303 (1.1%) tested positive for COVID-19 (COVID-19+). Outcomes were COVID-19+ by 11/01/20, hospitalization, ICU admission, or death within 60 days of a positive test. Main predictors were any ICD-10-CM SUDs, with substance-specific SUDs (cannabis, cocaine, opioid, stimulant, sedative) explored individually. Logistic regression produced unadjusted and covariate-adjusted odds ratios (OR; aOR).
Results: Among COVID-19+ patients, 19.25% were hospitalized, 7.71% admitted to ICU, and 5.84% died. In unadjusted models, any SUD and all substance-specific SUDs except cannabis use disorder were associated with COVID-19+(ORs=1.06–1.85); adjusted models produced similar results. Any SUD and all substance-specific SUDs were associated with hospitalization (aORs: 1.24–1.91). Any SUD, cocaine and opioid disorder were associated with ICU admission in unadjusted but not adjusted models. Any SUD, cannabis, cocaine, and stimulant disorders were inversely associated with mortality in unadjusted models (OR=0.27–0.46). After adjustment, associations with mortality were no longer significant. In ad hoc analyses, adjusted odds of mortality were lower among the 49.9% of COVID-19+ patients with SUD who had SUD treatment in 2019, but not among those without such treatment.
Conclusions: In VHA patients, SUDs are associated with COVID-19 hospitalization but not COVID-19 mortality. SUD treatment may provide closer monitoring of care, ensuring that these patients received needed medical attention, enabling them to ultimately survive serious illness.

1. Introduction

As of February, 2022, over 78 million Americans are known to have been infected with COVID-19, and over 925,000 have died (Johns Hopkins University and Medicine, 2022). Many remain unvaccinated, and highly contagious variants of the virus have appeared since the start of the pandemic, so greater knowledge of risk factors for COVID-19 infection and poor outcomes remains critical. Demographic risk factors for COVID-19 infection include non-Hispanic Black (Karmakar et al., 2021; Lopez et al., 2021; Wingert et al., 2021) or Hispanic

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race/ethnicity (Rogawski McQuade et al., 2021; Lopez et al., 2021); males may also be at higher risk of infection (Vahidy et al., 2021). Risk factors for hospitalization or death include older age (Wingert et al., 2021; Ebinger et al., 2020; Ahmad et al., 2021), obesity (Wingert et al., 2021; Zhang et al., 2021b), non-Hispanic Black or Hispanic race/-ethnicity (Gu et al., 2020; Ahmad et al., 2021), male sex (Ebinger et al., 2020), and medical conditions such as diabetes, neoplasms, cardiovascular, respiratory and kidney disease (Shi et al., 2021; Taylor et al., 2021; Harrison et al., 2021; Kaur et al., 2021).

Substance use disorder (SUD) is also a potential risk factor for COVID-19 infection and poor outcome. SUD may increase risk for infection due to homelessness, or to SUD-associated decision-making traits (Amlung et al., 2017; Childs et al., 2019; Bickel et al., 2014; Chen et al., 2020) that could increase COVID-19 exposure through preference for in-person interactions over maintaining social distance. Among those infected, SUD could increase the risk for poor outcomes through effects on the immune, respiratory, or cardiovascular systems (Volkow, 2020), indirect effects of medical conditions commonly co-occurring with SUD (Leece et al., 2015; Hulin et al., 2020; Palmer et al., 2012; Ghasemiesfe et al., 2018), or delays in seeking medical care (Meyer et al., 2013; Motavalli et al., 2021; Childs et al., 2019). To study the relationship of SUDs and COVID-19 outcomes, large-scale electronic health record (EHR) databases are needed to evaluate if SUD is associated with COVID-19 outcomes over and above the potentially confounding effects of other medical conditions that are associated with both SUD and COVID-19 outcomes.

To our knowledge, five US studies have examined SUD and COVID-19 in EHR databases (Wang et al., 2021; Allen et al., 2021; Baillargeon et al., 2021; Kelly et al., 2021; Qeadan et al., 2021). Two studies (Wang et al., 2021; Allen et al., 2021) addressed infection risk. One (Wang et al., 2021) found that SUD was associated with a positive COVID-19 test (hereafter, "COVID-19+") after adjustment for demographics, but did not further adjust for medical conditions. The other (Allen et al., 2021) found an unadjusted association of SUD with COVID-19+, but not after adjustment for medical illnesses that could confound the relationship by increasing the likelihood of COVID-19 testing among those in treatment for other conditions. Four studies examined SUD and hospitalization among COVID-19+ patients (Wang et al., 2021; Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021). Across several studies, SUD was associated with hospitalization before and after adjustment for medical conditions. Three of these studies (Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021) also found associations of SUD with aspects of intensive care, e.g., ICU admissions. These studies also addressed mortality (Wang et al., 2021; Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021), as did a study of social, behavioral and substance use risk factors for mortality in COVID-19+ veterans (Kelly et al., 2021). In the study without adjustment for medical conditions, SUD predicted increased COVID-19 mortality (Wang et al., 2021). Three studies found that SUD increased the unadjusted but not adjusted risk of COVID-19 mortality (Baillargeon et al., 2021; Qeadan et al., 2021). In the study of veterans (Kelly et al., 2021), substance use was inversely related to COVID-19 mortality, although the association was attenuated after adjusting for medical conditions (Kelly et al., 2021). Therefore, findings were mixed. The range in SUD prevalence in these studies (0.99%–12.9%) did not appear to account for their findings.

The Veterans Health Administration (VHA) is the largest U.S. integrated healthcare system, treating approximately 5.5 million veterans each year. EHR data are aggregated across the entire VHA system. Using a retrospective cohort design, we investigated relationships of SUD to COVID-19+ and COVID-19 outcomes among veterans treated at the VHA in 2019, including whether SUD was related to COVID-19+ up to 11/1/2020, and among the COVID-19+ subsample, whether SUD was related to hospitalization, ICU admission, and death.

2. Methods

2.1. Settings, procedures

Patients were included if in 2019, they lived in the 50 U.S. states or Washington DC, had at least 1 VA outpatient treatment visit and were not in hospice or palliative care. After excluding patients with missing values (n = 9, all due to a missing value for sex), the analytic cohort included the 5,556,315 patients alive on 02/20/2020. Institutional Review Boards at the VHA Puget Sound, New York Harbor Healthcare and New York State Psychiatric Institute approved this study.

2.2. Measures

Data on COVID-19 cases and outcomes came from the VHA COVID-19 Shared Data Resource (SDR). Additional medical information was obtained from the VA Corporate Data Warehouse (CDW).

2.2.1. COVID-19 diagnoses

SDR COVID-19 diagnoses came from two sources. One was a record in the EHR of a VHA SARS-CoV-2 real-time reverse transcription polymerase chain reaction (rRT-PCR) or antigen test. The other source was electronic chart notes. To provide COVID-19 testing as widely as possible to VHA-eligible veterans (U.S. Department of Veteran Affairs, 2021a,b), the VHA covered the costs of COVID-19 rRT-PCR or antigen test conducted by outside providers. Coverage of community care generally requires advance VHA authorization, resulting in a chart note in the electronic medical record. "Natural language processing of these notes was used to detect positive COVID-19 tests conducted outside the VHA (U.S. Department of Veteran Affairs, 2021d). Natural language processing involves computerized analysis of human language to extract information, for example, from text notations in electronic records. Note that natural language processing is a widely-used strategy in medical research (e.g., McCoy et al., 2016; Lynch et al., 2020; Yim et al., 2016; Murff et al., 2011). The SDR thus included positive and negative tests conducted at the VHA, and information about positive outside tests. To create a consistent timeframe, an index date variable was created to indicate the date of the first positive COVID-19 test or inpatient admission date closest to the first test within the 15 days prior to the test. We included COVID-19 tests from 02/20/20–11/01/2020.

2.3. Outcomes among those with COVID-19+

These included hospitalizations, ICU admissions, and death. To increase the likelihood that outcomes were related to COVID-19, only those occurring within 60 days of the index date were included. Thus, all outcomes had occurred by 12/31/2020.

2.4. Primary exposures: substance use disorder

ICD-10-CM SUD diagnoses received in 2019 were used, combining abuse and dependence because the criteria for these disorders form a unidimensional construct (Hasin et al., 2013). Substance disorders examined separately included cannabis (F12.1X, F12.2X), cocaine (F14.1X, F14.2X), opioids (F11.1X, F11.2X), stimulants (F15.1X, F15.2X) and sedatives (F13.1X, F13.2X). We also created an 'any SUD' variable by combining these, two additional categories too rare to examine separately (hallucinogen and inhalant use disorders, F16.1X, F16.2X, F18.10), and 'other' SUD (F19.1X, F19.2X), used when the specific substance is unknown. ICD-10-CM codes indicating remission were excluded.

For exploratory post hoc analyses of the mortality results, we created 2 additional SUD exposure variables. First, since SUD treatment could mitigate SUD effects on mortality through increased clinical monitoring and hospitalization at an early stage of COVID-19 illness that prevented later mortality (Kelly et al., 2021), we created a 3-level SUD variable

incorporating SUD treatment: no SUD (reference); any-SUD without SUD specialty treatment; and any-SUD with SUD specialty treatment. Treatment was indicated by any 2019 visits to a VHA SUD specialty care setting. Second, since SUD could affect mortality only in patients with severe SUD and having multiple polysubstance problems is an indicator of severity (Compton et al., 2021; Crummy et al., 2020), we created a 3-level variable indicating no SUD (reference), 1 SUD, or ≥ 2 SUDs.

2.5. Control covariates

ICD-10-CM medical conditions associated with poor COVID-19 prognosis included cardiovascular disease (I10-I28; I00; I34-I39; I42; I44-I50), respiratory disease (J40-J45; J47), diabetes (E08-E11; E13), HIV (B20; Z21), neoplasms (C00-C26; C30-C41; C43-C58; C72; C74-C80; C7A-C7B; C81-C96; D00-D49), and kidney disease (N18). Obesity is not associated with SUD but is associated with COVID-19 mortality (Zhang et al., 2021b) and is prevalent in VHA patients (Maciejewski et al., 2019), so we included body mass index (BMI), calculated from height and weight measured at the date closest to the index date. We also included ICD-10-CM mental disorders, as these may be related to SUD and to COVID-19 infection or poor prognosis (Vai et al., 2021; Fond et al., 2021; Ceban et al., 2021), including bipolar (F30.X, F31.X, F34.0), depressive (F32.X, F33.X, F34.1), psychotic (F20.X, F21, F22, F23, F24, F25.X, F28, F29), and posttraumatic stress disorders (F43.10, F43.12). Mental disorders in remission were excluded. Heavy drinking can impair lung functioning and increase risk for respiratory disease (Zhang et al., 2008; Yeligar et al., 2016; Mehta and Guidot, 2017), while smoking elevates risk for poor COVID-19 outcomes (Shi et al., 2021; Zhang et al., 2021a; Raines et al., 2021). Because both are associated with SUD, we also controlled for alcohol and nicotine use disorders (F10.1X, F10.2X; F17.2X, Z72.0, Z78.891). All diagnoses were from the 2019 EHR.

Demographic characteristics included sex (male/female), age (continuous) and race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, non-Hispanic Asian or Pacific Islander, non-Hispanic other, unknown). The 'other' category included American Indian/Alaskan Natives and patients with multiple race/ethnicities.

2.6. Analysis

Multivariable logistic regression modeled the association of 2019 any SUD diagnoses with 2020 COVID-19 outcomes, producing odds ratios (OR), adjusted odds ratios (aOR) and 95% confidence intervals (CI). We also modeled the association between 2019 substance-specific disorders and 2020 COVID-19 outcomes. When analyzing the substance-specific disorders, to account for multiple testing and potential increased risk of Type I error (incorrectly rejecting the null hypothesis of no association), we used an alpha level of 1%, calculating and reporting 99% confidence intervals. We evaluated any SUD and substance-specific disorders in separate models. We conducted analyses in 4 stages. The first was unadjusted for covariates, providing simple associations. The second adjusted for demographics (sex, race/ethnicity, age). The third further adjusted for medical conditions (including, for COVID-19+ outcomes, BMI≥30). The fourth further adjusted for mental, alcohol and nicotine use disorders to identify the unique effect of these additional, fully-legal SUDs on COVID-19 outcomes.

We also conducted 2 sets of post hoc exploratory analyses of mortality of mortality. In one, we replaced the binary any-SUD exposure variable with the 3-level variable incorporating information on SUD treatment. In the other, we replaced the binary any-SUD exposure variable with the 3-level SUD severity variable. These models were run using the same four adjustment stages described above.

3. Results

Table 1 shows characteristics of the full sample of 5,556,315 patients and the subset of the 62,303 COVID-19+ patients. In both groups, ~90% were male. In the full sample and COVID-19+ subset, respectively, 51.3% and 44.7% were ≥ 65 years, 66.8% and 52.5% non-Hispanic White, 17.6% and 28.5% non-Hispanic Black, and 5.5% and 10.1% Hispanic; 37.1% and 49.1% had cardiovascular disease, 20.9% and 30.7% had diabetes, 9.2% and 11.8% had neoplasms, 8.8% and 12.9% had respiratory conditions, 30.7% and 39.8% had a mental disorder, 6.0% and 7.4% had alcohol use disorder and 13.5% and 10.2% had nicotine use disorder. In the full sample and COVID-19+ subset, 3.8% and 4.7% had any ICD-10-CM substance use disorder, including 1.9% and 2.0% with cannabis use disorder, 1.1% and 1.3% with opioid use disorder, 0.9% and 1.7% with cocaine use disorder, 0.6% and 0.9% with stimulant use disorder and 0.2% and 0.3% with sedative use disorder.

Table 1
Characteristics of Veteran Health Affairs (VHA) patients: overall and those diagnosed with COVID-19.

	Patients with VHA visits in 2019 n = 5,556,315		VHA patients who tested positive for COVID-19 by 11/01/20 n = 62,303	
Characteristic	n	%	n	%
Gender				
Male	5,035,815	90.6	55,740	89.5
Female	520,500	9.4	6,563	10.5
Age				
18–34	482,300	8.7	5,588	9.0
35–49	870,996	15.7	11,016	17.7
50–64	1,353,797	24.4	17,863	28.7
65 and older	2,849,231	51.3	27,836	44.7
Race/ethnicity				
Non-Hispanic White	3,708,906	66.8	32,722	52.5
Non-Hispanic Black	975,858	17.6	17,750	28.5
Hispanic/Latino	304,965	5.5	6,289	10.1
Asian/Pacific Islander	97,900	1.8	952	1.5
Other	115,569	2.1	1,573	2.5
Unknown	353,126	6.4	3,017	4.8
Medical conditions in 2019				
Cardiovascular disease[a]	2,063,705	37.1	30,594	49.1
Respiratory condition[b]	491,419	8.8	8,019	12.9
Diabetes[c]	1,159,670	20.9	19,137	30.7
Kidney Disease[d]	272,532	4.9	5,602	9.0
Neoplasms[e]	511,789	9.2	7,333	11.8
BMI ≥ 30 [f]		–	32,044	51.7
HIV[g]	24,540	0.44	599	1.0
Psychiatric disorder[h]	1,707,815	30.7	24,815	39.8
Any SUD in 2019[i]	209,980	3.8	2,897	4.7
Cannabis Use Disorder	107,504	1.9	1,272	2.0
Cocaine Use Disorder	51,844	0.9	1,057	1.7
Opioid Use Disorder	58,705	1.1	837	1.3
Stimulant Use Disorder	35,440	0.6	585	0.9
Sedative Use Disorder	10,653	0.2	158	0.3
Fully-legal SUDs				
Alcohol Use Disorder[j]	332,492	6.0	4,627	7.4
Nicotine Use Disorder[k]	750,830	13.5	6,322	10.2

Notes: BMI=Body mass index; HIV=human immunodeficiency disorder; SUD=substance use disorder.
[a] Cardiovascular disease ICD-10-CM codes: I10-I28; I00; I34-I39; I42; I44-I50; [b] Respiratory condition ICD-10-CM codes: J40-J45; J47; [c] Diabetes codes: E08-E11; E13; [d] Kidney disease code: N18; Neoplasms codes: C00-C26; C30-C41; C43-C58; C72; C74-C80; C7A-C7B; C81-C96; D00-D49; [f] BMI is calculated from average height and weight closest to the index date; only available for VA patients diagnosed with COVID-19; [g] HIV codes: B20; Z21; [h] Psychiatric disorders include the following conditions: bipolar disorder (ICD-10: F30.X, F31.X, excluding in remission), depression disorders (F32.X, F33.X, excluding in remission), psychotic disorders (schizophrenia and related disorders: F20.X, F21, F22, F23, F24, F25.X, F28, F29), posttraumatic stress disorder (F43.10, F43.12). Patients with one or more of these disorders were categorized as having a psychiatric disorder. [I] Any drug use disorder including those listed in the table, plus those too rare or non-specific to include separately (hallucinogen use disorder, inhalant use disorder, other unspecified) based on medical record codes in 2019, excluding cases in remission. [j] Alcohol use disorder (F10.1X; F10.2X). [k] Nicotine disorder (F17.2X, Z72.0, Z78.891).

3.1. Positive COVID-19 test (COVID-19+; Table 2A–E)

Any SUD was associated with COVID-19+ in unadjusted models (OR=1.25), as were all substance-specific SUDs (significant OR range=1.08–1.85) except cannabis use disorder. After adjustments, all substance-specific SUDS remained associated with COVID-19 infection (aOR range=1.13–1.27) except cannabis use disorder (aOR=0.83).

3.2. Hospitalization (Table 3A–E)

Among COVID-19+ patients, 19.25% (n = 11,996) were hospitalized. In unadjusted models, any SUD was associated with hospitalization (OR=1.63) as were all substance-specific SUDs (OR range=1.28–2.52) except sedative disorder. After adjustments, any SUD and all substance-specific SUDs remained associated with hospitalization (aOR range=1.17–1.91).

3.3. ICU admission (Table 4A–E)

Among COVID-19+ patients, 7.71% (n = 4806) were admitted to an ICU. In unadjusted models, any SUD was associated with ICU admission (OR=1.27), as were cocaine and opioid disorders (OR=1.77, 1.38, respectively). After adjustment, no substance use disorders remained associated with ICU admission.

3.4. Mortality (Table 5A–E)

Among COVID-19+ patients, 5.84% (n = 3640) died within 60 days of the index date. In unadjusted models, any SUD (OR=0.46) and cannabis, cocaine, and stimulant disorders were inversely associated with mortality (OR=0.27–0.45). After adjustments, all inverse associations of SUDs with mortality were attenuated and no longer significant.

To better understand the mortality findings, we explored effects of SUD specialty treatment. Of the 2,897 COVID-19+ patients with SUD, 49.9% (n=1,445) had SUD specialty treatment in 2019. Replacing the any-SUD predictor with the 3-level SUD predictor reflecting treatment (no SUD; any SUD without SUD treatment; any SUD with 2019 SUD treatment; eTable 1), compared to patients with no SUD, patients with both untreated and treated SUD had lower unadjusted odds of mortality (OR=0.63 and 0.29, respectively). However, after adjustment, in the untreated patients, SUD was unrelated to mortality (aOR=0.98, CI=0.74–1.30), while an inverse relationship remained in the group who had SUD treatment (aOR=0.63, CI=0.42–0.95).

We also explored the role of SUD severity in the mortality results. Of the COVID-19+ patients with SUD, 62.5% (n=1,810) had 1 SUD and 37.5% (n=1,087) had ≥ 2 SUDs. Replacing the any-SUD predictor with the 3-level SUD severity predictor (eTable 2), having 1 or ≥ 2 SUDs were both associated with lower unadjusted odds of mortality (OR=0.44 and 0.49, respectively). Covariate adjustment attenuated the association for those with 1 SUD (aOR=0.75; CI=0.55–1.01), with a positive although non-significant association for the ≥ 2 SUD group (aOR=1.05; CI=0.72–1.54).

4. Discussion

In over 5.5 million veterans treated by the VHA in 2019, we investigated the relationship of substance use disorders (SUD) to testing positive for COVID-19, and among those positive, the association of SUD with hospitalization, ICU admission, and mortality. Analyses were conducted without adjustment, and with adjustment for demographic characteristics and medical conditions that increase the risk of poor COVID-19 outcome. We found that all SUDs except cannabis use disorder were associated with testing positive for COVID-19 (COVID-19+). Among COVID-19+ patients, 19.25% were hospitalized, 7.71% admitted to an ICU, and 5.84% died. SUDs were robustly associated with increased odds of hospitalization regardless of adjustments. After adjustment, no SUDs were associated with ICU admission. In contrast, in unadjusted results, any SUD and cannabis, cocaine, and stimulant disorders were inversely associated with mortality. However, associations became attenuated after adjustment and were no longer significant.

Previous studies of SUD and COVID-19 infection yielded conflicting results: one study without adjustment for medical conditions found a strong positive association (Wang et al., 2021), while another study with such adjustments found no association (Allen et al., 2021). While our results varied somewhat depending on the adjustments made in each model, in the final fully-adjusted models, all substance-specific SUDs were positively associated with COVID-19+ except cannabis use disorder. In studies of this relationship using EHR data, results may depend on factors influencing whether a COVID-19 test is conducted. VHA patients with SUDs other than cannabis use disorder may have been more likely to be tested because many of them were in SUD treatment, potentially providing closer monitoring of their medical status than others. Such monitoring and testing could help detect disease early and prevent further spread, but it complicates interpretation of findings on risk factors for infection. Since 2020, the VHA has greatly expanded its COVID-19 testing capacity (U.S. Department of Veteran Affairs, 2021c). Future studies should re-examine the relationship of SUD to infection using data from a broader sector of the VHA patient population.

Among VHA patients who tested positive for COVID-19, any SUD and all substance-specific SUDs were robustly associated with inpatient

Table 2
Association of substance use disorder (SUD) and testing positive for COVID-19 (COVID-19+) by 11/01/2020, Veteran Health Affairs patient, n = 5,556,315.

	A. Unadjusted		B. Adjusted for demographics[a]		C. Adjusted for demographics[a] and medical conditions[b]		D. Adjusted for demographics[a], medical[b], and psychiatric conditions[c]		E. Adjusted for demographics[a], medical[b], psychiatric conditions[c], and alcohol and nicotine use disorders	
	OR	(95%CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Any SUD	1.25	(1.19, 1.31)	1.09	(1.04, 1.15)	0.99	(0.94, 1.04)	0.90	(0.86, 0.95)	0.99	(0.94, 1.04)
	OR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)
Cannabis UD	1.06	(0.98, 1.14)	0.92	(0.85, 0.99)	0.85	(0.79, 0.92)	0.77	(0.72, 0.83)	0.83	(0.78, 0.91)
Cocaine UD	1.85	(1.71, 2.01)	1.37	(1.27, 1.49)	1.20	(1.10, 1.30)	1.09	(1.01, 1.19)	1.27	(1.17, 1.39)
Opioid UD	1.28	(1.17, 1.40)	1.26	(1.15, 1.38)	1.10	(1.01, 1.21)	1.02	(0.93, 1.12)	1.13	(1.03, 1.24)
Stimulant UD	1.49	(1.33, 1.65)	1.37	(1.24, 1.54)	1.23	(1.10, 1.37)	1.11	(1.00, 1.24)	1.27	(1.14, 1.43)
Sedative UD	1.33	(1.08, 1.63)	1.37	(1.12, 1.70)	1.20	(0.98, 1.48)	1.08	(0.88, 1.33)	1.20	(0.97, 1.47)

Notes: SUD=substance use disorder; OR=odds ratio; aOR=adjusted OR; CI=confidence interval
Each column shows results of a different model where the dependent variable is having a positive COVID-19 test up to November 1, 2020 among those who were VHA patients and had at least one VHA treatment visit in 2019.

[a] Adjusted for sex (male v. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Latino, Non-Hispanic Asian or Pacific Islander, Non-Hispanic Other), and age (continuous).

[b] Adjusted for the following medical conditions: cardiovascular disease, any respiratory condition, diabetes, kidney, neoplasms, and HIV.

[c] Adjusted for the following psychiatric disorders: bipolar, depressive, psychotic, and posttraumatic stress disorder.

Table 3
Association of substance use disorder (SUD) and hospitalization, among Veteran Health Affairs patients positive for COVID-19 (COVID-19+) up to 11/01/2020, n = 62,303.

	A. Unadjusted		B. Adjusted for demographics[a]		C. Adjusted for demographics[a] and medical conditions[b]		D. Adjusted for demographics[a], medical[b] and psychiatric conditions[c]		E. Adjusted for demographics[a], medical[b], psychiatric conditions[c], and alcohol and nicotine use disorders	
	OR	(95%CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Any SUD	1.63	(1.46, 1.82)	1.96	(1.75, 2.20)	1.79	(1.59, 2.01)	1.51	(1.47, 1.56)	1.17	(1.13, 1.21)
	OR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)
Cannabis UD	1.28	(1.08, 1.52)	1.68	(1.41, 2.03)	1.59	(1.32, 1.91)	1.38	(1.32, 1.44)	1.24	(1.07, 1.44)
Cocaine UD	2.52	(2.14, 2.98)	2.46	(2.07, 2.94)	2.21	(1.85, 2.64)	1.39	(1.32, 1.46)	1.75	(1.52, 2.02)
Opioid UD	1.59	(1.30, 1.95)	1.88	(1.52, 2.32)	1.65	(1.33, 2.04)	1.52	(1.45, 1.61)	1.41	(1.20, 1.67)
Stimulant UD	1.82	(1.44, 2.29)	2.27	(2.07, 3.38)	2.45	(1.91, 3.14)	1.52	(1.42, 1.61)	1.91	(1.58, 2.33)
Sedative UD	1.42	(0.89, 2.28)	2.26	(1.39, 3.70)	2.07	(1.25, 3.40)	1.68	(1.50, 1.87)	1.57	(1.07, 2.30)

Notes: SUD=substance use disorder; OR=odds ratio; aOR=adjusted OR; CI=confidence interval
Each column shows results of a different model where the dependent variable is having a positive COVID-19 test up to November 1, 2020 among those who were VHA patients and had at least one VHA treatment visit in 2019.
[a] Adjusted for sex (male v. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Latino, Non-Hispanic Asian or Pacific Islander, Non-Hispanic Other), and age (continuous).
[b] Adjusted for medical conditions: cardiovascular disease, any respiratory condition, diabetes, kidney, neoplasms, HIV, and BMI $\geq$ 30.
[c] Adjusted for psychiatric disorders: bipolar, depressive, psychotic, and posttraumatic stress disorder.

Table 4
Association of substance use disorder (SUD) and ICU admission among Veteran Health Affairs patients positive for COVID-19 (COVID-19+) to 11/01/2020, n = 62,303.

	A. Unadjusted		B. Adjusted for demographics[a]		C. Adjusted for demographics[a] and medical conditions[b]		D. Adjusted for demographics[a], medical[b], and psychiatric conditions[c]		E. Adjusted for demographics[a], medical[b], psychiatric conditions[c], and alcohol and nicotine use disorders	
	OR	(95%CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Any SUD	1.27	(1.07, 1.50)	1.48	(1.25, 1.76)	1.34	(1.12, 1.60)	1.32	(1.25, 1.39)	1.02	(0.96, 1.09)
	OR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)
Cannabis UD	0.90	(0.67, 1.20)	1.16	(0.86, 1.55)	1.08	(0.81, 1.46)	1.19	(1.09, 1.29)	0.90	(0.83, 0.98)
Cocaine UD	1.77	(1.39, 2.26)	1.68	(1.31, 2.16)	1.49	(1.15, 1.91)	1.17	(1.08, 1.28)	0.83	(0.75, 0.91)
Opioid UD	1.38	(1.02, 1.85)	1.60	(1.18, 2.16)	1.39	(1.03, 1.89)	1.33	(1.22, 1.46)	1.09	(0.996, 1.200)
Stimulant UD	1.17	(0.80, 1.70)	1.66	(1.13, 2.43)	1.52	(1.04, 2.25)	1.23	(1.09, 1.38)	0.91	(0.80, 1.02)
Sedative UD	0.55	(0.20, 1.50)	0.85	(0.31, 2.33)	0.77	(0.28, 2.13)	1.32	(1.07, 1.63)	1.02	(0.83, 1.26)

Notes: SUD=substance use disorder; OR=odds ratio; aOR=adjusted OR; CI=confidence intervalEach column shows results of a different model where the dependent variable is having a positive COVID-19 test up to November 1, 2020 among those who were VHA patients and had at least one VHA treatment visit in 2019.
[a] Adjusted for sex (male v. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Latino, Non-Hispanic Asian or Pacific Islander, Non-Hispanic Other), and age (continuous).
[b] Adjusted for medical conditions: cardiovascular disease, any respiratory condition, diabetes, kidney, neoplasms, HIV, and BMI $\geq$ 30.
[c] Adjusted for psychiatric disorders: bipolar,depressive, psychotic, and posttraumatic stress disorder.

Table 5
Association of substance use disorder (SUD) and mortality within 60 days of testing positive for COVID-19 (COVID-19+) up to 11/01/20 among Veteran Health Affairs patients, n = 62,303.

	A. Unadjusted		B. Adjusted for demographics[a]		C. Adjusted for demographics[a] and medical conditions[b]		D. Adjusted for demographics[a], medical[b], and psychiatric conditions[c]		E. Adjusted for demographics[a], medical[b], psychiatric conditions[b], and alcohol and nicotine use disorders	
	OR	(95%CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)	aOR	(95% CI)
Any SUD	0.46	(0.34, 0.61)	0.89	(0.66, 1.21)	0.86	(0.63, 1.16)	1.10	(0.96, 1.25)	0.96	(0.83, 1.10)
	OR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)	aOR	(99% CI)
Cannabis UD	0.27	(0.15, 0.47)	0.62	(0.35, 1.11)	0.62	(0.35, 1.10)	1.07	(0.88, 1.31)	0.93	(0.76, 1.14)
Cocaine UD	0.45	(0.28, 0.73)	0.77	(0.47, 1.27)	0.73	(0.44, 1.21)	1.02	(0.82, 1.27)	0.85	(0.67, 1.06)
Opioid UD	0.68	(0.43, 1.07)	1.21	(0.76, 1.93)	1.14	(0.71, 1.82)	1.26	(1.03, 1.56)	1.15	(0.93, 1.42)
Stimulant UD	0.34	(0.16, 0.71)	0.94	(0.44, 2.01)	0.94	(0.44, 2.02)	1.26	(0.93, 1.70)	1.08	(0.80, 1.46)
Sedative UD	0.31	(0.07, 1.40)	0.70	(0.15, 3.25)	0.69	(0.15, 3.24)	1.07	(0.63, 1.82)	0.94	(0.55, 1.61)

Notes: SUD=substance use disorder; OR=odds ratio; aOR=adjusted OR; CI=confidence interval
Each column shows results of a different model where the dependent variable is having a positive COVID-19 test up to November 1, 2020 among those who were VHA patients and had at least one VHA treatment visit in 2019.
[a] Adjusted for sex (male v. female), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic/Latino, Non-Hispanic Asian or Pacific Islander, Non-HispanicOther), and age (continuous).
[b] Adjusted for medical conditions: cardiovascular disease, any respiratory condition, diabetes, kidney, neoplasms, HIV, and BMI $\geq$ 30.
[c] Adjusted for psychiatric disorders: bipolar, depressive, psychotic, and posttraumatic stress disorder.

hospitalization before and after adjustments. These findings are consistent with several other studies (Wang et al., 2021; Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021). Taken as a whole, SUD appears to be associated with more severe COVID-19 requiring hospitalization even accounting for patients' co-existing medical and psychiatric conditions. This is also consistent with our findings on ICU admission and with other studies showing that SUD is associated with greater intensity of treatment among those hospitalized (Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021).

Of gravest concern is the relationship of SUD with COVID-19 mortality. Our unadjusted results suggested an inverse relationship between SUD and mortality; however, adjustment attenuated all of these associations. Our findings contrast with the prior study showing a positive relationship of SUD to COVID-19 mortality (Wang et al., 2021) that did not adjust for medical conditions; insufficient detail concerning this sample, design, and measures preclude full explanation of the discrepant results. Three other studies (Allen et al., 2021; Baillargeon et al., 2021; Qeadan et al., 2021) found a positive relationship of SUD with COVID-19 mortality before but not after adjustment for relevant medical conditions. Thus, results may vary depending on the adjustment strategy and population investigated. An additional study, also in veterans, found a protective effect of a non-specific substance use variable on COVID-19 mortality that was attenuated to the null after adjustment for medical conditions (Kelly et al., 2021). The authors speculated that their results were due to the strong VHA patient social and behavioral support programs, and called for empirical examination of this possibility. We did so, comparing COVID-19 mortality among those with no SUD, untreated SUD, and treated SUD. After adjustment, untreated SUD was unrelated to the odds of mortality, while those with treated SUD had lower odds of mortality, a finding consistent with research showing that among those with SUD, being in treatment reduces mortality risk (Paddock et al., 2017). In the present study, we therefore speculate that SUD treatment among those with SUD may have been protective against mortality due to greater contact with providers, leading to earlier identification and treatment of COVID-19. In addition to the contact with providers of substance disorder treatment, this speculation would be consistent with other studies showing that those with substance use disorders tend to be greater users of medical/healthcare services than others (de Weert-van Oene et al., 2017; Hunter et al., 2015). Further interrogation of these results was not possible due to small cell sizes, but is warranted as more data become available. We also explored the relationship of SUD severity to mortality, finding that odds of mortality were not elevated if only one SUD was present, but appeared elevated among those with two or more SUDs, although results were imprecise due to small cell sizes. While number of SUDs is not a direct SUD severity indicator, our results suggest that reported elevations in risk of mortality among those with SUD in other studies are driven by patients with severe SUDs. Future studies should examine this point when more data become available.

Study limitations are noted. Patients diagnosed with COVID-19 after 11/01/20 were not included in order to define a 60-day window for COVID-19 outcomes that occurred before the end of 2020. This may have limited the prevalence of COVID-19+ that was found in the VA (1.1%), since the last two months of the year were omitted in the numerator (case count) but the entire patient population was included in the denominator. In addition, patients who were tested and found to be positive outside the VA but whose test results were never noted in the patient charts would have been missed in the VA dataset. The rate of COVID-19+ that we found (1.1%) was lower than the U.S. rate overall for 2020 (16.8%; (Pei et al., 2021)). This lower rate in VA patients may have been due to missed cases, or, alternatively, due to the fact that VA patients are largely older and have fully-integrated healthcare, and may therefore have been more receptive to the ample messages about COVID-19 mitigation strategies that were disseminated to all VA patients in 2020, helping them to minimize their infection rates. Another limitation is that using the retrospective cohort design, covariates were from 2019; future studies could incorporate diagnoses and care utilization up to the COVID-19 index date. Our analyses of COVID-19 infection did not incorporate information on external circumstances that may have affected infection rates, e.g., state policies and COVID-19 regulations, including preventive measures such as mask mandates. In addition, the VHA SDR did not record negative COVID-19 tests conducted outside the VHA, limiting complete knowledge about those tested and leaving open the possibility of misclassification. Some patients may have had SUDs unknown to providers and not noted in the EHR, or hospitalizations or ICU treatment outside the VHA not noted in the EHR. Environmental variables not included in our study (e.g., county rurality, density of treatment facilities, poverty) should be examined in future studies. Finally, VHA patients do not represent all veterans or all US adults, limiting generalizability.

In contrast, however, the study had several considerable strengths. These included the large sample size, transparent source of patient data, and electronic health records from a nationwide integrated healthcare system that provided a unique opportunity to investigate SUD and COVID-19 in a manner not possible in other studies, and to explore possible explanations of the reasons that SUD was not related to increased mortality risk in the VHA patients. We also provide information from what can be considered an index or reference period in the COVID-19 pandemic, namely, the period in which vaccines were not yet available and the Delta variant was starting to emerge. Future studies will need to incorporate information on vaccine status and subsequent pandemic periods defined by predominant virus strain when evaluating the relationship of SUD to the COVID-19 outcomes.

In conclusion, data from over 5.5 million VHA patients suggest that having a substance use disorder increased the odds of a positive COVID-19 test, and among those infected, inpatient hospitalization. However, SUD was not associated with COVID-19 mortality, perhaps due to the high proportion of patients with SUD who received SUD treatment and hence were likely to have relatively regular contact with providers. The VHA strongly supports providing evidence-based SUD care to patients who need it, in contrast to the fragmented SUD treatment in much of the rest of the US healthcare system. In an integrated healthcare system with adequate access to SUD treatment, an unanticipated benefit may be closer monitoring of patients' medical status, ensuring that when patients need it, they receive medical treatment and ultimately survive serious illnesses.

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CRediT authorship contribution statement

Deborah S. Hasin: concept and design; acquisition, analysis, or interpretation of data; drafting of manuscript; critical revision of manuscript; obtained funding; administrative, technical, or material support; Supervision. **David S. Fink**: data analysis, Writing – review & editing. **Mark Olfson**: Conceptualization or design, interpretation of data, revising critically for intellectual content. **Andrew J. Saxon**: conceptualization, data collection, reviewing/editing. **Carol Malte**: data collection/analysis, manuscript review. **Katherine M. Keyes**: writing, reviewing/editing. **Jaimie L. Gradus**: conceptualization, writing, editing/reviewing. **Magdalena Cerdá**: interpretation of results, reviewing/editing for critical content. **Charles C. Maynard**: reviewing/editing. **Salomeh Keyhani**: reviewing/editing. **Silvia S. Martins**: reviewing/editing. **Ofir Livne**: reviewing/editing. **Zachary L. Mannes**: reviewing/editing. **Scott E. Sherman**: writing, reviewing/editing,

supervision. **Melanie M. Wall**: conceptualization, writing, data analysis.

Conflicts of interest

Dr. Hasin reports funding from Syneos Health for unrelated projects on the validation and use of a measure of opioid addiction among patients with chronic pain. Andrew J. Saxon reports the following disclosures that are outside the submitted work: advisory board for Indivior, Inc., advisory board for Alkermes, Inc., travel support for Alkermes, Inc., and royalties for UpToDate, Inc. All other authors report no conflicts of interest.

Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jece.2021.105652.

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