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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

ORIGINAL ARTICLE

COVID-19 patients with documented alcohol use disorder or alcohol-related complications are more likely to be hospitalized and have higher all-cause mortality

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Abstract

Background: Coronavirus Disease 2019 (COVID-19) has affected every country globally, with hundreds of millions of people infected with the SARS-CoV-2 virus and over 6 million deaths to date. It is unknown how alcohol use disorder (AUD) affects the severity and mortality of COVID-19. AUD is known to increase the severity and mortality of bacterial pneumonia and the risk of developing acute respiratory distress syndrome. Our objective is to determine whether individuals with AUD have increased severity and mortality from COVID-19.

Methods: We utilized a retrospective cohort study of inpatients and outpatients from 44 centers participating in the National COVID Cohort Collaborative. All were adult COVID-19 patients with and without documented AUDs.

Results: We identified 25,583 COVID-19 patients with an AUD and 1,309,445 without. In unadjusted comparisons, those with AUD had higher odds of hospitalization (odds ratio [OR] 2.00, 95% confidence interval [CI] 1.94 to 2.06, $p < 0.001$). After adjustment for age, sex, race/ethnicity, smoking, body mass index, and comorbidities, individuals with an AUD still had higher odds of requiring hospitalization (adjusted OR [aOR] 1.51, CI 1.46 to 1.56, $p < 0.001$). In unadjusted comparisons, individuals with AUD had higher odds of all-cause mortality (OR 2.18, CI 2.05 to 2.31, $p < 0.001$).

After adjustment as above, individuals with an AUD still had higher odds of all-cause mortality (aOR 1.55, CI 1.46 to 1.65, $p < 0.001$).

Conclusion: This work suggests that AUD can increase the severity and mortality of COVID-19 infection. This reinforces the need for clinicians to obtain an accurate alcohol history from patients hospitalized with COVID-19. For this study, our results are limited by an inability to quantify the daily drinking habits of the participants. Studies are needed to determine the mechanisms by which AUD increases the severity and mortality of COVID-19.

KEYWORDS
alcoholic, ARDS, EtOH, SARS-CoV-2, smoking, viral pneumonia

INTRODUCTION

The Coronavirus Disease 2019 COVID-19 pandemic, caused by the SARS-CoV-2 virus, has swept the globe, with over 173 million cases and over 6 million deaths worldwide to date (Dong et al., 2020). Several factors have been shown to increase mortality in COVID-19 pneumonia. These include advanced age (Mueller et al., 2020), male sex (Peckham et al., 2020), obesity (Popkin et al., 2020), smoking (van Zyl-Smit et al., 2020), preexisting lung disease (Esposito et al., 2020; Pranata et al., 2020b), and the number of comorbidities (Knight et al., 2020).

Several groups suggest that heavy alcohol intake might predispose COVID-19 patients to poor clinical outcomes (Bailey et al., 2021; Saengow et al., 2021; Testino, 2020). This suggestion, however, has remained only conjecture because alcohol intake was not assessed in most studies of risk factors for COVID-19 infection and severity (Chang et al., 2020; Gao et al., 2021; Jordan et al., 2020; Li et al., 2020; Zheng et al., 2020). This omission is despite the fact that over 2.4 billion people (43% of the total population) worldwide consume alcohol regularly (WHO, 2019).

Heavy alcohol intake and alcohol use disorder (AUD) are also known to have profound effects on the innate and adaptive immunity of the lung (Bailey et al., 2019). In terms of innate immunity, alcohol can suppress cough (Calesnick & Vernick, 1971) and blunt mucociliary clearance from the lung (Sisson et al., 2005). Cytokine production, another component of the innate immune response, is altered in those with AUD. For instance, the chemokine RANTES (Burnham et al., 2013) and the inflammatory cytokines IL-6 and IL-8 (Bailey et al., 2015) were increased in the bronchoalveolar lavage fluid of those with AUD. These changes in the lung alter the earliest responses to infection, which can potentially change the lung's defense against viral infection. In animal models of pulmonary viral infections, alcohol administration is associated with changes that make infection more likely (Simet et al., 2013). In addition, alcohol administration is associated with increased morbidity and mortality in the animals (Meyerholz et al., 2008) as well as higher viral titers and more severe pathology (Jerrells et al., 2007; Warren et al., 2016, 2019).

In humans, AUDs are known to be an independent risk factor for the development of community-acquired bacterial pneumonia. This is thought to be dose-dependent, and it is estimated that for every 10 to 20 g increase in daily alcohol consumption, there is an 8% increase in the risk of developing community-acquired pneumonia (Simou et al., 2018a). This corresponds to an increase of approximately one standard drink (14 g of alcohol) which is contained in one 12 oz beer, a 1.5 oz shot of liquor, or 5 oz of wine.

Those with AUD are also more likely to develop acute respiratory distress syndrome (ARDS; Moss & Burnham, 2003, 2006; Moss et al., 2003; TenHoor et al., 2001). ARDS is a condition of respiratory failure due to the rapid development of noncardiogenic pulmonary edema. ARDS is diagnosed frequently in cases of severe COVID-19 pneumonia that frequently requires mechanical ventilation (Marini & Gattinoni, 2020). Patients with ARDS who drink more than three alcoholic drinks per week have higher mortality (TenHoor et al., 2001).

It is not known how AUD impacts the severity of COVID-19 disease. Given what is known about alcohol increasing the severity of other lung infections and ARDS, we hypothesized that AUD would increase hospitalization and mortality in COVID-19.

METHODS

National COVID Cohort Collaborative (N3C initiative)

The National COVID Cohort Collaborative (N3C) is a centralized, secure repository of clinical data housed at, and managed by, the National Institutes of Health (NIH) National Center for Advancing Translational Science (NCATS). N3C aggregates and harmonizes electronic health record (EHR) data across clinical organizations in the United States and is designed to support collaborative, community-driven, reproducible, and transparent COVID-19 secondary data analyses. As of October 1, 2021, N3C is the largest central repository of COVID-19 EHRs in the United States with records for more than 8 million patients, of which, 2.8 million tested positive for COVID-19 from 65 institutions (i.e., data partners). These institutions are listed in Table S1.

N3C data enclave

The N3C data enclave is a secure platform through which harmonized clinical data is provided by contributing data partners. The N3C systematically collects data derived from the electronic medical

record of patients that were tested for SARS-CoV-2 or had a diagnosis of COVID-19 from a provider.

The data enclave is described in detail here (Haendel et al., 2021). Briefly, the data enclave includes EHR or Health Information Exchange (HIE) data (with a 2-year "lookback" to January 1, 2018) on all patients with COVID-19. As of September 30, 2021 (release 47), this includes data from 65 data partners representing 8,350,600 patients, of whom 2,856,925 were diagnosed with COVID-19. Data are collected as part of routine medical care and submitted to the N3C database under a Health Insurance and Portability and Accountability Act (HIPAA) waiver via one of four common data models (CDMs): Observational Medical Outcomes Partnership (OMOP; Dixon et al., 2020), Patient-Centered Clinical Research Network (PCORnet; Bian et al., 2020), TriNetX (Topaloglu & Palchuk, 2018), or Accrual to Clinical Trials (ACT; Visweswaran et al., 2018). Submitted data are then checked for quality using methods tailored to each of the four CDMs before being harmonized into the OMOP 5.3.1.8 CDM followed by additional data quality checks prior to release (Haendel et al., 2021). Harmonization includes mapping codes, such as ICD-10 or SNOMED, to common concepts defined in the OMOP CDM. Submitted data is ingested and released on a weekly basis.

Research ethics

Data collection activities for N3C are approved under the authority of the NIH Institutional Review Board (IRB, IRB00249128) with Johns Hopkins University School of Medicine as the central IRB. Institutional IRBs at each data partner either approved the study protocol or ceded to this single IRB. The University of Nebraska Medical Center contributed data and completed a data use agreement with the N3C. The investigators for this study also completed a data use request that was approved by the N3C (RP-E5D34E). We used a de-identified dataset that did not contain direct identifiers of individual patients such as name, medical record number, date of birth, date(s) of service (all dates are shifted by up to 180 days), site, address or zip codes, or any other HIPAA identifier. The investigators agreed to abide by the N3C data user code of conduct. This code of conduct included an agreement not to attempt to re-identify any individual or site. Additional information can be found in Supplementary Methods.

Inclusion and exclusion criteria for data partners

Data partners reporting data to the N3C have varying levels of data completeness. To overcome this problem, we developed a data robustness screening matrix to determine minimum fact reporting per patient across key domains. This follows a similar approach used by the four source data models, which all rely on data quality dashboards to enhance site reporting for inclusion in network studies: OMOP, ACT, TriNetX, and PCORnet.

We excluded data partners that did not provide sufficient data to calculate body mass index (BMI) for at least 33% of their patients and those that reported limited death information, resulting in 44 out of 65 possible data partners being included in our final analyses. Once we finalized the set of reliable data partners, we included patients diagnose with COVID-19 or with a positive lab test for SARS-CoV-2 who were 19 years old or older. Patients with missing age or gender were excluded. Figure 1 includes a flow chart of study inclusion and exclusion criteria.

Data extraction from the N3C enclave

Data were extracted on October 1, 2021, (N3C release 47) in the OMOP Common Data Model version 5.3.1. All clinical concept sets were created collaboratively within the N3C Enclave, with at least one informatician and one clinical subject-matter expert reviewing each relevant concept set. Concept sets contain standardized terminology corresponding to clinical domains (e.g., LOINC, SNOMED CT, ICD-10, and RxNorm). For more information on the N3C enclave, data characteristics, data analysis, and cohort definition in the N3C data enclave, please refer to the Supplemental Methods. In addition, all codesets used to define AUD, COVID-19 positivity, covariates, and outcomes of interest are provided in Table S2.

Primary exposure

The primary exposure in this study was AUD. Subjects were considered to have an AUD if they had either (1) a documented diagnosis of AUD or (2) an alcohol-related complication. AUD was defined as a diagnosis of alcoholism, AUD, alcohol abuse, or alcohol dependence in the medical record. Alcohol-related complications included: a disorder caused by alcohol, alcoholic liver disease, alcoholic polyneuropathy, alcoholic cardiomyopathy, or alcoholic nervous system disease.

Outcomes

Primary outcomes were (1) hospitalization within 14 days of testing positive for SARS-CoV2 and (2) all-cause mortality. All-cause mortality was defined as any reported death or transition to hospice care. Secondary outcomes include a diagnosis of acute kidney injury and the need for invasive mechanical ventilation.

Other covariates

Confounders, which were determined a priori through directed acyclic graphs, clinical expertise, and relevant literature, included age (continuous and categorical), sex, race/ethnicity (non-Hispanic White, Black or African American, Hispanic or Latino, Missing/unknown, or other), smoking status (nonsmoker vs. current or former smoker), BMI (continuous and categorical), and the following comorbid conditions: hypertension, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, rheumatologic disease, hemiplegia or

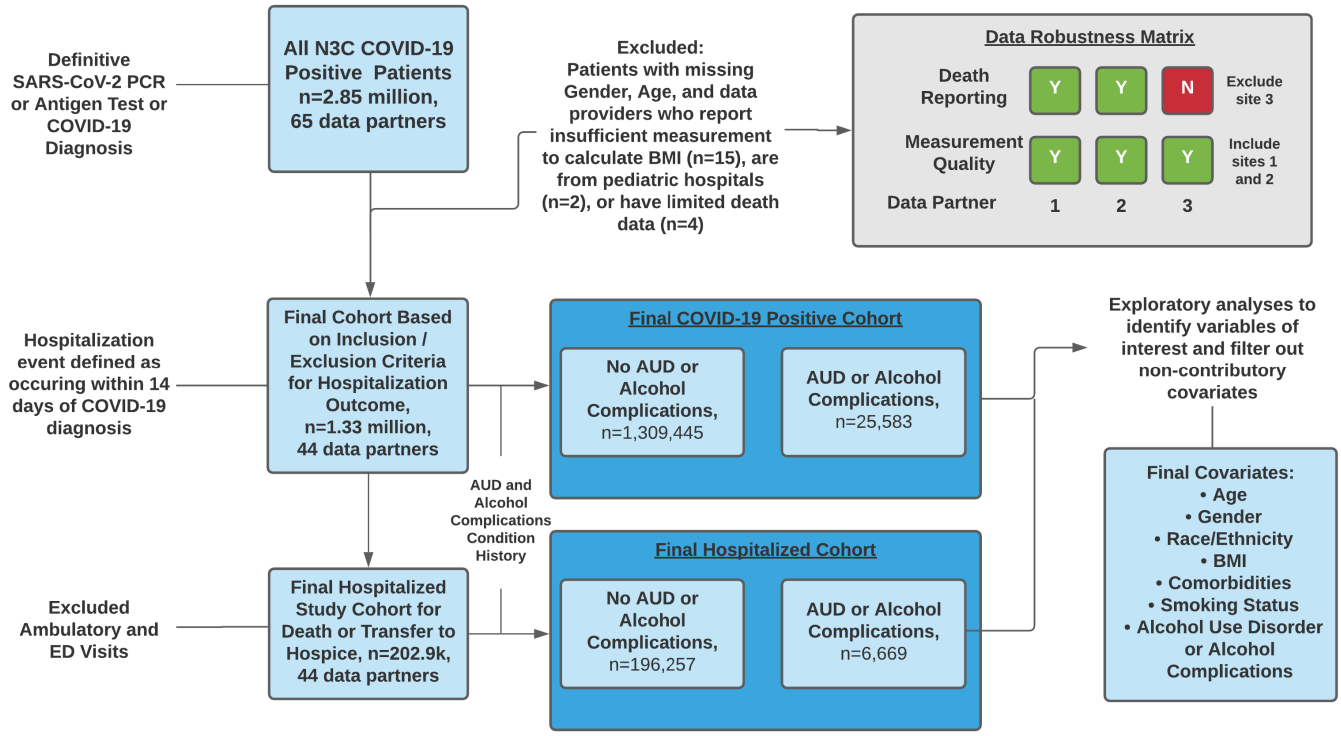

FIGURE 1 Summary of the analysis strategy. AUD, alcohol use disorder; BMI, body mass index; ED, emergency department

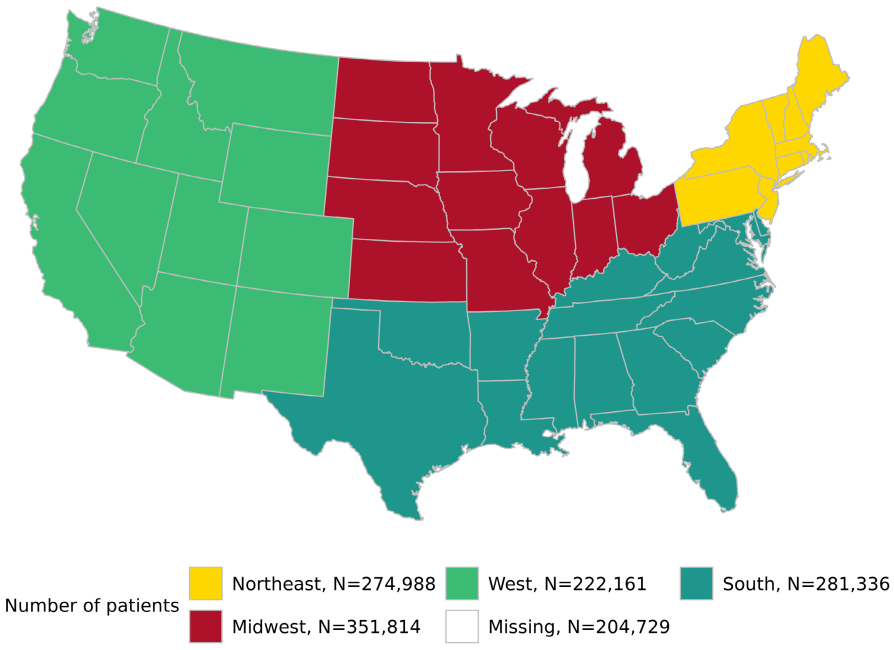

FIGURE 2 Geographic distribution of the cohort

paraplegia, renal disease, and HIV/AIDS). Data on the regional location of subjects was also collected.

Statistical analysis

Analysis was conducted first on the total cohort of patients meeting our inclusion/exclusion criteria and then on the subset of such patients who required hospitalization. Frequencies and percentages or medians and interquartile ranges of all demographic, clinical, and outcome measures within each of these cohorts were calculated. Comparisons of measures between those with and without AUD in the full cohort and those with and without AUD in the hospitalized cohort were made using chi-squared tests or Wilcoxon rank-sum tests. A multiple logistic regression model was used to evaluate the risk of hospitalization between those with and without AUD in

the full cohort while controlling for age, sex, race/ethnicity, smoking, BMI, hypertension, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, rheumatologic disease, hemiplegia or paraplegia, renal disease, and HIV/AIDS. A similar logistic regression model was used to compare all-cause mortality rates between those with and without AUD, first overall, and then limited to those within the hospitalized cohort. The logistic regression models included individual comorbidities as opposed to a composite index such as the Charlson Comorbidity index to avoid including disease states that may lie in the casual pathway between AUD and outcomes of interest. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Geographic distribution of the cohort

The cohort is evenly distributed within the continental United States. The Northeast had 21% of subjects, Midwest 26%, West 16%, and South 21%, while 15% had missing geographic data (Figure 2).

Demographics of the overall cohort

After our inclusion and exclusion criteria were satisfied, there were 1,335,028 COVID-19 patients. We identified 25,583 (1.9%) participants with a history of AUD or medical complications of alcohol use, and 1,309,445 without. Their characteristics are summarized in Table 1.

The percentage of people aged 65 or older was the same (19%) in those with and without AUD. However, there were more middle-aged people (50 to 64 years) in the AUD group (35% vs. 26%). There were more males (65%) in the AUD group compared to the No AUD group (44%). In terms of race and ethnicity, there were more non-Hispanic whites (56% vs. 51%) in the AUD group compared to the No AUD group. A higher number of those with AUDs were former or current smokers (38%) compared to those without AUD (22%). Those with AUD had similar rates of obesity (33%) as those without (36%). Those with AUD, however, were more likely to be underweight (4% vs. 1.8%), normal weight (25% vs. 16%), and overweight (29% vs. 22%) compared to those without AUD. There were higher levels of "unknown" BMI in those without AUD (Table 1).

COVID-19 patients with AUD were more likely to be admitted to the hospital

COVID-19 patients with AUD were more likely to be admitted to the hospital (26%) compared to those without AUD (15%; $p < 0.001$). Those with AUD were also twice as likely to die or be transitioned to hospice care (4.9% vs. 2.3%, $p < 0.001$; Table 1). The unadjusted odds ratio (OR) for hospitalization for those with AUD versus those without was 2.00 (confidence interval [CI] 1.94 to 2.06, $p < 0.001$; Table 2a). After adjusting for age, sex, race/ethnicity, smoking, BMI, hypertension, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, rheumatologic disease, hemiplegia or paraplegia, renal disease, and HIV/AIDS, those with an AUD still had higher odds of requiring hospitalization (OR = 1.51, 95% CI 1.46 to 1.56, $p < 0.001$; Table 2b).

COVID-19 patients with AUDs had a higher all-cause mortality

In the full cohort, the crude OR for all-cause mortality in the full cohort for AUD versus no AUD was 2.18 (CI 2.05 to 2.31, $p < 0.001$; Table 3a). After adjusting for age, sex, race/ethnicity, smoking, BMI, hypertension, diabetes, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, rheumatologic disease, hemiplegia or paraplegia, renal disease, and HIV/AIDS, those with an AUD still had higher odds of mortality or transfer to hospice of (OR = 1.55, 95% CI 1.46 to 1.65, $p < 0.001$; Table 3b).

COVID-19 in a cohort of hospitalized patients

We investigated outcomes in hospitalized patients alone because the most reliable and timely death data are available in EHRs of hospitalized patients.

Demographics of hospitalized COVID-19 patients with and without AUDs

Demographic, clinical, and outcome statistics for the COVID-19 patients who were hospitalized are presented in Table 4. Those with AUD were younger, with only 28% being over the age of 65 compared to 40% of those without AUD. The majority were male (72%), compared to those without AUDs (50%). Those with AUD were more likely to be non-Hispanic whites (51%) versus those without AUD (45%). Those with AUD were more likely to be underweight and normal weight than those without AUD. Rates of obesity were lower in those with AUD (35%) compared to those without AUD (46%). Those with AUD were more likely to have multiple comorbidities (84%) than those without AUD (49%). As expected, those with AUD were more frequently diagnosed with cirrhosis (22%) than those without (1.5%; Table 4).

Hospitalized COVID-19 patients with AUDs had higher all-cause mortality than those without AUDs

In unadjusted comparisons, COVID-19 patients with AUD were somewhat more likely to develop acute kidney injury (18%) compared

TABLE 1 Baseline characteristics of all COVID-19 patients with and without alcohol use disorder or alcohol complications

	No AUD or alcohol complication *n* = 1,309,445[a]	AUD or alcohol complication *n* = 25,583[a]	*p* value**
Age, median Interquartile range (IQR)	47 (33, 61)	51 (38, 62)	<0.001
Age group			<0.001
<29	249,220 (19%)	3068 (12%)	
30 to 49	463,697 (35%)	8671 (34%)	
50 to 64	341,367 (26%)	8918 (35%)	
≥65	255,161 (19%)	4926 (19%)	
Male Sex	571,884 (44%)	16,709 (65%)	<0.001
Race/ethnicity			<0.001
Non-Hispanic White	671,494 (51%)	14,302 (56%)	
Black or African American	186,521 (14%)	4601 (18%)	
Hispanic or Latino	218,949 (17%)	4083 (16%)	
Other	135,715 (10%)	2165 (8.5%)	
Missing/unknown	96,766 (7.4%)	432 (1.7%)	
Current or former smoker	292,698 (22%)	9760 (38%)	<0.001
BMI, median (IQR)	29 (25, 34)	28 (24, 33)	<0.001
BMI categories			<0.001
Underweight (<18.5)	23,039 (1.8%)	1022 (4.0%)	
Normal weight (18.5 to 24.9)	213,666 (16%)	6427 (25%)	
Overweight (25.0 to 29.9)	282,861 (22%)	7522 (29%)	
Obese (≥30.0)	428,757 (33%)	9093 (36%)	
Unknown/missing	361,122 (28%)	1519 (5.9%)	
Comorbidities			
Hypertension	317,401 (24%)	13,691 (54%)	<0.001
Diabetes mellitus	169,737 (13%)	6590 (26%)	<0.001
Myocardial infarction	24,828 (1.9%)	1679 (6.6%)	<0.001
Congestive heart failure	49,445 (3.8%)	3070 (12%)	<0.001
Peripheral vascular disease	60,277 (4.6%)	3197 (12%)	<0.001
Stroke	47,860 (3.7%)	2779 (11%)	<0.001
Dementia	13,361 (1.0%)	819 (3.2%)	<0.001
Chronic pulmonary disease	149,024 (11%)	6832 (27%)	<0.001
Rheumatologic disease	40,694 (3.1%)	1219 (4.8%)	<0.001
Peptic ulcer disease	9839 (0.8%)	1103 (4.3%)	<0.001
Cirrhosis	7241 (0.6%)	3354 (13%)	<0.001
Hemiplegia or paraplegia	6851 (0.5%)	463 (1.8%)	<0.001
Renal disease	63,104 (4.8%)	2932 (11%)	<0.001
Any malignancy (except skin)	70,030 (5.3%)	2420 (9.5%)	<0.001
Metastatic solid tumor	12,567 (1.0%)	491 (1.9%)	<0.001
HIV/AIDS	7464 (0.6%)	618 (2.4%)	<0.001
Multiple comorbidities	495,307 (38%)	19,117 (75%)	<0.001
Outcomes			
Hospitalized after COVID diagnosis	196,257 (15%)	6669 (26%)	<0.001
Death or transfer to hospice	30,533 (2.3%)	1264 (4.9%)	<0.001

**Wilcoxon rank sum test; Pearson's Chi-squared test.

[a]Median (IQR) or *n* (%).

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TABLE 2 Association of alcohol use disorder and hospitalization in COVID-19 positive cohort

	OR	CI	*p* value
(a) Unadjusted OR for hospitalization			
History of AUD or alcohol complications	2.00	1.94, 2.06	<0.001
(b) Adjusted odds ratio for hospitalization			
Age	1.04	1.04, 1.04	<0.001
Male sex	1.37	1.35, 1.38	<0.001
Race/Ethnicity			
Non-Hispanic White (reference)			
Black or African American	2.21	2.18, 2.24	<0.001
Hispanic or Latino	1.90	1.87, 1.93	<0.001
Missing/unknown	0.87	0.85, 0.90	<0.001
Other	1.68	1.65, 1.71	<0.001
Smoking status			
Nonsmoker (reference)			
Current or former	1.11	1.09, 1.12	<0.001
BMI			
<18.5	1.14	1.10, 1.18	<0.001
18.5 to 24.9 (reference)			
25 to 29.9	1.00	0.99, 1.02	0.9
≥30	1.34	1.32, 1.36	<0.001
Missing/unknown	0.31	0.31, 0.32	<0.001
Comorbidities			
Hypertension	0.65	0.64, 0.66	<0.001
Diabetes	1.01	1.00, 1.03	0.061
Myocardial infarction	1.32	1.28, 1.36	<0.001
Congestive heart failure	1.84	1.80, 1.88	<0.001
Peripheral vascular disease	1.01	0.99, 1.03	0.2
Stroke	1.16	1.14, 1.19	<0.001
Dementia	1.76	1.69, 1.82	<0.001
Chronic pulmonary disease	0.91	0.89, 0.92	<0.001
Rheumatologic disease	0.79	0.77, 0.81	<0.001
Hemiplegia or paraplegia	2.05	1.94, 2.16	<0.001
Renal disease	1.70	1.66, 1.73	<0.001
HIV/AIDS	0.68	0.64, 0.72	<0.001
Adjusted OR for hospitalization for those with AUD or alcohol complication	1.51	1.46, 1.56	<0.001

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; OR, odds ratio.

to those without AUD (17%; $p < 0.001$). The two groups had similar rates of requiring invasive mechanical ventilation (9.5% vs. 9.1% ($p = 0.3$)). Those with AUD also had somewhat higher rates of death or transfer to hospice care (13%) compared to those without AUD (12%; $p = 0.002$; Table 4). The rates of discharge to hospice were not significantly different between those with AUD (0.7%) and without AUD (0.6%).

The crude OR for death or transfer to hospice for AUD versus no AUD was 1.12 (CI 1.04 to 1.20, $p = 0.002$; Table 5a). After adjusting for all relevant confounders as previously described, those with AUD or alcohol complications had 15% higher odds of all-cause mortality, with an OR of 1.15 (95% CI 1106 to 1.24, $p < 0.001$; Table 5b).

DISCUSSION

In this analysis, we have demonstrated that COVID-19 patients with an AUD documented in the medical record are more likely to be hospitalized for COVID-19 and had higher all-cause mortality than patients without an AUD. One of the strengths of this analysis was that we were able to use a large, multicenter database that included 44 centers. This analysis included more than one million cases of COVID-19 throughout the United States. It includes centers in rural areas as well as urban. Temporally, it includes patients not only from the initial surge but also included patients from later stages of the pandemic.

In this cohort, those with AUD had higher rates of several comorbidities. Because of this, we corrected for comorbidities in our analysis. Those with AUD had higher rates of cirrhosis. A small, multicenter trial reported that cirrhosis patients with COVID-19 ($n = 37$) had a 30% mortality, similar to those hospitalized with cirrhosis alone (20% mortality), but higher mortality than those with COVID-19 alone (13% mortality). Like our findings, the cirrhosis groups had significantly higher current alcohol use (10% to 25%) compared to subjects with COVID-19 alone (2%; Bajaj et al., 2021). It is likely that both cirrhosis and AUD affect the severity of COVID-19. Likewise, those with AUD had higher rates of chronic pulmonary diseases, likely due to their higher rates of smoking (Table 1). Chronic Obstructive Pulmonary Disease (COPD) is thought to increase the severity and mortality of COVID-19 pneumonia (Lippi & Henry, 2020; Wu et al., 2020). In the N3C database, the risk of death was two times higher in those with COPD (Meza et al., 2021). Early in the pandemic, it was reported that hypertension was very common comorbidity with COVID-19 (Guan et al., 2020). There is evidence that patients with hypertension may have more severe outcomes with COVID-19 infection, including worse mortality (Du et al., 2021; Pranata et al., 2020a; Roncon et al., 2020; Zuin et al., 2020). Likewise, diabetes is an important comorbidity that leads to worse outcomes in those with COVID-19 (Singh et al., 2020). This is true for both Type I and Type II Diabetes (Barron et al., 2020).

Having an AUD is a known risk factor for developing ARDS (Moss et al., 2003), a severe complication of COVID-19. AUD is also a risk factor for developing multisystem failure with ARDS (Moss & Burnham, 2003). Unfortunately, in this cohort, we were unable to determine whether ARDS was increased in those with AUD due to widely variable ways of defining ARDS at the different centers. This is an important topic that needs further study.

TABLE 3 Death or transfer to hospice in the COVID-19 positive cohort

Covariate	OR	CI	*p* value
(a) Unadjusted OR for death or transfer to hospice			
History of AUD or alcohol complications	2.18	2.05, 2.31	<0.001
(b) Adjusted OR for death or transfer to hospice			
Age	1.08	1.08, 1.08	<0.001
Male sex	1.68	1.64, 1.72	<0.001
Race/ethnicity			
Non-Hispanic White (reference)			
Black or African American	1.54	1.49, 1.59	<0.001
Hispanic or Latino	1.54	1.49, 1.60	<0.001
Missing/unknown	1.03	0.96, 1.10	0.4
Other	1.47	1.42, 1.53	<0.001
Smoking status			
Nonsmoker (reference)			
Current or former	1.11	1.08, 1.14	<0.001
BMI			
<18.5	1.46	1.37, 1.56	<0.001
18.5 to 24.9 (reference)			
25 to 29.9	0.82	0.80, 0.85	<0.001
≥30	1.10	1.06, 1.13	<0.001
Missing/unknown	0.45	0.43, 0.48	<0.001
Comorbidities			
Hypertension	0.66	0.64, 0.68	<0.001
Diabetes	1.14	1.10, 1.17	<0.001
Myocardial infarction	1.18	1.12, 1.23	<0.001
Congestive heart failure	1.81	1.74, 1.87	<0.001
Peripheral vascular disease	1.07	1.03, 1.11	<0.001
Stroke	1.14	1.09, 1.18	<0.001
Dementia	1.96	1.87, 2.05	<0.001
Chronic pulmonary disease	1.08	1.05, 1.11	<0.001
Hemiplegia or paraplegia	1.91	1.76, 2.08	<0.001
Renal disease	1.80	1.74, 1.86	<0.001
HIV/AIDS	0.95	0.82, 1.08	0.4
Adjusted OR for death or transfer to hospice for those with a history of AUD or alcohol complications	1.55	1.46, 1.65	<0.001

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; OR, odds ratio.

In this study, we report higher hospitalization rates in those with AUD. Our results are in contrast to a smaller UK study of 750 COVID-19 cases that showed that heavy alcohol consumption was not related to COVID-19 hospitalization (Hamer et al., 2020). However, interestingly, the reference group for this study was those with "moderate" alcohol intake (defined as ≤3 drinks per day for men and ≤2 drinks per day for women), rather than the never drinkers, which may have affected the analysis.

Our analysis has several limitations that must be taken into consideration. A major limitation of this analysis was that AUD Identification Test scores, and Short Michigan Alcohol Screening tests were not available. Likewise, we were unable to accurately quantify how many standard drinks each subject was drinking per day or per occasion prior to, or at the time of COVID-19 diagnosis. Unfortunately, alcohol use was not well documented in the medical records of most participating sites. Because of this, we had to rely on a diagnosis of AUD or alcohol-related complications. It is well known that AUDs are underreported in the medical record (Gryczynski et al., 2020). This means that we have likely only studied only those with very severe AUD. In addition, our "No AUD" group likely includes individuals who have AUD that is not documented. It is known that those who drink even 2 to 3 drinks a day have a higher risk of ARDS (Simou et al., 2018b), and we were unable to assess this in this cohort.

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TABLE 4 Demographics of hospitalized COVID-19 patients with and without AUD

	No AUD or alcohol complication *n* = 196,257[a]	AUD or alcohol complication *n* = 6669[a]	*p* value[2]
Age, median (IQR)	60 (44, 72)	57 (44, 66)	<0.001
Age group			
<29	16963 (8.6%)	412 (6.2%)	<0.001
30 to 49	45618 (23%)	1831 (27%)	
50 to 64	54844 (28%)	2572 (39%)	
≥65	78832 (40%)	1854 (28%)	
Male sex	97510 (50%)	4787 (72%)	<0.001
Race/ethnicity			<0.001
Non-Hispanic white	88789 (45%)	3372 (51%)	
Black or African American	41955 (21%)	1537 (23%)	
Hispanic or Latino	37648 (19%)	1064 (16%)	
Other	22123 (11%)	596 (8.9%)	
Missing/unknown	5742 (2.9%)	100 (1.5%)	
Current or former smoker	54983 (28%)	2883 (43%)	<0.001
BMI categories			<0.001
Underweight (<18.5)	5074 (2.6%)	386 (5.8%)	
Normal weight (18.5 to 24.9)	33031 (17%)	1880 (28%)	
Overweight (25.0 to 29.9)	50377 (26%)	1848 (28%)	
Obese (≥30.0)	89540 (46%)	2327 (35%)	
Unknown/missing	18235 (9.3%)	228 (3.4%)	
Individual comorbidities			
Hypertension	71045 (36%)	4383 (66%)	<0.001
Diabetes mellitus	43925 (22%)	2281 (34%)	<0.001
Myocardial infarction	9858 (5.0%)	777 (12%)	<0.001
Congestive heart failure	21165 (11%)	1435 (22%)	<0.001
Peripheral vascular disease	17811 (9.1%)	1240 (19%)	<0.001
Stroke	16024 (8.2%)	1127 (17%)	<0.001
Dementia	6476 (3.3%)	421 (6.3%)	<0.001
Chronic pulmonary disease	29264 (15%)	2147 (32%)	<0.001
Rheumatologic disease	7496 (3.8%)	347 (5.2%)	<0.001
Peptic ulcer disease	2635 (1.3%)	427 (6.4%)	<0.001
Cirrhosis	2968 (1.5%)	1448 (22%)	<0.001
Hemiplegia or paraplegia	2880 (1.5%)	197 (3.0%)	<0.001
Renal disease	24650 (13%)	1352 (20%)	<0.001
Any malignancy (except skin)	16931 (8.6%)	846 (13%)	<0.001
Metastatic solid tumor	3828 (2.0%)	210 (3.1%)	<0.001
HIV/AIDS	1188 (0.6%)	160 (2.4%)	<0.001
Multiple comorbidities	97017 (49%)	5633 (84%)	<0.001
Outcomes			
Acute kidney injury	32630 (17%)	1232 (18%)	<0.001
Invasive mechanical ventilation	18728 (9.5%)	609 (9.1%)	0.3
Death or transfer to hospice	23397 (12%)	878 (13%)	0.002
Inpatient therapies			
Steroids	39220 (20%)	1011 (15%)	<0.001
Remdesivir	5246 (2.7%)	265 (4.0%)	<0.001
Transfusion	15062 (7.7%)	497 (7.5%)	0.5
Vasopressor	39220 (20%)	1011 (15%)	<0.001

[2]Wilcoxon rank sum test; Pearson's Chi-squared test.

[a]Median (IQR); *n* (%).

TABLE 5 Association of alcohol use disorder and inpatient death or transfer to hospice in hospitalized COVID-19 positive cohort

Covariate	OR	CI	*p* value
(A) Unadjusted OR for inpatient death or transfer to hospice			
History of AUD or alcohol complications	1.12	1.04, 1.20	0.002
(B) Adjusted OR for inpatient death or transfer to hospice			
Age	1.05	1.05, 1.05	<0.001
Male sex	1.47	1.42, 1.51	<0.001
Race/ethnicity			
Non-Hispanic White (reference)			
Black or African American	1.03	0.99, 1.07	0.2
Hispanic or Latino	1.11	1.06, 1.15	<0.001
Missing/unknown	1.41	1.30, 1.54	<0.001
Other	1.07	1.02, 1.12	0.008
Smoking status			
Nonsmoker (reference)			
Current or former	1.14	1.10, 1.17	<0.001
BMI			
<18.5	1.23	1.14, 1.34	<0.001
18.5 to 24.9 (reference)			
25 to 29.9	0.89	0.85, 0.93	<0.001
≥30	1.04	1.00, 1.09	0.030
Missing/unknown	0.86	0.81, 0.91	<0.001
Comorbidities			
Hypertension	0.81	0.78, 0.85	<0.001
Diabetes	1.06	1.03, 1.10	0.001
Myocardial infarction	1.04	0.98, 1.10	0.2
Congestive heart failure	1.38	1.33, 1.45	<0.001
Peripheral vascular disease	1.07	1.02, 1.11	0.005
Stroke	1.09	1.04, 1.14	<0.001
Dementia	1.40	1.32, 1.48	<0.001
Chronic pulmonary disease	1.05	1.01, 1.10	0.010
Rheumatologic disease	0.96	0.89, 1.03	0.2
Hemiplegia or paraplegia	1.41	1.28, 1.55	<0.001
Renal disease	1.47	1.41, 1.53	<0.001
HIV/AIDS	0.96	0.79, 1.14	0.6
Adjusted OR for inpatient mortality or transfer to hospice for those with a history of AUD or alcohol complications	1.15	1.06, 1.24	<0.001

Abbreviations: AUD, alcohol use disorder; BMI, body mass index; CI, confidence interval; OR, odds ratio.

An interesting issue in alcohol-related EHR studies is the association between AUD and cigarette smoking (Falk et al., 2006). Cigarette smoking is twice as common in those with AUD and those without (Weinberger et al., 2019). To address this issue, we have corrected for former or current cigarette smoking in all of our analyses. Due to constraints with the N3C database, we were not able to separately correct for former and current smoking. Early on in the pandemic, there were controversial reports that current smokers were spared from COVID-19 infection (Huang et al., 2020). Since then, the Centers for Disease Control (CDC) has acknowledged that both former and current smoking are both risk factors for severe disease and the concept has been relegated to a myth (Berlin & Thomas, 2020; Hopkinson et al., 2021; Kaur et al., 2020; Lowe et al., 2021; Mohsin et al., 2021; Neira et al., 2021; Patanavanich & Glantz, 2020, 2021; Peng et al., 2021; Rodgers et al., 2021; Shastri et al., 2021; Umnuaypornlert et al., 2021; van Westen-Lagerweij et al., 2021; Zhang et al., 2021).

Another limitation is that our data suggest that those with a diagnosis of AUD were better known to the health care system. For instance, we had lower numbers of missing or unknown race/ethnicity

and BMI in those that had a diagnosis of AUD, which could be due to more frequent clinic visits or hospitalizations prior to testing positive for COVID-19. This may have increased the documentation of comorbidities in those with AUD compared to those without. Of interest, in this cohort of patients with COVID-19, those with AUD had a significantly higher number of medical comorbidities documented. This included liver disease, hypertension, diabetes, history of myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, chronic pulmonary disease, rheumatologic disease, hemiplegia or paraplegia, and renal disease. Having significant comorbidities is a known risk factor for poor outcomes in COVID-19 (Ejaz et al., 2020; Yang et al., 2020). AUD is known to increase many of these comorbidities such as liver disease (Mandayam et al., 2004), diabetes (Carlsson et al., 2005), stroke (Reynolds et al., 2003), hypertension (Saunders et al., 1981), dementia (Rehm et al., 2019) renal disease (Perneger et al., 1999), and HIV/AIDs (Ferguson et al., 2020). So, it is not clear if the comorbidities are higher or better documented in those with AUD.

Likewise, there are many limitations of our research that are related to the limitations of the N3C database. For example, we could not include site effects or timing of the infection in the analysis due to blinding to site and date shifting in the cohort. However, it is important to note that our cohort was fairly equally distributed throughout the United States (Figure 2), and was spread over a period of time that included surges in several geographic areas. Another limitation is the lack of availability of vaccination status. Vaccination is an important tool to prevent hospitalization and death due to COVID-19. Those with substance abuse disorders (including AUD) are known to have more breakthrough infections with COVID-19 (Wang et al., 2022). However, reliable vaccination status was only available in a few sites where the EHR was connected to state HIEs or other agencies.

This analysis suggests that those with AUD are more likely to be hospitalized for COVID-19 and have higher all-cause mortality. It is not clear whether this is simply due to alcohol intake or if this is related to comorbidities caused by heavy alcohol intake, although our adjustment for these conditions in statistical modeling does indicate independent effects of AUD. Further research is needed to determine whether AUD is an independent risk factor for poor outcomes with viral pneumonia such as COVID-19.

However, given the strong association of AUD with the need for hospitalization in COVID-19 pneumonia, clinicians should ask patients about alcohol use and misuse. Those with AUD or alcohol misuse should be carefully observed for deterioration and clinicians should have a low threshold for admission to the hospital and transfer for ICU care if needed.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

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