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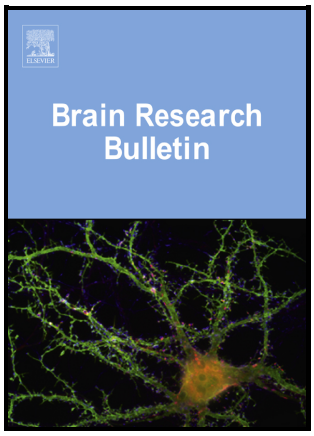

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Alcohol, nicotine, and COVID-19: A retrospective study of health outcomes in central Pennsylvania

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Abstract

Individuals with substance abuse disorder are at increased risk for the development of severe disease following COVID-19 infection. Furthermore, individuals in rural populations where access to healthcare is limited and rates of substance abuse tend to be higher are at increased risk compared to other regions. The Penn State Health Network serves 29 counties in central Pennsylvania that are largely rural. The current study assessed the electronic medical records for individuals in this population that were reported as having alcohol dependence, nicotine dependence or both (co-users) in addition to individuals with no history of drug use and the rate of developing primary and secondary health outcomes following COVID-19 infection. All patients in this study were determined to be COVID+ while in care. We found that overall, risk for requiring ventilation, developing pneumonia, and mortality within 30 days of diagnosis all increased with any substance use history, across both males and females and across all age groups. Moreover, rates of these outcomes were considerably higher in patients that were both

alcohol and nicotine dependent suggesting additive effects of co-use. Rates of secondary effects also increased substantially across all use categories with these patients showing greater risk of developing liver, kidney, and pancreas maladies compared to patients with no history of substance use. Taken together, these findings reinforce previous studies showing that substance use increases the risks of significant disease following COVID-19 infection, giving insights into the health disparities that exist in rural populations.

Introduction

The onset of the COVID-19 pandemic brought on significant new challenges in healthcare. A seemingly novel threat but with similar implications to previous disease outbreaks – namely that individuals with pre-existing conditions and comorbidities would prove to be at the greatest risk for the development of severe illness (1). In particular, individuals with substance use disorders (SUD's) are at greater risk (2, 3), even those that are fully vaccinated against COVID-19 (4). In the United States, 11.7% of the adult population were actively involved in substance abuse as of 2021 and the prevalence of substance use disorders has only risen during the pandemic (2).

Alcohol and nicotine abuse are two of the most common causes of preventable death world-wide (5). Moreover, in the US, as many as 85% of adults with an alcohol use disorder also use tobacco products (6) making co-use extremely common. When nicotine and alcohol are used in combination, negative health outcomes increase substantially. For example, rates of esophageal cancer increased 12- to 19- fold in men and women co-users, respectively (7), with similar increases for rates of head and neck cancers (8). In Pennsylvania, more than 3,800 adults die each year from alcohol-related causes and 22,000 from smoking-related causes (9). When alcohol and tobacco are consistently used in combination, negative health outcomes including

rates of several cancers, liver disease, lung disease, and heart failure also increase significantly (7, 10-13). Furthermore, chronic alcohol and tobacco use are both implicated in lung injury and the development of pulmonary diseases including pneumonia, tuberculosis, influenza, infection from respiratory syncytial virus (RSV), and acute respiratory distress syndrome (10, 14), further increasing the risk of severe disease following COVID-19 infection. Moreover, the pandemic has exacerbated these effects with evidence that both alcohol consumption and use of tobacco products have increased during this period (15, 16). Moreover, there is growing evidence that the pandemic has had an outsized effect on individuals with a history of substance use. For example, risk of COVID infection in vaccinated patients with a history of tobacco use is nearly double that of patients with no history of substance use (17). Health outcomes are further exacerbated in substance users in the criminal justice system. COVID infection rates in incarcerated individuals are 5 times that of the general population and these individuals are 3 times as likely to die from COVID-related causes (18-20).

COVID-19 typically presents with respiratory symptoms, including cough, shortness of breath and in severe cases the development of pneumonia (CDC, 2021). There is also a growing list of secondary health outcomes associated with COVID-19. For example, between 15 and 53% of COVID patients are diagnosed with liver damage, identified by hepatomegaly (enlarged liver) with ultrasound (21, 22). Furthermore, over 25% of hospitalized COVID-19 patients have developed acute kidney injury, likely stemming from chronic immune activation following infection (23). There have also been increasing reports of acute pancreatitis in COVID-19 patients, particularly in patients diagnosed with COVID-related pneumonia (24-27). Chronic alcohol and tobacco use also produce marked effects on the liver, kidneys, and pancreas (28-34).

There is growing evidence that

As such, we were interested in understanding whether a history of alcohol dependence, nicotine dependence, or both exacerbated both primary and secondary health outcomes in COVID+ patients.

COVID-19 has had a severe impact across the country however certain communities have been more impacted than others. Rural communities in particular have been some of the hardest hit by COVID-19 (35). Rural areas tend to have less intensive care unit (ICU) beds per capita compared to those of urban areas. Furthermore, rural residents tend to be older with greater rates of co-morbidities compared to resident of urban areas (35, 36). Following these national trends, between March 2020 and March 2021, of the ten Pennsylvania counties with the highest rates of COVID-19, eight were rural counties (37). To gain insights into how substance abuse may disproportionately affect rural COVID patients, the current study assesses patient populations within the Penn State Health Network which serves 29 counties in central Pennsylvania that are comprised of largely rural areas.

In the current study, we investigated COVID+ patients with a history of alcohol, nicotine, or alcohol+nicotine co-use, along with individuals with no substance use history occurring between March 2020 and June 2022 for 3 primary health outcomes of COVID-19: Patients requiring ventilation, developing pneumonia, and 30-day mortality. In addition, we also assessed secondary health outcomes including prevalence of hepatomegaly, acute kidney injury, and acute pancreatitis within this population. As an important control, we also assessed all of the above measures in individuals from a matching period of time pre-COVID (March 2017-June 2019). These studies utilized the Trinetx medical record system to analyze the electronic medical records (EMRs) of 586,300 patients that sought care through the Penn State Health Network for the date ranges above. All patients analyzed from March 2020-June 2022 were diagnosed as

COVID-19 positive at the time that care was sought (n=24,900). We hypothesized that rates of primary health outcomes would be significantly increased in patients with a history of substance use. Moreover, we predicted that patients with a history of co-use would show the highest rates of primary health outcomes. For secondary health outcomes, we hypothesized that patients with a history of alcohol dependence (alone or in combination with nicotine) would show the highest rates of secondary health outcomes.

Methods

Study Population

We retrieved data consolidated from electronic health records (EHRs) from the Penn State Health Network using the TriNetX platform. TriNetX Analytics is a global federated health research network that allows access to de-identified patient data and aggregate counts of EHR data which can include demographics, diagnoses, procedures, medications, laboratory results, and genomics. Many HCOs can be associated with a particular network which may include academic medical centers, community hospitals, and private practice. All patient data analyses were performed through the browser based TriNetX platform.

The Penn State Network comprised of 1,668,190 patients in the single HCO. The local Pennsylvania system provides a framework to represent the rural transitional population in Central PA. Within the Penn State network, we analyzed 24,900 patients who were confirmed to have a COVID-19 infection between March 2020 and June 2022 using the ICD-10 diagnosis code of the positive lab test of “SARS coronavirus 2 and related RNA” (TNX:LAB:9088), “COVID-19” (U07.1), and “Other coronavirus as the cause of diseases classified elsewhere” (B97.29). We then further queried the study populations based on the substance use disorder

(SUD) status, using ICD-10 diagnosis codes, at any instance occurring on or before the instance of a COVID-19 diagnosis. 19,860 COVID-19 patients with no history of substance use served as the control group. The status of alcohol use disorder was queried on the ICD-10 code of "alcohol related disorders" (F10) without nicotine use which included 330 patients; that of nicotine use disorder based on the code of "personal history of nicotine dependence" (Z87.891) and "Nicotine dependence" (F17) without alcohol use which included 4,290 patients; that of alcohol and nicotine co-use based on both aforementioned codes which included 420 patients. Additionally, we performed the same analyses minus coding for COVID infection for patients reporting for care between March 2017 and June 2019 in order to assess normal rates of these negative health outcomes in this population. In total, 561,400 patient records were analyzed from this control time period including 1,910 patients with history of alcohol use disorder, 79,980 patients with history of nicotine dependence, 2,010 patients with history of both alcohol and nicotine dependence, and 477,500 patients with no history of substance use.

The primary health outcome variables considered for COVID-19 patients were defined as the need for ventilators based on the code of "ventilation assist and management, initiation of pressure or volume preset ventilators for assisted or controlled breathing" (1014859); diagnosis of pneumonia based on the code of "pneumonia due to coronavirus disease 2019" (J12.82); and all-cause mortality based on the code of "deceased" within 30 days of the confirmed COVID-19 diagnosis. In addition, secondary health outcomes were also investigated beyond the typical respiratory symptoms of COVID-19 given the history of alcohol, nicotine, and general substance use disorders within the cohorts. We assessed how the history of substance use and COVID-19 infection can lead to various types of peripheral disease states including symptoms of liver, kidney and pancreatic-related disorders. Using the ICD-10 diagnosis codes, "hepatomegaly, not

elsewhere classified" (R16.0); "acute kidney injury/failure (nontraumatic)" (N17); and "acute pancreatitis" (K85) after the confirmed diagnosis of COVID-19 were the secondary outcomes measured.

Data Analysis

We analyzed patient cohorts based on the demographic data of sex and age. Sex was categorized based on male and female, and age was grouped based on the age at the time of the positive COVID-19 diagnosis, separating patients into three age groups: 18 to 34, 35 to 60, and 61 to 85 years of age. We then compared these patient cohorts using the built-in TriNetX analytical package which provides Measures of Association and Kaplan-Meier Analysis between matched cohorts. Using this system, we assessed the rates of the primary and secondary health outcomes between the various substance use disorder groups and the COVID-19 patients with no history of substance use.

Results

Table 1 shows the demographics of the study cohorts in addition to the demographics of the entire Penn State Health network for both time periods assessed. The patients are predominantly white, which is reflective of the overall Penn State Health network. This is reflected not only in the control group (NSU) but also across all substance use categories, both Pre-COVID and during COVID. Table 2-5 break down primary and secondary health outcomes by sex (Table 2/3) and age group (Table 4/5). Finally, Table 6 includes percentages of these patients determined to have factors impacting their health including socioeconomic status, housing vulnerability, employment-related risk to health, and others (ICD-10 codes Z55-65). As rates of

these different factors did not significantly differ from one another for any cohort, they are collapsed into "SES and related factors" for Table 6.

Pre-COVID Patient Population

As shown in Table 2/3, rates of ventilator use in the Pre-COVID NSU population were extremely low with less than 0.1% of patients requiring a ventilator. All-cause mortality was slightly higher but still under 0.3% which was largely accounted for by the 61-85 age group (0.21%). In assessing the substance use groups, patients with a history of substance abuse showed significantly higher rates of both ventilation and all-cause mortality compared to the NSU group. Moreover, rates in patients with both a history of AUD and NUD showed higher still levels of these primary outcomes. Similar patterns were observed in assessing secondary health outcomes (Tables 4/5). Rates in NSU patients were under 0.5% across all secondary outcomes. Rates of secondary health outcomes in substance using patients were significantly higher than NSU patients, albeit still remaining under 3% in most cases. Interestingly, additive effects of combined alcohol and nicotine use on secondary health outcomes were not observed in the pre-COVID patient population.

COVID+ Patient Population

As shown in Table 2/3, in the NSU group (control group), rates (as a percent of total NSU patients) were under 4% for all primary health outcomes in both males and females at large. When we break this down into age groups, we see that rates are very low in adults age 18-34 (>2%) and increase with age with the oldest group, age 61-85, showing prevalence between 4.4-6.2% for these measures. However, those rates – and associated risk ratios – increase

significantly in patients that have a history of substance use with individuals in the AUD+NUD group having the worst outcomes overall by sex and age group. Notably, rates of all negative health outcomes in pre-COVID NSU patients, across both males and females, and across all age groups was below 0.5%, 10-fold lower than COVID+ NSU patients suggesting that both the primary and secondary health outcomes analyzed are uncommon in the non-substance using population under normal, pre-pandemic circumstances. Moreover, these findings suggest that COVID infection may coincide with higher rate, even in the NSU population.

Patients Requiring Ventilation

As shown in Table 2, males in the COVID+ AUD+NUD group show nearly a 6 fold increase in the percent of patients that require ventilation compared to the NSU group (18.18% v 3.13%; RR = 5.818 [95% CI 3.821-8.859] $p < 0.0001$). In females, this increase is even greater at 14.29% compared to only 1.78% in the NSU group (RR = 8.022 [95% CI 4.409-14.596] $p < 0.0001$). Similar trends are observed when analyzing the different age groups. As shown in Table 3, 50% of patients in the 18-34 group of AUD+NUD patients required ventilation compared to 0.91% of the NSU group (RR = 55 [95% CI 31.267-96.748] $p < 0.0001$). This comes with the important caveat that there were only 20 individuals in this particular group so these findings might be exaggerated. However, we still observe considerable increases in both the 35-60 and 61-85 age groups. In the 35-60 group, ventilation increased to 12.5% compared to 2.67% in the NSU group (RR = 4.677 [95% CI 2.551-8.574] $p < 0.0001$) and 25% vs 4.48% in the 61-85 age group (RR = 5.577 [95% CI 3.682-8.446] $p < 0.0001$). Furthermore, putting this in the context of pre-COVID patients in which <2% of AUD and NUD patients required ventilation. However, combined use

still elevates risk for ventilation considerably over AUD or NUD alone (4.11% in males, 7.27% in females).

Patients diagnosed with COVID-related Pneumonia

Similar to ventilation, patients in the AUD+NUD group showed significantly higher rates of COVID-related pneumonia diagnoses. In males, 18.18% of the AUD+NUD group compared to 3.62% in the NSU group (RR = 5.025 [95% CI 3.311-7.626] $p < 0.0001$) were diagnosed with pneumonia. This was considerably higher in females with 28.57% in the AUD+NUD group compared to 3.29% in the NSU group (RR = 8.69 [95% CI 5.88-12.845] $p < 0.0001$). The different age groups also looked fairly similar to rates of ventilation. In the 18-34 group, 50% were diagnosed with pneumonia compared to 1.82% in the NSU (RR = 27.5 [95% CI 16.598-45.563] $p < 0.0001$). This comes with the same caveat as earlier (n=20). In the 35-60 age group, 25% were diagnosed with pneumonia compared to 4.45% in the NSU (RR = 5.613 [95% CI 3.751-8398] $p < 0.0001$). In the 61-85 age group, 12.5% compared to 5.52% were diagnosed with pneumonia (RR = 2.266 [95% CI 1.245-4.124] $p = 0.0079$). As would be expected, rates of COVID-related pneumonia are zero in the pre-COVID patient set and thus are not included.

Mortality

Of the 16,060 COVID+ patients in this study, 446 (2.7%) were deceased within 30 days of confirmed COVID-19 diagnosis with the largest losses by percentage observed in the substance abuse cohorts. In males, 30-day mortality rate was 6.67% in the AUD group (RR = 3.11 [95% CI 1.671-5.785] $p = 0.0002$), 8.80% in the NUD group (RR = 4.105 [95% CI 3.221-5.23] $p < 0.0001$), and 7.69% in the AUD+NUD group (RR = 3.588 [95% CI 1.935-6.654] $p < 0.0001$)

compared to 2.14% in the NSU group. In females, 30-day mortality rate was 10% in the AUD group (RR = 6.123 [95% CI 3.32-11.294] $p < 0.0001$), 5.04% in the NUD group (RR = 3.087 [95% CI 2.288-4.166] $p < 0.0001$), and 14.29% in the AUD+NUD group (RR = 8.747 [95% CI 4.807-15.917] $p < 0.0001$) compared to 1.63% in the NSU group. Interestingly, when assessing age groups, differential effects emerged depending on drug use history. In the youngest cohort (18-34), 30-day mortality rate was 0% for both the AUD and AUD+NUD groups whereas the NUD group had a 30-day mortality rate of 4.76% compared to 0.28% in the NSU group (RR = 16.81 [95% CI 7.075-39.939] $p < 0.0001$) suggesting that younger people are more at risk from smoking-related causes. In the middle age group (35-60), 30-day mortality rate was highest in the AUD+NUD group at 11.11% compared to 1.04% in the NSU group (RR = 10.733 [95% CI 5.625-20.481] $p < 0.0001$). However, 30-day mortality was still significantly increased in both the AUD group (7.69%, RR = 7.431 [95% CI 3.855-14.323] $p < 0.0001$) and NUD group (2.44%, RR = 2.356 [95% CI 1.41-3.936] $p = 0.0008$). In the older group (61-85), 30-day mortality was highest in the AUD group at 16.67% compared to 4.49% in the NSU group (RR = 3.714 [95% CI 2.062-6.691] $p < 0.0001$). Mortality rate was also significantly increased in the NUD group (8.87%) and AUD+NUD group (10%) for the older age group. As would be predicted, overall 30-day mortality was highest in the older age group accounting for 56% of the deceased. Similar to ventilation, all-cause mortality within 30 days of visit is low in the pre-COVID population with NSU patients showing rates of <0.15% and AUD and NUD patients showing rates <2%. Similar to above, patients with both AUD and NUD show double the rate of all-cause mortality compared to either alone, further supporting a potentially additive effect of combined use.

Secondary Health Outcomes – Hepatomegaly

Given the marked effects that long-term alcohol abuse has on the liver, we would expect the percentage of patients exhibiting this condition to be higher in patients with AUD. As shown in Table 4, this was true of both males and females with males showing prevalence of 7.14% in AUD compared to 0.49% in NSU (RR = 14.476 [95% CI 7.219-29.029] $p < 0.0001$) and females showing prevalence of 11.11% in the AUD group compared to 0.69% in the NSU group (RR = 16.222 [95% CI 8.5-30.961] $p < 0.0001$). Interestingly, hepatomegaly was only increased in the AUD+NUD males in which 9.09% exhibited the condition (RR = 18.424 [95% CI 9.237-36.748] $p < 0.0001$). By contrast, none of the 70 females in the AUD+NUD group exhibited hepatomegaly which might suggest a level of protection in females. Further assessing hepatomegaly by age group, interesting patterns emerged. As shown in Table 5, the only age group to exhibit the condition in AUD patients was the 35-60 age group where it had a prevalence of 8.33% compared to 0.89% in the NSU group (RR = 9.354 [95% CI 4.792-18.259] $p < 0.0001$). However, it remerged in all age groups in both the NUD and AUD+NUD patients suggesting that nicotine exposure is an important factor in the development of the condition. Rates of hepatomegaly were very low in the pre-COVID patient set further highlighting how high they are in the COVID+ population, with the greatest difference in patients that use both alcohol and nicotine (<0.5% versus up to 50%, a 100-fold increase).

Acute Kidney Injury or Failure (non-traumatic)

The next secondary health outcome we assessed was dysfunction of the kidneys. As shown in Table 4, both males and females in the AUD+NUD group showed the highest rates of kidney injury/failure with males showing prevalence of 18.18% compared to 2.63% in the NSU group

(RR = 6.909 [95% CI 4.517-10.567] p < 0.0001) and females showing prevalence of 14.29% compared to 2.19% in the NSU group (RR = 6.518 [95% CI 3.599-11.805] p < 0.0001). Somewhat surprisingly, kidney injury/failure was high in all age groups in AUD+NUD patients. Indeed, prevalence in the 18-34 group was 50% compared to 0.61% in the NSU group (RR = 82.5 [95% CI 44.431-153.188] p < 0.0001). Rates dropped in the other age groups but were still higher than all other conditions with the 35-60 age group showing prevalence of 12.5% compared to 2% in NSU (RR = 6.236 [95% CI 3.372-11.532] p < 0.0001) and the 61-85 group increasing prevalence to 25% compared to 5.52% in the NSU group (RR = 4.531 [95% CI 3.012-6.816] p < 0.0001). Rates of acute kidney injury were also considerably higher in the COVID+ population compared to the pre-COVID population. Indeed, we found that acute kidney injury was fairly rare in the pre-COVID populations with the highest rates in the 61-85 NUD and AUD+NUD groups (~3%). These rates soar to as high as 50% in the AUD+NUD group in the COVID population.

Acute Pancreatitis

Finally, we assessed was the prevalence of acute pancreatitis in this population. As shown in Table 4, males and females in the AUD+NUD group again show the highest prevalence compared to the NSU group. Prevalence in males was 9.09% compared to 0.33% (RR = 27.636 [95% CI 13.248-57.653] p < 0.0001). Prevalence in females was 14.29% compared to 0.27% in the NSU group (RR = 52.143 [95% CI 25.338-107.305] p < 0.0001). Interestingly, in females, pancreatitis was absent in the AUD group and very low in the NUD group (1.79%) suggesting a synergistic effect of alcohol and nicotine use in this group. Across age groups, rates of pancreatitis were highest in the AUD+NUD group. In the 18-34 group, 50% exhibited

pancreatitis compared to 0.3% in the NSU group (RR = 165 [95% CI 77.293-353.23] p < 0.0001). In the 35-60 group, prevalence was 12.5% compared to 0.45% in the NSU group (RR = 28.063 [95% CI 13.575-58.011] p < 0.0001). In the 61-85 group, prevalence was 12.5% compared to 0.35% in the NSU group (RR = 36.25 [95% CI 15.526-84.636] p < 0.0001). Its also worth noting that in the 18-34 group, pancreatitis was present in 20% of patients which may suggest a prevalence of binge-drinking behavior in this age group (33, 38). Similar to above, rates of pancreatitis in the substance using groups in the pre-COVID patient set were relatively low (generally under 2%), a 20-fold difference from COVID+ patients in the AUD+NUD group.

Socioeconomic and Related Factors

As shown in Table 6, patients in the NSU group show relatively low rates - 3-5% reported as having socioeconomic or employment-related factors affecting their health. By contrast, up to 25% of patients with a history of alcohol abuse, up to 14% of patients dependent on nicotine, and as many as 40% of patients with both alcohol and nicotine dependence are reported as having these factors affecting their health. These findings fall in line with our findings of negative health outcomes above. Taken together, these findings further show the complicated relationship between substance abuse and health outcomes.

Discussion

Substance abuse continues to be a key indicator for increased risks of severe COVID-19 infection (1, 2, 4). Substance users are often hesitant to seek medical care or have limited ability to seek that care. Moreover, enduring stigmas about substance abusers have reduced the overall care they receive (39). Rural communities are a subset of the country that has been particularly

effected by both substance use and the pandemic, creating a new challenge for healthcare. Indeed, rates of tobacco use and binge drinking, particularly in young adults, outpaces suburban and larger metro communities (40). For this reason, the current study focused on the Penn State Health Network which serves largely rural communities in central Pennsylvania. Moreover, the majority of counties in Pennsylvania that have been hardest hit by COVID are rural counties (37). Moreover, as we show in Tables 2-5, these negative health outcomes have low occurrence rates in the pre-COVID patient population, in some cases 100-fold less likely. This would suggest that COVID infection may increase the risks of developing these negative health outcomes. Moreover, as we show in Table 6, these outcomes seem to go hand in hand with other socioeconomic factors known to influence health.

Primary health outcomes are worse in patients with history of drug dependence

As we show, national trends are not only present in this population, but amplified. When looking at severe primary health outcomes (requiring ventilation and developing pneumonia), we find that individuals with a history of alcohol dependence, nicotine dependence, or both, are significantly more likely to have these outcomes than individuals with no history of substance use. Strikingly, co-use of alcohol and nicotine seems to be synergistic on many of these negative effects, mirroring other clinical outcomes (12). For instance, in males, rates of ventilation and pneumonia go from <8% and <10% in AUD and NUD respectively, to >18% in the AUD+NUD group. In females, rates of pneumonia nearly triple in the AUD+NUD group compared to AUD or NUD alone. Moreover, we find that rates of negative outcomes in younger populations are elevated compared to the general population. Individuals in the 18-34 age group, show dramatic increases in rates of ventilation and pneumonia, particularly in individuals with a history of

alcohol use (AUD alone or AUD+NUD) where between 20 and 50% of these patients exhibited these outcomes, outpacing middle age and older populations considerably. An important caveat, as noted in the results section, the 18-34 AUD+NUD group only contains 20 individuals so these findings need to be considered in that context.

Substance use increases mortality rates

In addition to increasing incidence rates of negative respiratory health outcomes, we also found that 30-day mortality rates also increased significantly in individuals with a history of substance use. This was true across sexes and all age groups. The only exceptions were individuals from the 18-34 AUD and AUD+NUD groups where the 30-day mortality rate was 0. All other substance use conditions showed significantly increased rate of 30-day mortality compared to having no history of substance use.

Evidence for increased liver disorder in COVID+ substance users

Hepatomegaly is a condition in which the liver is enlarged and is generally considered a marker of larger liver disease/dysfunction (41). In a growing number of cases, this condition has been identified in COVID patients during treatment. Interestingly, liver maladies were also identified in the previous SARS epidemic in which 60% of patients were diagnosed with various forms of liver disease (42, 43). In the current studies, we show that individuals with a history of alcohol use (alone or in combination with nicotine), show an increased risk of developing hepatomegaly with the exception of females in the AUD+NUD group where the incidence rate was 0. Moreover, although significantly increased, rates of hepatomegaly were relatively low in the NUD group (<2% in both males and females) compared to 7.14% in AUD males and 11.11% in

AUD females. This was surprising given evidence that smoking induces considerable liver injury (31). Another surprising finding was that only middle aged individuals (34-60) in the AUD group presented with hepatomegaly whereas all age groups presented with the condition in the NUD and AUD+NUD groups. This may suggest different patterns of use in these age groups leading to differential impact of alcohol, nicotine, or co-use on liver outcomes.

Evidence for increased acute kidney injury/failure in COVID+ substance users

Emerging evidence from the US and Europe paint a startling picture where as many as 45% of COVID patients in intensive care present with severe kidney injury, many requiring transplant (44, 45). In the present study, we found that across all substance use conditions with the exception of the 18-34 AUD group, rates of acute kidney injury were significantly increased compared to individuals with no history of substance use. In particular, individuals in the AUD+NUD group showed considerably higher rates compared to AUD or NUD alone. Acute kidney injury is associated with both alcohol and nicotine use. Alcohol effects the kidneys directly through disrupting ion concentration of bodily fluids and blood pH and indirectly through its actions on the liver. Indeed, individuals with alcoholic liver disease often present with enlarged kidneys or kidney failure as a result of further ion disruption and fluid handling (30). Smoking has been shown to speed the progression of kidney disease and leads to damage of the renal arteries (28, 29). Interestingly, in our study, where we observe hepatomegaly we also see increased rates of kidney injury/failure whereas in the 18-34 AUD group, we don't observe hepatomegaly or kidney injury which may further suggest a relationship between these conditions.

Acute Pancreatitis and COVID-related Pneumonia

There have been a growing number of cases of acute pancreatitis in COVID patients. Moreover, within this group, many are diagnosed following the development of COVID-related pneumonia (24-27). The current dataset shows there is striking consistency between patient groups diagnosed with pneumonia and those diagnosed with acute pancreatitis. In particular, in the AUD and AUD+NUD groups, rates of both pneumonia and acute pancreatitis are high: 8-20% in the AUD group and 12-50% in the AUD+NUD group. Rates of pancreatitis were considerably lower in the NUD group which may suggest smoking as a risk factor but not a driver of this effect. Indeed, smoking has been shown to increase risk of developing acute pancreatitis (34).

Limitations and Future Studies

This study is an initial dive into the complicated relationship between substance abuse and disease and is focused on a relatively small population. Moreover, this is a chart study based on patient records that are often incomplete or inaccurate. Furthermore, the current study relied on a diagnosis or patient report of a history of alcohol dependence, nicotine dependence, or both. This was necessary in order to parse charts but it has the potential to undercount the number of individuals that are occasional to chronic users who either don't report or are not diagnosed. For instance, our AUD cohort is only 230 individuals – 1.4% of the study population – despite national rates of AUD hovering around 7% (NIAAA, 2021). Along these lines, generalizing the findings of a study like this is difficult as we only have patient data if the individual sought care. Finally, our secondary measures were intended to be an initial screen of negative outcomes. Conditions such as hepatomegaly should be further investigated to determine if other forms of disease manifested later. Taken together, future studies would benefit from 1) accessing larger

patient databases, 2) broadening our scope of substance use (i.e., dependence in addition to occasional to moderate users), 3) adding additional secondary outcomes. Furthermore, this study was constrained by the analysis capabilities native to the Trinetx platform. Future studies would benefit from gaining access to a more detailed dataset and utilizing a multivariate regression design in order to assess the impact of each variable.

Conclusions

The current analyses reinforce a growing literature that a history of substance abuse puts an individual at significantly increased risk of developing severe infection and other negative outcomes. Moreover, as described by (17), we need to fundamentally change the way we think about study groups in the development of treatments for infectious disease. As we continue to develop effective treatments and countermeasures for COVID-19 and prepare for future infectious disease events, we always need to continue our focus on helping and treating those with substance use disorders. In doing so, policy needs to ensure that individuals in the criminal justice system are not overlooked as rates of both substance abuse and COVID infection are considerably higher in these populations (19, 20). If these individuals are identified earlier, treatment could be expedited, improving not only their health outcomes but the health outcomes of our communities as a whole (46).

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Table 1: Cohort Information

	Pre-COVID (March 2017 - June 2019)					COVID + (March 2020 - June 2022)				
	NSU	**AUD**	**NUD**	**A/NUD**	**All Patients[#]**	**NSU**	**AUD**	**NUD**	**A/NUD**	**All Patients[#]**
n	4,77,750	3,210	33,140	2,000	5,14,580	19,860	330	4,280	420	5,98,580
Age* (mean +/- SD in years)	43 ± 25.4	50.8 ± 15.9	58.2 ± 18.1	55.6 ± 14.8	44.1 ± 25.2	37.8 ± 24.2	49 ± 15.8	57.7 ± 17.9	54.3 ± 15.5	42 ± 25.5
Sex (% Male)	45%	68%	53%	73%	45%	45%	58 %	49%	62%	46%
Race, n (%)										
White	348,280 (73)	2,570 (80)	27,940 (84)	1,730 (86)	379,230 (74)	13,360 (67)	260 (78)	3,450 (81)	350 (83)	413,660 (69)

Unknown Race	89,730 (19)	370 (12)	2,590 (8)	130 (6)	92,690 (18)	4,030 (21)	40 (12)	400 (9)	30 (7)	134,240 (23)
Black or African American	28,950 (6)	230 (7)	2,260 (7)	140 (7)	31,460 (6)	1,580 (8)	40 (12)	360 (8)	40 (9)	35,470 (6)
Asian	9,620 (2)	30 (1)	280 (1)	10 (<1)	9,920 (2)	850 (4)	10 (3)	90 (2)	10 (2)	13,850 (2)
American Indian or Alaska Native	430 (<1)	10 (<1)	60 (<1)	10 (<1)	840 (<1)	30 (<1)	0 (0)	10 (<1)	0 (0)	930 (<1)
Native Hawaiian or Other Pacific Islander	770 (<1)	10 (<1)	30 (<1)	0 (0)	450 (<1)	20 (<1)	0 (0)	10 (<1)	0 (0)	450 (<1)

#Total PSH network patients that saught care during each period, regardless of COVID status

****Age is defined as age at time of COVID-19 diagnosis***

Table 2: Primary Health Outcomes by Sex March 2017-June 2019 (Pre-COVID)

		NSU		AUD			NUD			AUD+NUD	
Sex	**Health Outcomes**	**%**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**
Male	**Ventilator**	0.08 %	1.58%	20.973 (13.219,33.276)	< 0.001	1.71 %	22.766 (18.803,27.564)	< 0.001	4.11%	54.732 (40.864,73.307)	< 0.001
	All-Cause Mortality	0.12 %	1.58%	12.907 (8.218,20.271)	< 0.001	1.99 %	16.345 (13.932,19.176)	< 0.001	4.11%	33.681 (25.559,44.385)	< 0.001
	n	*2130*		*1270*			*17550*			*1460*	

Female	**Ventilator**	0.05%	1.56%	34.428 (18.146,65.321)	< 0.001	0.70%	15.37 (12.529,18.856)	< 0.001	7.27%	160.248 (113.159,226.933)	< 0.001
	All-Cause Mortality	0.11%	1.56%	14.755 (7.89,27.593)	< 0.001	1.23%	11.654 (10.146,13.386)	< 0.001	3.64%	34.339 (21.986,53.632)	< 0.001
	n	*2644 10*		*640*			*62430*			*550*	

March 2020-June 2022

Sex	**Health Outcomes**	**NSU %**	**%**	**AUD RR (95% CI)**	**P**	**%**	**NUD RR (95% CI)**	**P**	**%**	**AUD+NUD RR (95% CI)**	**P**
Male	**Ventilator**	3.13%	7.14%	2.286 (1.238,4.221)	0.0077	9.40%	3.009 (2.399,3.773)	< 0.001	18.18%	5.818 (3.821,8.859)	< 0.001
	Pneumonia due to COVID	3.62%	7.14%	1.974 (1.071,3.637)	0.0289	8.55%	2.362 (1.881,2.967)	< 0.001	18.18%	5.025 (3.311,7.626)	< 0.001
	All-Cause Mortality	2.14%	6.67%	3.11 (1.671,5.785)	0.002	8.80%	4.105 (3.221,5.23)	< 0.001	7.69%	3.588 (1.935,6.654)	< 0.001
	n	*6080*		*140*			*1170*			*110*	
Female	**Ventilator**	1.78%	11.11%	6.239 (3.395,11.468)	< 0.001	5.36%	3.008 (2.23,4.058)	< 0.001	14.29%	8.022 (4.409,14.596)	< 0.001

	Pneumonia due to COVID	3.29 %	11.11 %	3.38 (1.86,6.142)	< 0.001	7.14 %	2.173 (1.7,2.776)	< 0.001	28.57 %	8.69 (5.88,12.845)	< 0.001
	All-Cause Mortality	1.63 %	10.00 %	6.123 (3.32,11.294)	< 0.001	5.04 %	3.087 (2.288,4.166)	< 0.001	14.29 %	8.747 (4.807,15.917)	< 0.001
	n	*7300*		*90*			*1120*			*70*	

Table 3: Primary Health Outcomes by Age Group. March 2017-June 2019 (Pre-COVID)

		NSU		**AUD**			**NUD**			**AUD+NUD**	
Age	**Health Outcomes**	**%**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**
18-34	**Ventilator**	0.03 %	2.17%	72.297 (35.551,147.023)	< 0.001	0.66 %	21.927 (13.231,36.341)	< 0.001	5%	151.167 (74.815,305.436)	< 0.001
	All-Cause Mortality	0.02 %	2.17%	108.446 (51.044,230.398)	< 0.001	0.22 %	10.964 (5.135,23.409)	< 0.001	5%	226.75 (107.378,478.826)	< 0.001
	n	99770		460			4550			220	
35-60	**Ventilator**	0.04 %	2.25%	58.863 (1.679,5.791)	< 0.001	0.89 %	23.218 (16.629,32.418)	< 0.001	2.55%	66.9 (48.339,92.588)	< 0.001
	All-Cause Mortality	0.05 %	1.12%	24.526 (12.598,47.749)	< 0.001	0.65 %	14.071 (10.074,19.656)	< 0.001	1.77%	38.596 (27.874,53.443)	< 0.001
	n	130970		890			12410			5550	

61-85	**Ventilator**	0.07%	1.89%	26.023 (13.616,49.736)	< 0.001	2.03%	28.049 (22.155,35.51)	< 0.001	2%	32.143 (24.365,42.404)	< 0.001
	All-Cause Mortality	0.21%	3.77%	18.016 (11.525,28.163)	< 0.001	2.45%	11.718 (9.99,13.745)	< 0.001	4%	19.218 (15.976,23.119)	< 0.001
	n	1241 30		530			14260			5340	

March 2020-June 2022

Age	**Health Outcomes**	**NSU %**	**%**	**AUD RR (95% CI)**	**P**	**%**	**NUD RR (95% CI)**	**P**	**%**	**AUD+NUD RR (95% CI)**	**P**
	Ventilator	0.91%	20.00%	22 (11.383,42.521)	< 0.001	5.26%	5.789 (2.873,11.665)	< 0.001	50%	55 (31.267,96.748)	< 0.001
18-34	**Pneumonia due to COVID**	1.82%	20.00%	11 (5.986,20.213)	< 0.001	5.26%	2.895 (1.506,5.563)	0.001	50%	27.5 (16.598,45.563)	< 0.001
	All-Cause Mortality	0.28%	0.00%	-	0.6797	4.76%	16.81 (7.075,39.939)	< 0.001	0%	-	0.8116
	n	3310		50			190			20	
35-60	**Ventilator**	2.67%	8.33%	3.118 (1.679,5.791)	0.002	5.20%	1.944 (1.37,2.757)	0.002	12.50%	4.677 (2.551,8.574)	< 0.001
	Pneumonia	4.4	8.3	1.871	0.0	6.	1.458	0.0	25	5.613	<

	due to COVID	5%	3%	(1.018,3.439)	443	49%	(1.08,1.968)	14	%	(3.751,8.398)	0.001
	All-Cause Mortality	1.04%	7.69%	7.431 (3.855,14.323)	< 0.001	2.44%	2.356 (1.41,3.936)	0.008	11.11%	10.733 (5.625,20.481)	< 0.001
	n	4490		120			770			80	
	Ventilator	4.48%	16.67%	3.718 (2.061,6.709)	< 0.001	9.48%	2.115 (1.656,2.702)	< 0.001	25%	5.577 (3.682,8.446)	< 0.001
61-85	**Pneumonia due to COVID**	5.52%	16.67%	3.021 (1.682,5.425)	0.002	9.48%	1.719 (1.361,2.17)	< 0.001	12.50%	2.266 (1.245,4.124)	0.079
	All-Cause Mortality	4.49%	16.67%	3.714 (2.062,6.691)	< 0.001	8.87%	1.977 (1.554,2.515)	< 0.001	10%	2.229 (1.211,4.101)	0.01
	n	2900		60			1160			80	

Table 4: Secondary Health Outcomes by Sex March 2017-June 2019 (Pre-COVID)

		NSU		**AUD**			**NUD**			**AUD+NUD**	
Sex	**Health Outcomes**	**%**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**
Male	**Hepatomegaly**	0.05%	0.79%	15.253 (8.003,29.073)	< 0.001	0.17%	3.311 (2.212,4.957)	< 0.001	0.69%	13.268 (6.959,25.297)	< 0.001
	Acute Kidney Injury/Failure (nontraumatic)	0.23%	0.79%	3.496 (1.873,6.523)	< 0.001	2.28%	10.118 (8.869,11.544)	< 0.001	3.43%	15.203 (11.414,20.251)	< 0.001

	Acute pancreatitis	0.04%	0.79%	20.973 (10.894, 40.38)	<0.001	0.29%	7.589 (5.332,10.801)	<0.001	2.06%	54.732 (36.09,83.004)	<0.001
	n	*2130*		*1270*			*17550*			*1460*	
	Hepatomegaly	0.05%	0.00%	-	0.564	0.13%	2.365 (1.775,3.15)	<0.001	0%	-	0.593
Female	**Acute Kidney Injury/Failure (nontraumatic)**	0.16%	1.56%	9.837 (5.279,18.328)	<0.001	0.95%	5.968 (5.252,6.781)	<0.001	1.82%	11.446 (6.148,21.311)	<0.001
	Acute pancreatitis	0.03%	2%	45.905 (23.995, 87.819)	<0.001	0.20%	5.78 (4.375,7.636)	<0.001	1.82%	53.416 (27.943,102.112)	<0.001
	n	*2644*		*640*			*62430*			*550*	

March 2020-June 2022

Sex	**Health Outcomes**	**NSU %**		**AUD RR (95% CI)**	**P**		**NUD RR (95% CI)**	**P**		**AUD+NUD RR (95% CI)**	**P**
Male	**Hepatomegaly**	0.49	7.14	14.476 (7.219,2	<0.0	1.71	3.464 (1.974,6	<0.0	9.09	18.424 (9.237,36	<0.0

		%	%	9.029)	001	%	.079)	001	%	.748)	001
	Acute Kidney Injury/Failure (nontraumatic)	2.63 %	7.14 %	2.714 (1.465,5.028)	0.0012	11.97 %	4.547 (3.656,5.655)	<0.0001	18.18 %	6.909 (4.517,10.567)	<0.0001
	Acute pancreatitis	0.33 %	7.14 %	21.714 (10.356, 45.529)	<0.0001	0.86 %	2.598 (1.219,5.537)	0.0103	9.09 %	27.636 (13.248,57.653)	<0.0001
	n	*6080*		*140*			*1170*			*110*	
	Hepatomegaly	0.69 %	11.11 %	16.222 (8.5,30.961)	<0.0001	1.79 %	2.607 (1.558,4.362)	0.0002	0 %	-	0.4872
Female	**Acute Kidney Injury/Failure (nontraumatic)**	2.19 %	11.11 %	5.069 (2.771,9.275)	<0.0001	7.14 %	3.259 (2.511,4.23)	<0.0001	14.29 %	6.518 (3.599,11.805)	<0.0001
	Acute pancreatitis	0.27 %	0 %	-	0.619	1.79 %	6.518 (3.518,12.075)	<0.0001	14.29 %	52.143 (25.338,107.305)	<0.0001
	n	*7300*		*90*			*1120*			*70*	

Table 5: Secondary Health Outcomes by Age Group March 2017-June 2019 (Pre-COVID)

		NSU		**AUD**			**NUD**			**AUD+NUD**	
Age	**Health Outcomes**	**%**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**	**%**	**RR (95% CI)**	**P**
1	**Hepatomegaly**	0.	0.	-	0.7	0.	7.309	<	0	-	0.7

8-34		30%	00%		099	22%	(3.575,14.942)	0.0001	%		97
	Acute Kidney Injury/Failure (nontraumatic)	0.08%	2.17%	27.111 (14.139, 51.985)	<0.0001	0.44%	5.482 (3.361,8.94)	<0.0001	0%	-	0.674
	Acute pancreatitis	0.30%	0.00%	-	0.7099	0.22%	7.309 (3.575,14.942)	<0.0001	5%	151.167 (74.815,305.436)	<0.0001
	n	9977 0		460			4550			220	
	Hepatomegaly	0.07%	1.12%	16.351 (8.536,31.321)	<0.0001	0.24%	3.518 (2.328,5.316)	<0.0001	0.39%	5.718 (3.525,9.275)	<0.0001
35-60	**Acute Kidney Injury/Failure (nontraumatic)**	0.14%	1.12%	8.175 (4.34,15.402)	<0.0001	0.81%	5.863 (4.595,7.482)	<0.0001	1.38%	10.006 (7.603,13.169)	<0.0001
	Acute pancreatitis	0.05%	1.12%	24.526 (12.598, 47.749)	<0.0001	0.32%	7.036 (4.718,10.492)	<0.0001	1.57%	34.308 (24.577,47.891)	<0.0001
	n	1309 70		890			12410			5550	
61-85	**Hepatomegaly**	0.08%	2%	23.421 (12.295, 44.614)	<0.0001	0.14%	1.741 (1.078,2.813)	0.0218	0.42%	5.26 (3.257,8.494)	<0.0001
	Acute Kidney Injury/Failure	0.35	1.89	5.323 (2.861,9.	< 0.0	2.81	7.913 (6.919,9	< 0.0	3%	8.368 (6.934,10.	< 0.0

	(nontraumatic)	%	%	905)	001	%	.051)	001		098)	001
	Acute pancreatitis	0.06 %	2 %	33.458 (17.343, 64.546)	< 0.0001	0.28 %	4.974 (3.374,7.333)	< 0.0001	1.06 %	18.785 (13.083,26.972)	< 0.0001
	n	1241 30		530			14260			5340	
March 2020-June 2022											
Age	**Health Outcomes**	**NSU %**		**AUD RR (95% CI)**	**P**		**NUD RR (95% CI)**	**P**		**AUD+NUD RR (95% CI)**	**P**
	Hepatomegaly	0.30 %	0.00 %	-	0.6967	5.26 %	17.368 (7.318,41.219)	< 0.0001	50 %	165 (77.293,352.23)	< 0.0001
18-34	**Acute Kidney Injury/Failure (nontraumatic)**	0.61 %	0.00 %	-	0.5809	5.26 %	8.684 (4.123,18.291)	< 0.0001	50 %	82.5 (44.431,153.188)	< 0.0001
	Acute pancreatitis	0.30 %	20.00 %	66 (28.755, 151.489)	< 0.0001	5.26 %	17.368 (7.318,41.219)	< 0.0001	50 %	165 (77.293,352.23)	< 0.0001
	n	3310		50			190			20	
35-6	**Hepatomegaly**	0.89 %	8.33 %	9.354 (4.792,18.259)	< 0.0000	2.60 %	2.916 (1.714,4.96)	< 0.0000	12.50	14.031 (7.276,27.06)	< 0.0000

0				1			1	%		1
	Acute Kidney Injury/Failure (nontraumatic)	2.00 %	8.33 %	4.157 (2.219,7.788)	< 0.0001	6.49 %	3.24 (2.312,4.538)	< 0.0001	12.50 %	6.236 (3.372,11.532)	< 0.0001
	Acute pancreatitis	0.45 %	8.33 %	18.708 (8.952,39.099)	< 0.0001	1.30 %	2.916 (1.37,6.205)	0.037	12.50 %	28.063 (13.575,58.011)	< 0.0001
	n	4490		120			770			80	
	Hepatomegaly	0.69 %	0 %	-	0.518 6	0.86 %	1.25 (0.587,2.662)	0.562 3	12.50 %	18.125 (8.771,37.456)	< 0.0001
61-85	**Acute Kidney Injury/Failure (nontraumatic)**	5.52 %	16.67 %	3.021 (1.682,5.425)	0.0002	12.07 %	2.188 (1.762,2.716)	< 0.0001	25 %	4.531 (3.012,6.816)	< 0.0001
	Acute pancreatitis	0.35 %	0 %	-	0.648 7	0.86 %	2.5 (1.043,5.991)	0.033 5	12.50 %	36.25 (15.526,84.636)	< 0.0001
	n	2900		60			1160			80	

Table 6: Patients with health factors associated with socioeconomic status, vulnerable housing status, or employment related factors

March 2020-June 2022

		NSU	**AUD**	**NUD**	**AUD/NUD**
n(%)	**Males**	**300 (3)**	**30 (15)**	**180 (8)**	**60 (22)**
	Females	**410 (5)**	**30 (21)**	**290 (13)**	**40 (24)**

18-34	**160 (3)**	**10 (14)**	**80 (14)**	**20 (40)**
35-60	**290 (5)**	**40 (21)**	**180 (10)**	**60 (27)**
61-85	**200 (5)**	**20 (25)**	**190 (10)**	**30 (19)**