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Assessing the risk of COVID-19 reinfection and severe outcomes among individuals with substance use disorders: a retrospective study using real-world electronic health records

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ABSTRACT

Objective Despite advancement in vaccines and treatments for COVID-19 over the past 2 years, many concerns remain about reinfection and waning immunity against COVID-19 and its variants, especially among people with substance use disorder (SUD). The study assessed the risk of COVID-19 reinfection and severe illness among adults with SUD and their vaccination status to inform management in this vulnerable population as the pandemic continues.

Design Retrospective cohort study.

Setting Nationwide electronic health records (TriNetX database) in the USA among adults with COVID-19 infection from January 2020 to June 2022.

Participants Adults (age ≥18 years) who were infected by COVID-19, excluding those who had cancer or lived in nursing homes or palliative care facilities.

Outcome measures COVID-19 reinfection was defined as a new diagnosis after 45 days of the initial infection. Logistic regression was applied to assess the OR of COVID-19 reinfection and severe outcomes within 30 day of reinfection for adults with alcohol (AUD), opioid (OUD), cocaine (CUD), stimulant (STUD), cannabis (CAUD) and other use disorders, controlled for demographic and comorbid conditions.

Results The SUD cohort was 13%–29% more likely to be reinfected by COVID-19 and had significantly higher 30-day mortality. Adults with AUD, STUD and OUD were at greater risks (adjusted ORs, AORs=1.69–1.86) of emergency department, hospital and intensive care admissions after 30 days of reinfection. Individuals with SUD and multiple vaccines doses were associated with decreased risks of worse COVID-19 outcomes. Lower COVID-19 reinfection rates (AORs=0.67–0.84) were only found among individuals with AUD, CUD or CAUD who had COVID-19 vaccination.

Conclusions Individuals with SUD had greater risks of COVID-19 reinfection and poor outcomes, especially those with OUD, STUD and AUD. Multiple vaccinations are recommended to reduce severe illness after COVID-19 reinfection in the SUD population.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used large-scale electronic health record-based data, which provide a wide range of medical, psychiatric and demographic factors to assess the risk of COVID-19 reinfection and severe complications among adults with substance use disorders.
⇒ Our findings can help elucidate substance use disorder subtypes that are at the greatest risk of COVID-19 reinfection and poor outcomes, and thus, could inform public health effort to promote the importance of multiple vaccinations in the subtypes.
⇒ We could not control for data completed at facilities outside of the participating research network, and therefore, there may be uncaptured information with use of the electronic health records, potentially limiting the generalisability of the results.
⇒ Further limitations of this study consist of inability to control for socioeconomic contexts and inability to quantify severity or stage of comorbid conditions, which may require future research to address the impact of these factors on COVID-19 reinfection.

INTRODUCTION

The COVID-19 pandemic has led to unprecedented public health challenges in the USA, especially for individuals experiencing drug abuse and addiction problems.[1 2] Lacking access to screening and treatments during the pandemic has resulted in care disruption for people with substance use disorder (SUD) and those in recovery. Individuals with SUD are found to have increased risk of COVID-19 infection and severe complications[2] due to compromised immune systems,[3] respiratory-related functions[4] and cardiovascular conditions.[5] With the continuation of the COVID-19 pandemic, persons previously recovered from COVID-19 can be reinfected by the disease. Despite advancement in vaccines and treatments for COVID-19 over the past 2 years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD.

The risk of COVID-19 infection and outcomes was also found to vary by the subtype of SUD.[4 6 7] The highest risk of infection was found among individuals with opioid use disorder (OUD), followed by cocaine use disorder (CUD) and alcohol use disorder (AUD).[4] People with AUD or OUD tended to have severe complications likely to require hospital admission and intensive care compared with those with cannabis use disorder (CAUD) and CUD. Specific pharmacological effects from different drugs might contribute to this outcome variation among SUD subtypes.

The efficacy of COVID-19 vaccination also varies among individuals with multiple chronic conditions and weak immune systems.[8] Compared with vaccinated persons without SUD, vaccinated persons with SUD still experience significantly greater COVID-19 infection risk,[9] potentially due to higher prevalence of comorbid conditions and negative socioeconomic statuses in the SUD population. As more people with SUD receive COVID-19 vaccination, additional research is required to examine the vaccine effect on preventing COVID-19 reinfection and poor outcomes.

Furthermore, individuals with SUD are more likely to have coexistent mental health conditions, including depression, anxiety and bipolar disorder,[10–13] which can be risk factors for severe COVID-19 reinfection.[14 15] The SUD population has also been shown at increased risk of hypertension, obesity, diabetes and cardiovascular conditions.[2] These conditions can negatively influence immune and respiratory systems, increasing vulnerability to the SARS-CoV-2 virus infection[16] and its complications.[17 18] These co-occurring mental and physical conditions may also lead to a higher reinfection risk.

The large scale of the pandemic has raised the need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for people with SUD. While prior research has found higher COVID-19 infection rates among persons with SUD, little is known about how reinfection and outcomes vary by vaccination status and SUD subtype. The objective of this study is to assess the risk of COVID-19 reinfection and severe illness among adults with SUD to inform clinical treatment and public policy decisions pertaining to this unique population.

METHODS

Study design and data sources

This was a retrospective cohort study using electronic health records (EHRs) of 57 healthcare organisations sourced from the TriNetX research network database (Cambridge, Massachusetts, USA). TriNetX is a large health data network that contains deidentified EHRs (demographics, diagnoses, procedures, medications and laboratory tests) of more than 80 million patients from participating healthcare organisations predominately from the USA. Data in the TriNetX database have undergone extensive curation and mapping to common clinical entities and terminologies to ensure high usability as well as consistency with the Reporting of studies Conducted using Observational Routinely collected Data guidelines.[19]

Cohort description

The study population consisted of adults (age ≥18 years) who were diagnosed with COVID-19 between 1 January 2020 and 30 April 2022, based on the combination of one or more disease indicators, including the International Classification of Diseases, Tenth Revision, (ICD-10) diagnosis codes and positive laboratory test results (see online supplemental table S1 for details).[20 21] The initial COVID-19 infection episode during the study assessment period was considered the 'index' infection. Individuals whose index COVID-19 infection occurred prior to the age of 18 were excluded from the study. Health data for adults with a valid index infection continued to be collect through 30 June 2022, to capture additional COVID-19 reinfection. Individuals were excluded if they had cancer or lived in nursing homes or palliative care facilities prior to COVID-19 infection.

Substance use disorders

This analysis focused on the relationship of COVID-19 reinfection with the following SUD subtypes: AUD, OUD, CUD, stimulant (STUD), CAUD and other (other-UD). The other-UD category included sedative use disorder, hallucinogen use disorder, inhalant use disorder and other psychoactive use disorder. A person's SUD diagnosis must have predated the index COVID-19 infection to be identified with the condition. Each subtype measure included a binary variable (yes/no) indicating whether patients had the specific subtype of SUD. This study allowed for inclusion of individuals with multiple SUD subtypes, as is common in the clinical setting. Regression modelling was able to control for each subtype so that interpretation of the effect of each individual SUD subtype can be observed. The list of diagnosis codes for each SUD subtype is provided in online supplemental table S1.

COVID-19 vaccination

COVID-19 vaccination was identified through the presence of COVID-19 vaccine codes specified by the Current Procedural Terminology of the American Medical Association (see online supplemental table S1). The total number of COVID-19 vaccine doses of individuals experiencing reinfection was computed based on the sum of vaccine doses received prior to the reinfection incident. The number of COVID-19 vaccinations of individuals without reinfection was estimated as the sum of vaccine doses received during the study period. To understand the effect of vaccine doses, this analysis categorised COVID-19 vaccine dosing to three dose levels: 0 (unvaccinated), 1 (one dose only) and 2+ (people receiving at least two doses).

Baseline demographics and comorbid characteristics

Patient demographics and health comorbidities were extracted at the time of the first COVID-19 infection. The

available demographic data included sex (male/female), age group (18–39, 40–65, 65+), ethnicity (Hispanic/non-Hispanic) and race (white/black/other). Data on conditions known to be associated with the COVID-19 complications were also collected, including the diagnoses of medical conditions (obesity, diabetes, chronic kidney disease, cardiovascular disorders[17 20]) and mental health disorders (depression, anxiety, bipolar).[22] Because the current status of tobacco use/smoking was unavailable in the EHR data, the presence of the tobacco/nicotine use disorder diagnoses was used to serve as the proxy of smoking/tobacco use. Detailed information on the diagnostic codes for the conditions extracted in this study is provided in online supplemental table S1.

Outcome measures

COVID-19 reinfection was defined as a new COVID-19 diagnosis reported 45 or more days after the first infection. Reinfection analysis was completed based on the first reinfection; subsequent reinfections were not analysed. Because a person could be infected by the virus multiple times, the reinfection analysis of the study focused on the reinfection incident after the first COVID-19 episode in the study period. The reinfection indicator was given a value of 1 for individuals reinfected by COVID-19; otherwise, a value of 0 was assigned to the reinfection indicator.

Severe COVID-19 outcomes were identified by emergency department (ED) visits, hospital admission, intensive care unit (ICU) stay and death within 30 days of reinfection. These outcome measures were captured as dichotomous variables, with '1' assigned if a target outcome occurred within 30 days of reinfection, and '0' assigned if a target variable did not occur in 30 days of reinfection.

Data analysis

Descriptive statistics were computed to summarise sample characteristics in relation to each outcome measure. Differences in continuous variables were compared using the t-test for parametric or equivalent tests for non-parametric analyses. Proportion differences in categorical variables were evaluated using the χ^2 test.

Multiple logistic regression modelling was used to assess the risk of reinfection and serious medical complications of COVID-19, including ED visit, hospitalisation, ICU admission and death within 30 days of COVID-19 reinfection (binary dependent variables, yes/no), controlled for demographics and both medical and mental health comorbidities known to contribute to the COVID-19 severity risk. A subcategory analysis was also conducted by each SUD subtype to assess the impact of vaccination on the risk of reinfection and severe outcomes.

The regression analysis was conducted using the maximum likelihood estimation method, which provided regression coefficients, SEs, Wald 95% CIs for the coefficients and p values for each of the model variables. The likelihood ratio test, the global test of parameters in the regression model, was assessed first; if the model's likelihood ratio test was significant (p<0.05), individual variables' coefficients and p values were then considered. The adjusted OR (aOR) and 95% CI of each variable was also calculated to predict the risk of the outcome measure. The significance level was determined based on two-tailed p<0.05. All statistical analyses were performed using PROC LOGISTIC procedure (VV.9.4, SAS Institute).

Patient 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 2 682 433 adults met the study criteria between 1 January 2020 and 31 July 2022, including 872 446 (32.5%) with COVID-19 reinfection and 1 809 987 (67.5%) without reinfection. The time between the initial infection and reinfection for persons with SUD (mean=211 days, median=164 days) was shorter than the time for individuals without SUD (mean=229 days, median=187 days). Of all people reinfected by COVID-19, about 18.7% (163 012) were admitted to ED, 5.2% (45 362) to hospital, 1.5% (12,782) to ICU and 0.7% (5858) died within 30 days of reinfection. Compared with those without reinfection, the reinfection group had a greater percentage of females and white individuals, was slightly younger, and had higher prevalence of chronic medical and mental health conditions, and smoking/tobacco dependency. COVID-19 reinfection was more common in persons with SUD than those without SUD (45.6% vs 32.2%, p<0.01). Reinfection prevalence was inversely proportional to the number of vaccination doses received for SUD and non-SUD persons. The details of the summary statistics are provided in online supplemental table S2.

Substance use disorder

Regression analysis controlled for medical and mental health comorbidities showed increased risk of COVID-19 reinfection among individuals with SUD compared with those without SUD. The aOR (all significant to 95% CIs) of the reinfection rate was 1.29 for OUD, 1.28 for CUD, 1.26 for AUD, 1.18 for CAUD, 1.13 for STUD and 1.22 for the other SUD type (see figure 1). Similarly, people with SUD diagnoses were more likely to be admitted to ED/hospital/ICU and die within 30 days of reinfection, though there was no significant association found between 30-day mortality and CUD. AUD was found to have the highest risk of hospitalisation (aOR 1.77, 95% CI 1.66 to 1.89), ICU (aOR 1.86, 95% CI 1.67 to 2.07) and 30-day mortality (aOR 1.76, 95% CI 1.46 to 2.12), while STUD showed the highest risk of ED visits after reinfection (aOR 1.69, 95% CI 1.57 to 1.83). Both OUD and STUD were consistently found in the top three highest risks of other severe outcome measures. The details of the

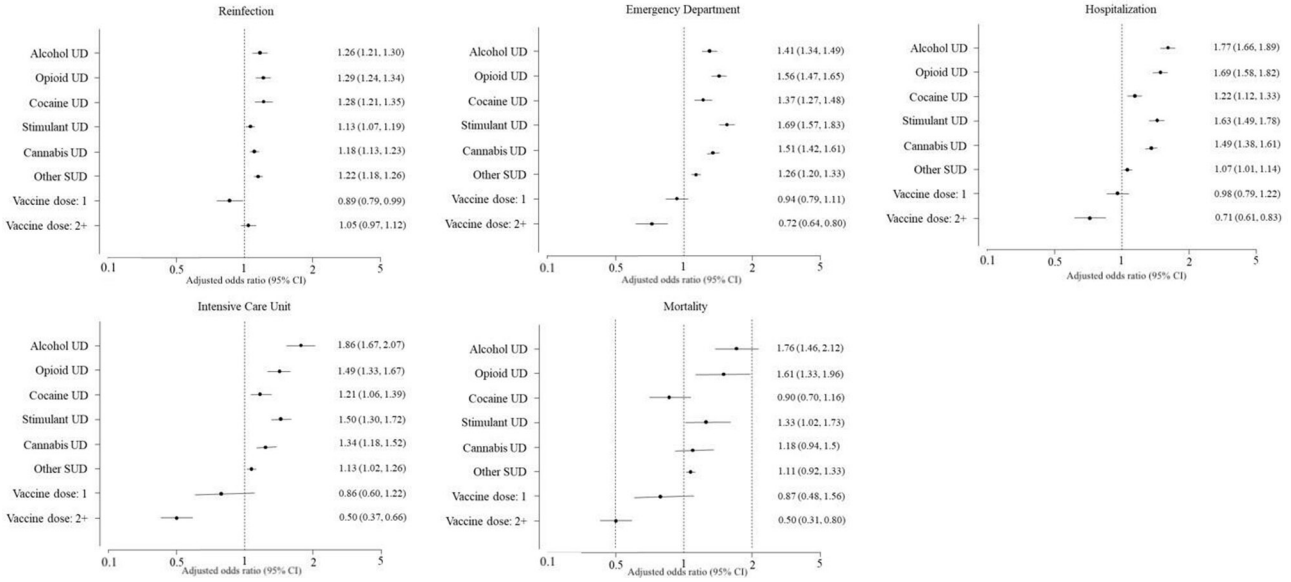

Figure 1 Risk of COVID-19 reinfection and severe outcomes by SUD subtype and vaccination. SUD, substance UD; UD, use disorder.

regression models are provided in online supplemental table S3.

Vaccination

Overall vaccination effect

Persons receiving COVID-19 vaccination generally showed a lower rate of COVID-19 reinfection and severe outcomes, though no significant association was found between vaccination and the 30-day mortality rate (see figure 1). Compared with unvaccinated individuals, people who received one COVID-19 vaccine dose were 11% less likely to be reinfected than those unvaccinated (aOR 0.89, 95% CI 0.79 to 0.99). No significant difference was found in the reinfection rate between unvaccinated individuals and those receiving at least two doses. The analysis showed that individuals with two or more COVID-19 vaccinations had significantly lower 30-day admission rates to ED (aOR 0.72, 95% CI 0.64 to 0.83), hospital (aOR 0.71, 95% CI 0.61 to 0.83), ICU (aOR 0.50, 95% CI 0.37 to 0.66) and 30-day mortality (aOR 0.50, 95% CI 0.31 to 0.80), compared with those unvaccinated. There were no significant differences between these groups in ED visits, hospital admission or ICU admission between unvaccinated individuals and those receiving only one dose.

Vaccination effect by SUD subtype

Mixed results were found in the vaccination effect on COVID-19 reinfection and severe outcomes by SUD subtype (see table 1). In the AUD and CAUD groups, lower reinfection rates were shown only among people receiving one dose (aOR 0.84, 95% CI 0.73 to 0.98 for AUD; aOR 0.76, 95% CI 0.59 to 0.98 for CAUD) than individuals unvaccinated. Persons with CUD were 33% less likely to be reinfected when they received two vaccinations or more (aOR 0.67, 95% CI 0.50 to 0.89). There was no association between vaccination and reinfection in the OUD, STUD and other SUD groups.

The vaccination effect on ED, hospital and ICU admissions also varied by SUD subtype. Table 1 shows that, in the AUD, OUD, STUD, CAUD and other SUD groups, individuals with multiple vaccinations were found 25%–76% less likely to utilise ED and ICU services after being reinfected by COVID-19, compared with the unvaccinated. Moreover, in the AUD and other SUD groups, people receiving two or more doses were found 28%–36% less likely to require hospitalisation after COVID-19 reinfection than the unvaccinated. In general, there was no significant difference in ED, ICU and hospital admissions between unvaccinated individuals and those receiving only one dose.

Lastly, compared with the unvaccinated, two or more vaccine doses showed decreased risk of 30-day mortality among individuals with AUD (aOR 0.53, 95% CI 0.30 to 0.93) and the other SUD types (aOR 0.39, 95% CI 0.17 to 0.89). People with STUD and at least one vaccine dose were also found 40% less likely to die within 30 days of reinfection (aOR 0.60, 65% CI 0.45 to 0.80).

DISCUSSION

SUDs and COVID-19 reinfection

The COVID-19 pandemic has presented persistent healthcare challenges, particularly among individuals with a history of SUDs. Literature shows that persons with SUD are at increased risk of contracting SARS-CoV-2, requiring hospitalisation and dying from the virus infection, due to compromised immune systems and comorbid conditions.[4 6 14] As the community spread of COVID-19 continues, individuals recovered from COVID-19 can be reinfected by the SARS-COV-2 virus and its variants.

Table 1 Effect of vaccine dose on COVID-19 reinfection and outcomes

SUD subtype/ vaccine dose (ref: none)	Reinfection, aOR (95% CI)	Individuals with COVID-19 reinfection: outcomes within 30 days of reinfection			
		Emergency department, aOR (95% CI)	Hospitalisation, aOR (95% CI)	Intensive care, aOR (95% CI)	Death, aOR (95% CI)
Alcohol					
1	0.84 (0.73 to 0.98)	0.92 (0.73 to 1.16)	0.99 (0.76 to 1.31)	0.75 (0.48 to 1.18)	1.09 (0.57 to 2.1)
2+	1.02 (0.93 to 1.13)	0.68 (0.58 to 0.78)	0.64 (0.52 to 0.78)	0.49 (0.34 to 0.70)	0.53 (0.3 to 0.93)
Opioid					
1	0.90 (0.72 to 1.12)	0.96 (0.70 to 1.32)	1.28 (0.90 to 1.81)	0.70 (0.37 to 1.31)	0.39 (0.10 to 1.61)
2+	1.06 (0.89 to 1.25)	0.64 (0.50 to 0.81)	0.77 (0.57 to 1.03)	0.50 (0.29 to 0.87)	0.49 (0.20 to 1.22)
Cocaine					
1	0.88 (0.64 to 1.22)	1.44 (0.88 to 2.37)	0.89 (0.54 to 1.46)	0.60 (0.26 to 1.41)	0.22 (0.03 to 1.58)*
2+	0.67 (0.50 to 0.89)	0.75 (0.48 to 1.15)	1.32 (0.84 to 2.06)	0.43 (0.17 to 1.07)	
Stimulant					
1	0.84 (0.61 to 1.16)	1.02 (0.62 to 1.67)	1.57 (0.97 to 2.55)	0.84 (0.37 to 0.90)	0.60 (0.45 to 0.80)*
2+	0.85 (0.66 to 1.10)	0.46 (0.32 to 0.67)	0.74 (0.48 to 1.14)	0.24 (0.09 to 0.69)	
Cannabis					
1	0.76 (0.59 to 0.98)	0.95 (0.63 to 1.41)	1.04 (0.66 to 1.64)	0.26 (0.08 to 0.85)	0.25 (0.06 to 1.02)*
2+	1.21 (1.01 to 1.46)	0.67 (0.52 to 0.86)	0.90 (0.66 to 1.24)	0.26 (0.11 to 0.61)	
Other					
1	0.95 (0.80 to 1.13)	0.99 (0.77 to 1.29)	0.91 (0.66 to 1.26)	0.74 (0.43 to 1.26)	0.82 (0.33 to 2.04)
2+	1.02 (0.90 to 1.16)	0.75 (0.62 to 0.89)	0.78 (0.61 to 0.99)	0.35 (0.21 to 0.59)	0.39 (0.17 to 0.89)

*Individuals with 1 and 2+ doses were combined into one category to ensure sufficient testing power.
aOR, adjusted OR; SUD, substance use disorder.

Despite potential protection from previous COVID-19 infections or vaccines, little is known about the frequency and severity of reinfections in this vulnerable population. The study used a nationwide EHR database to assess the risk for COVID-19 reinfection and severe outcome adults with SUD. The use of the nationwide database allowed researchers to capture the longitudinal clinical events of the large patient population, to generate important insights into the frequency and severity of COVID-19 reinfection among individuals with SUD at the population level.

Our study shows that, in general, persons with medical/mental health comorbidities are more likely than those without medical/mental comorbidities to be reinfected by COVID-19, regardless of the presence of SUD diagnoses. Controlled for medical and mental health comorbidities, the study reveals that people with SUD are more likely to be reinfected by COVID-19, suggesting that persons with SUD continue to experience greater risk of reinfection after recovering from previous COVID-19 illness. Higher reinfection risk may stem from the same causative factors of higher initial infection risk among SUD patients with coexisting mental and behavioural problems,[23 24] whose conditions may limit their ability to adopt critical safety and preventive measures about COVID-19.[25 26] Individuals with SUD are also likely to experience poverty and other socioeconomic disadvantages.[27] They tend to live in large households without sufficient self-isolation space or work in jobs unable to provide them remote options, which put them at greater risk of reinfection by the virus.

Severity of COVID-19 reinfection

People with SUD have also been shown more likely to suffer severe complications from COVID-19 infection.[4] Our study also found that adults with SUD were at increased risk of experiencing severe illness after becoming reinfected by COVID-19, compared with those without SUD. The relatively high rate of severe outcomes could be contributed to their existing cardiac, respiratory and immune problems potentially caused by drug abuse. The population with SUD is also known to have poor health insurance coverage and stigma concern.[28] These barriers can pose challenges to people with SUD seeking treatment for COVID-19 in time, leading to delay in care and worsened outcomes.

Moreover, our analysis found that the risk of severe COVID-19 outcomes varied by the subtype of SUD. OUD, STUD and AUDs were consistently shown a greater likelihood to require ED visits, hospitalisation and ICU admissions, as well as die within 30 days of reinfection. COVID-19 further intensified challenges and stress on already limited

healthcare resources and workforce required to care for individuals in the midst of the alcohol, opioid and stimulant overdose crisis.

COVID-19 vaccination, reinfection and severity

Despite advancement in vaccines and treatments for COVID-19 in the past 2 years, many concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. While one vaccination decreased reinfection in individuals with SUD, multiple vaccinations may not increase protection against reinfection. This may be due to a multitude of viral and host factors. Recent research suggests that there may be immune system fatigue with emergence of new variants over time,[29] and with increased time since pandemic onset comes increased likelihood that individuals have received more than one vaccine. In addition, there may be perceived protection from having received multiple vaccinations which may result in decreased social distancing, masking, and other preventive measures, thus increasing infection risk.[30] Individuals highly recommended to receive boosters also likely have increased immunological comorbidities that put them at higher risk of COVID-19 reinfection. Some newer studies are showing that vaccine-induced protection against infection may be short-lived.[31]

Recent research has also suggested that the protective effect of the COVID-19 vaccination against hospitalisation and death from severe COVID-19 illness may gradually reduce after multiple vaccine doses[32]; however, our study shows multiple vaccinations are associated with a reduction of severe outcomes in individuals with SUD, while one vaccination was not. This suggests that ≥2 vaccinations may be required for an adequate immunological response in those with SUD. Public health strategies to mitigate reinfection risk in this population may benefit from counselling on the importance of multiple vaccinations.

Limitations

Most data on the impact of SUDs on COVID-19 outcomes came from a single hospital or regional health systems, which are costly, time and effort intensive, and often based on non-representative samples. The strengths of this study include leveraging real-world EHR data from a large nationwide research network which offers access to existing longitudinal, clinically relevant, real-life data on all health system's patients during the COVID-19 pandemic period. The use of the big dataset could also enable evaluation of rare or underdiagnosed conditions on a larger scale. This study has limitations common to all research using EHR data. First, the COVID-19 diagnosis or testing could have been completed at facilities outside of the participating research network, and therefore, be uncaptured in the TriNetX database. The index episode of a person's COVID-19 infection in the analysis was the first known record observed in the database, but it might not be the first ever COVID-19 infection record. Second, the overall percentage of patients with any COVID-19 vaccination of the analysis was lower than the CDC reported national average of vaccinated individuals in the USA, suggesting that those marked as unvaccinated may have received vaccination outside of the research network. Third, we were unable to determine whether a given SUD was active vs in remission at the time of the COVID-19 infection. Fourth, our study sample showed that, in the population with SUD, 66% were diagnosed with one SUD type, 19% diagnosed with two SUD types and 15% diagnosed with three or more SUD types. While the study applied multiple regression modelling to assess the main effect of each SUD type, the regression analysis did not include interaction terms to assess the effect of polysubstance use disorders. We were unable to directly estimate the risk of reinfection for people with multiple SUD types. Nonetheless, all SUD types had an OR greater than one, suggesting that persons with multiple SUD types would be more likely to be reinfected or experience poor outcomes after reinfection. Fifth, the EHR data did not contain information related to patients' socioeconomic contexts (eg, insurance, education and income levels), which would have been included as confounders in the analysis. Sixth, we were unable to quantify the severity or stage of comorbid conditions in relation to COVID-19 infection, which may limit the generalisability of comorbid outcomes. (Eg, well-controlled diabetes might be expected to carry greater health risks than uncontrolled diabetes.) Lastly, there may be unobserved or unknown confounders present that we did not account for in statistical analysis. These limitations are partially mitigated by the large sample size available through the TriNetX database, which enables data analysis across a wide range of medical, psychiatric and sociodemographic factors. Future analyses using advanced data mining techniques and advanced analytical approaches, using artificial intelligence or machine learning algorithms, might better elucidate currently unidentified yet important confounders.

CONCLUSIONS

The COVID-19 pandemic has disproportionately affected people with SUD, who are at greater risk of severe COVID-19. Despite the increased availability of vaccines and treatments for COVID-19 in recent years, concerns remain about reinfection and waning immunity against the SARS-CoV-2 virus and its variants, especially among people with SUD. Our study found that adults with SUD were at greater risk of being reinfected by COVID-19, regardless of the SUD subtype. They were more likely to be admitted to the ED, hospital and ICU within 30 days of reinfection. Significantly, higher 30-day mortality was also observed among individuals with OUD, STUD or AUDs. Mixed findings were shown in vaccine effects among different SUD subtypes. People with two or more vaccine doses were generally found to have lower rates of severe illness and mortality, compared with those with one or no dose. However, the vaccination effect was undetermined in the population with CUD. The persistent pandemic has raised challenges to our healthcare practice, and there remains a need for better knowledge of containing ongoing and emerging outbreaks to reduce subsequent mortality and morbidity for individuals with SUD. The big data analytics developed in this study offers researchers a method to

routinely assess COVID-19 impacts and vaccines effectiveness, to facilitate clinical decisions and inform public health policy.

Contributors All authors were involved in revisions, read and approved the final manuscript. W-JT is responsible for the overall content as the guarantor. W-JT contributed to the planning and design of the work, literature review, data analysis, interpretation and writing the manuscript. HMK and RPL contributed to literature review, data analysis, interpretation and writing the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The study used deidentified TriNetX research datasets and was determined to be exempt from the Institutional Review Board oversight by the Pennsylvania State University's Human Research Protection Programme.

Provenance and peer review Not commissioned; externally peer reviewed.

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