Impact of Alcohol Misuse on Requirements for Critical Care Services and Development of Hospital Delirium in Patients With COVID-19 pneumonia

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OBJECTIVES: Alcohol misuse has been associated with increased morbidity in the setting of pulmonary infections, including the need for critical care resource utilization and development of delirium. How alcohol misuse impacts morbidity and outcomes among patients admitted with COVID-19 pneumonia is not well described. We sought to determine if alcohol misuse was associated with an increased need for critical care resources and development of delirium among patients hospitalized with COVID-19 pneumonia.

DESIGN: Retrospective cohort study.

SETTING: Twelve University of Colorado hospitals between March 2020 and April 2021.

PATIENTS: Adults with a COVID-19 diagnosis.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was admission to the ICU. Secondary outcomes included need for mechanical ventilation, development of delirium, and in-hospital mortality. Alcohol misuse was defined by *International Classification of Diseases*, 10th Revision codes. Of 5,979 patients hospitalized with COVID-19, 26% required ICU admission and 15.4% required mechanical ventilation. Delirium developed in 4.5% and 10.5% died during hospitalization. Alcohol misuse was identified in 4%. In analyses adjusted for age, sex, body mass index, diabetes, and liver disease, alcohol misuse was associated with increased odds of ICU admission (adjusted odds ratio [aOR], 1.46; $p < 0.01$), mechanical ventilation (aOR, 1.43; $p = 0.03$), and delirium (aOR, 5.55; $p < 0.01$) compared with patients without misuse. Mortality rates were not associated with alcohol misuse alone, although the presence of both alcohol misuse and in-hospital delirium significantly increased odds of in-hospital death (aOR, 2.60; $p = 0.04$).

CONCLUSIONS: Among patients hospitalized with COVID-19, alcohol misuse was associated with increased utilization of critical care resources including ICU admission and mechanical ventilation. Delirium was an important modifiable risk factor associated with worse outcomes in hospitalized patients with alcohol misuse, including increased odds of death.

KEY WORDS: alcohol use disorder; intensive care; mechanical ventilation

The COVID-19 pandemic has stressed healthcare systems as well as the physical and mental health of populations around the world. Early in the COVID-19 pandemic, rates of alcohol use disorders (AUDs) accelerated for multiple reasons including increased isolation, use of alcohol as a coping mechanism, and lack of readily available abstinence resources (1–3).

KEY POINTS

Question: Is the identification of alcohol misuse in patients hospitalized with COVID-19 pneumonia associated with utilization of critical care resources or differences in in-hospital outcomes?

Findings: In patients hospitalized for COVID-19 pneumonia, identification of alcohol misuse was associated with increased need for ICU admission, initiation of mechanical ventilation, and risk of in-hospital death. Delirium was identified as a key modifiable condition associated with increased risk of death in critically ill patients with concomitant alcohol misuse.

Meaning: Preexisting alcohol misuse history may identify hospitalized COVID-19 pneumonia patients at high risk for utilization of increased healthcare resources. Further, interventions to reduce frequency and duration of delirium may represent a modifiable risk factor for improving outcomes and reducing need for critical care services in hospitalized COVID-19 patients with alcohol misuse.

Prior investigations have demonstrated dose-dependent associations between alcohol misuse and poorer outcomes in patients hospitalized with pneumonia including increased risk for prolonged hospital and ICU lengths of stay and development of the acute respiratory distress syndrome (ARDS) (4–15). While changes in alcohol consumption have been consistently observed during the COVID-19 pandemic, the impact of alcohol misuse on healthcare outcomes related to COVID-19 are conflicted. Through the relatively short period of the pandemic, numerous factors have been established that may predispose patients to more severe COVID-19 pneumonia including older age, obesity, and certain comorbid conditions (16–18); therefore, alcohol misuse may represent a modifiable risk factor that similarly influences outcomes.

Mechanisms underlying the relationship between alcohol misuse on pneumonia outcomes are incompletely defined and likely multifactorial. While alcohol misuse is itself associated with direct organ injury, it is also possible that alcohol compounds the effects of critical illness on proper organ function. In particular, alcohol misuse has been associated with increased rates of delirium (19, 20). Delirium that develops in

critically ill patients is associated with increased short- and long-term morbidity and mortality, including ICU-related complications, prolonged hospitalizations, and increased rates of cognitive dysfunction in the year after critical illness (21). However, investigations evaluating the interplay between alcohol misuse and delirium on critical illness related to COVID-19 are limited. One multicenter study involving critically ill patients with COVID-19 suggested that patients categorized as having current smoking or alcohol abuse had higher odds for development of delirium and fewer days alive and free of coma or delirium (22).

Given the changing pattern of alcohol use during the COVID-19 pandemic (23, 24), we sought to determine whether prehospital alcohol misuse was associated with ICU admission and critical care resource utilization. Further, given the previously demonstrated association between alcohol misuse and delirium (22, 25), we wished to determine the impact of alcohol misuse on hospital outcomes in patients with COVID-19, including in-hospital mortality. We hypothesized that patients hospitalized with COVID-19 pneumonia who had prehospital alcohol misuse would be more likely to require utilization of critical care resources and develop delirium and would be less likely to survive hospitalization.

METHODS

We performed a retrospective cohort study using electronic health record (EHR) data from 12 hospitals within the University of Colorado Health (UCHealth) system. Data extraction services were provided by the Health Data Compass Data Warehouse project (healthdatacompass.org). Data collected from March 2020 to April 2021 were included in the analysis. The project was approved by the Colorado Multiple Institutional Review Board (Institutional Review Board protocol number 20-0690 "COVID-19 Hospitalizations"). All study procedures were followed in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975.

Patients 18 years and older with an identified COVID-19 diagnosis (defined by the presence of a positive polymerase chain reaction (PCR) test or a COVID-19–associated diagnosis code documented in the UCHealth EHR were included in the analysis. Using this strategy, given the time frame of data collection (early in U.S. pandemic through early 2021,

prior to widespread vaccinations), it is presumed that all patients had COVID-19 pneumonia as their primary diagnosis. Where patients had been hospitalized more than once, only the data from each patient's initial hospitalization for COVID-19 were included to further increase the likelihood that patients in the study cohort had acute COVID-19 pneumonia rather than nonresolving COVID-19 infection. Patients with an obstetrics-related level of care who were admitted by an obstetrics service were excluded to minimize the possibility of including patients with incidental COVID-19 positivity in the cohort. Patients who were still hospitalized at the time of data delivery were also excluded.

The primary outcome of interest was "admission to the ICU," defined as the receipt of ICU-level care of any duration. Secondary outcomes included "mechanical ventilation," determined by documentation of endotracheal tube placement in the EHR lines/drains/airways flowsheet; "development of in-hospital delirium" (referred to subsequently as "delirium"), as presence of a billing or encounter diagnosis code for generalized and/or alcohol-associated delirium during the hospitalization (R41.0, F05.*, F10.1 [2,3]1, F10.921), and "in-hospital death" during the hospitalization of interest. The primary predictor, "evidence of alcohol misuse," was defined using previously validated diagnosis codes (F10.1*, F10.2*, F10.9*) from the hospitalization of interest or recorded inpatient history (26, 27). Subgroups including patients with alcohol use in remission (F.10.11, F.10.21) and patients with a diagnosis of alcohol withdrawal (F10.13*, F10.23*, F10.93*) were identified using the codes relevant to these diagnoses.

Additional outcomes of interest included duration of mechanical ventilation support, ICU length of stay, total hospitalization length of stay, development of ARDS defined by *International Classification of Diseases*, 10th Revision coding, need for vasopressors, and proportion discharged to home or self-care. Administration of COVID-specific therapies (remdesivir, dexamethasone, tocilizumab, and baricitinib) were also recorded.

Comparisons of patients with and without alcohol misuse were performed using *t* tests (or nonparametric equivalent) or chi-square tests (or exact equivalent), as appropriate. Age was stratified into three categories (< 40, 40–65, and > 65 yr), given the known differences in alcohol use patterns across the lifespan (28). Self-reported race and ethnicity information

was restructured into Hispanic, regardless of race, non-Hispanic White, non-Hispanic Black/African American, and other/unknown/refused; information regarding English proficiency was also obtained. Hospital information collected included payer source and hospital region. Admission body mass index (BMI) was recorded. The Charlson Comorbidity Index (CCI) for each patient was calculated using available diagnosis codes for preexisting conditions that included chronic lung conditions (i.e., chronic obstructive pulmonary disease) and liver disease, among others. Information regarding each diagnosis present in the CCI was noted.

Univariable logistic regression was used to explore associations between alcohol misuse and the primary outcomes of interest. Multivariable mixed effects logistic regression models were used to estimate effects of alcohol misuse after adjusting for age at time of admission, sex, BMI, diabetes, and liver disease, given these factors' reported associations with COVID-19 risk and outcomes (29, 30). For multivariable models, diabetes was defined in patients who met the criteria for diabetes or moderate/severe diabetes in the CCI, or in patients with any hemoglobin A1c value obtained during hospitalization greater than or equal to 6.5%. Liver disease was categorized among patients who met either the CCI definition for mild or moderate/severe liver disease. Age and liver disease are known to be associated with respiratory failure development and poorer outcomes (including ARDS) unrelated to COVID-19 (29, 31, 32). A random effect for hospital region was included in the models, although random effects for individual hospitals could not be supported by modeling due to small numbers.

Separate models with delirium as an outcome were also adjusted for ICU admission (yes or no), given its higher prevalence in that setting, along with covariates previously mentioned (33). We also explored the interaction between alcohol misuse and delirium on in-hospital mortality in a separate model. All analyses were performed with R statistical software (Version 3.6.0; R Development Core Team, University of Auckland, Auckland, New Zealand). *p* values of less than 0.05 were considered statistically significant.

RESULTS

We identified 5,979 patients who met our inclusion criteria (**Fig. 1**). The average age of the cohort was 61
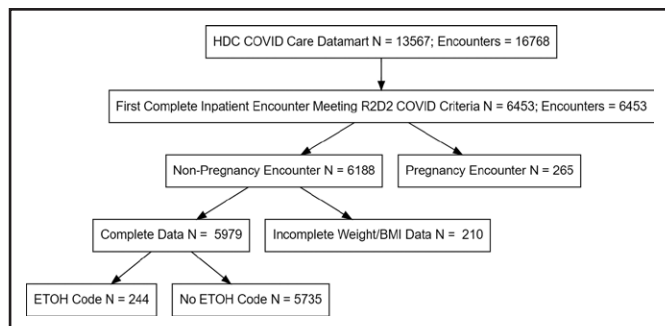
Figure 1. Cohort derivation from the Health Data Compass (HDC) datamart. Participants were excluded from the study if the admission was not their first encounter for COVID-19, if they were pregnant, or if there were missing weight/body mass index (BMI) data. A total of 5,979 patients were included in the final cohort. ETOH = alcohol misuse present, R2D2 = Reliable Response Data Discovery for COVID-19 Consortium.

years old and 56% were male. In the total cohort, 1,541 (26%) required ICU admission, with 1,291 (22%) requiring the ICU greater than 24 hours. In total, 925 (16%) required mechanical ventilation, and 847 (14%) required mechanical ventilation greater than 24 hours. Delirium was diagnosed in 273 (4.5%), with the majority (249, 91%) coded as having unspecified delirium. Twenty-four (9%) were coded with alcohol-related delirium. Overall, 629 patients died (10.5%) in the hospital, while 3,863 (65%) were discharged home.

A total of 244 patients (4%) met specified criteria for alcohol misuse. Among these 244 patients, 75 (31%) were coded as having alcohol withdrawal, 124 (51%) had another alcohol-related code, and 45 (18%) were coded as having alcohol misuse in remission. In the subset of 75 patients coded as having alcohol withdrawal, 23 were diagnosed with either alcohol-related or nonspecified delirium, representing 9% of the 244 patients in the alcohol misuse cohort as a whole.

Patients were stratified into subgroups according to alcohol misuse criteria. Patients with alcohol misuse were younger and more likely to be male, but race/ethnicity was not different between these groups; however, patients with alcohol misuse were less likely to require an interpreter (**Table 1, top**). Patients with alcohol misuse were more likely to have Medicaid than those without alcohol misuse. BMI was lower and diabetes more infrequent among those with alcohol misuse, but patients with alcohol misuse were more likely to have comorbid liver disease. Patients with alcohol misuse were less likely to receive remdesivir (29 vs 52%; $p < 0.01$), while the use of dexamethasone did not differ.

In terms of in-hospital outcomes, in univariable analyses, patients with alcohol misuse were more likely to require ICU admission (34 vs 25%; $p < 0.01$) and initiation of mechanical ventilation (23 vs 15%; $p < 0.01$) than those without misuse (**Table 1, bottom**). Further, the proportion of patients with alcohol misuse who required more than 24 hours in the ICU was also higher (27% vs 21.4%; $p = 0.04$). However, the median duration of mechanical ventilation was shorter for patients with alcohol misuse as was the overall ICU length of stay. Further, patients with alcohol misuse were more likely to have a delirium diagnosis compared with those without misuse (17 vs 4%; $p < 0.01$). In-hospital mortality did not differ significantly between the groups; approximately two-thirds of patients in both groups discharged home with self-care after their hospitalization. No differences in the frequency of ARDS were observed. Development of shock with need for vasopressor agents did not vary between the groups. The median hospital length of stay did not differ significantly between the two groups.

Multivariable analyses adjusted for age, gender, BMI, diabetes, and liver disease examining the association between alcohol misuse and the need for critical care resource utilization, including ICU admission and initiation of mechanical ventilation, are presented in **Table 2**. In these adjusted models, we observed that alcohol misuse was associated with a 46% increase in the odds of ICU admission, and a 43% increase in the odds of requiring mechanical ventilation initiation. Male gender, presence of diabetes mellitus, and/or presence of liver disease remained associated with both need for ICU admission and mechanical ventilation in adjusted models. In a model adjusted for age, gender, BMI, diabetes, liver disease, and ICU admission, patients with alcohol misuse experienced a 5.6-fold increase in risk of delirium compared with patients without misuse. Additional factors associated with increased risk of delirium included ICU admission and advanced age. Finally, in a model adjusted for age, gender, BMI, diabetes, and liver disease, alcohol misuse was not significantly associated with in-hospital death. In a separate interaction model, we identified a significant difference in odds of mortality when comparing patients with delirium and alcohol abuse codes to those with neither code type (**Fig. 2**; and **Digital Table 1**, http://links.lww.com/CCX/B114). Patients with delirium and no alcohol misuse exhibited a 58% increase in their risk of

TABLE 1.

Cohort Stratified by the Presence of an *International Classification of Diseases*, 10th Revision-Defined Prehospital Alcohol Use Disorder

Baseline Characteristic	No Alcohol Misuse, n = 5,735	Alcohol Misuse, n = 244	p
Mean age at admission (SD)	61.47 (17.1)	52.33 (15.1)	< 0.001
65 or older = true (%)	2,635 (45.9)	56 (23.0)	< 0.001
Categorical age (%)			< 0.001
≥ 65	2,635 (45.9)	56 (23.0)	
40 to < 65	2,391 (41.7)	130 (53.3)	
< 40	709 (12.4)	58 (23.8)	
Male gender (%)	3,238 (52.3)	197 (76.7)	< 0.001
Categorical race/ethnicity (%)			0.703
Black or African American, non-Hispanic	474 (8.3)	25 (10.2)	
Hispanic (regardless of race)	1,820 (32.6)	75 (30.7)	
Other, non-Hispanic/unknown	526 (9.2)	24 (9.8)	
White, non-Hispanic	2,915 (50.8)	120 (49.2)	
Interpreter needed (%)	1,005 (17.5)	29 (11.9)	0.028
Payer source (%)			< 0.001
Commercial/managed	1,483 (25.9)	37 (15.2)	
Medicaid/managed Medicaid	948 (16.5)	108 (42.0)	
Medicare/managed Medicare	2,566 (44.7)	73 (28.3)	
Other/unknown	738 (12.9)	35 (14.3)	
Body mass index, mean (SD)	31.33 (8.19)	27.78 (7.52)	< 0.001
CCI components (%)			
Acute myocardial infarction	390 (6.8)	< 20 (< 8%)	0.128
Congestive heart failure	676 (11.8)	24 (9.8)	0.434
Peripheral vascular disease	174 (3%)	< 20 (< 8%)	0.288
Dementia	280 (4.9%)	< 20 (< 8%)	0.909
Pulmonary disease	183 (3.2%)	< 20 (< 8%)	0.805
Connective tissue disorder	56 (1%)	< 20 (< 8%)	1.0
Peptic ulcer	< 20	< 20	Not available
Mild liver disease	240 (4.2)	47 (19.3)	< 0.001
Diabetes	1,328 (23)	32 (13.1)	0.009
Paraplegia	23 (0.4%)	< 20 (< 8%)	1.0
Renal disease	412 (7.2%)	< 20 (< 8%)	1.0
Cancer	62 (1.1%)	< 20 (< 8%)	0.52
Moderate to severe liver disease	34 (0.6)	21 (8.6)	< 0.001
HIV	23 (0.4%)	< 20 (< 8%)	1.0
Total CCI score, median (IQR)	0.00 (0.00–1.00)	0.00 (0.00–2.00)	0.001
COVID-19–specific therapies (%)			
Dexamethasone	1,878 (32.7)	67 (27.5)	0.098
Remdesivir	3,008 (52.4)	71 (29.1)	< 0.001
Tocilizumab	172 (3.0)	< 20	0.001
Baricitinib	< 20	< 20	0.99

(*Continued*)

TABLE 1. (*Continued*).
Cohort Stratified by the Presence of an *International Classification of Diseases*, 10th Revision-Defined Prehospital Alcohol Use Disorder

Baseline Characteristic	No Alcohol Misuse, n = 5,735	Alcohol Misuse, n = 244	p
In-hospital outcomes			
ICU admission (%)	1,457 (25.4)	84 (34.4)	0.002
ICU admission > 24 hr (%)	1,225 (21.4)	66 (27.0)	0.042
ICU days, median (IQR)	6.53 (1.83–15.04)	3.61 (1.09–8.83)	0.006
Mechanical ventilation (%)	870 (15.2)	55 (22.5)	0.002
Mechanical ventilation > 24 hr (%)	804 (14.0)	43 (17.6)	0.137
Mechanical ventilation days, median (IQR)	10.52 (4.92–18.66)	4.60 (1.26–9.05)	< 0.001
Diagnosis of delirium (%)	232 (4.0)	41 (16.8)	< 0.001
In-hospital death (%)	603 (10.5)	26 (10.7)	1.000
Discharged to home with self-care (%)	3,698 (64.5)	165 (67.6)	0.350
Diagnosis of acute respiratory distress syndrome (%)	783 (13.7)	26 (10.7)	0.213
Shock with documented receipt of vasopressor agents (%)	851 (14.8)	41 (16.8)	0.452
Median hospital length of stay (IQR)	4.97 (2.96–10.00)	4.93 (3.10–9.28)	0.861

CCI = Charlson Comorbidity Index, IQR = interquartile range.

death, while those with delirium and alcohol misuse exhibited a 2.6-fold increase in odds for death compared with those patients without evidence of delirium nor alcohol misuse. The interaction term did not reach statistical significance ($p = 0.658$).

In additional analyses restricting the cohort to patients with codes suggesting active alcohol misuse (i.e., excluding patients with alcohol use in remission), associations we observed in our multivariable analyses were more pronounced. However, the magnitude and the direction of the associations were unchanged.

Among the subset of 1,547 patients who required ICU admission (**Digital Table 2**, http://links.lww.com/CCX/B114), 903 (58%) required initiation of mechanical ventilation. Not included in this subset were 22 patients who required mechanical ventilation but were not categorized as having an ICU admission (2% of entire cohort receiving mechanical ventilation). These 22 patients had either been extubated prior to ICU transfer (either due to rapid recovery or death) or transferred to another facility in less than 24 hours. In the ICU subset, in-hospital outcomes were consistent with findings from univariate analyses including the entire cohort. Notably, the requirement for initiation of mechanical ventilation among patients who required ICU services was quantitatively higher among those with alcohol misuse (58% vs 64%; $p = 0.33$), although the number of days on mechanical ventilation among those with alcohol misuse was substantially less.

DISCUSSION

In this large cohort of patients with COVID-19 pneumonia hospitalized across a regional healthcare system, alcohol misuse was associated with an increased need for critical care services, namely, ICU admission and initiation of mechanical ventilation. Patients with alcohol misuse were more likely to experience delirium, and those with alcohol misuse and delirium had associated increased odds for in-hospital death. Our results support prior studies identifying alcohol misuse and delirium as potentially modifiable risk factors contributing to adverse outcomes in hospitalized patients. Our findings expand the literature in COVID-19 pneumonia implicating alcohol misuse as a potential factor in disease severity.

TABLE 2.

Adjusted Logistic Regression for Risk of Outcomes (*n* = 5,979)

Variable	OR (95% CI) Estimate (Lower Limit–Upper Limit)	p
A) ICU admission		
Alcohol misuse	1.46 (1.10–1.94)	0.01
Age (per 10-yr interval)	1.03 (0.99–1.06)	0.20
Male sex	1.51 (1.34–1.71)	< 0.01
Body mass index	1.01 (1.00–1.02)	0.05
Diabetes mellitus	1.68 (1.48–1.90)	< 0.01
Liver disease	1.52 (1.20–1.94)	< 0.01
B) Mechanical ventilation		
Alcohol misuse	1.43 (1.03–1.98)	0.03
Age (per 10-yr interval)	0.99 (0.95–1.04)	0.77
Male sex	1.75 (1.50–2.03)	< 0.01
Body mass index	1.02 (1.01–1.02)	< 0.01
Diabetes mellitus	1.74 (1.50–2.20)	< 0.01
Liver disease	1.83 (1.40–2.38)	< 0.01
C) Delirium		
Alcohol misuse	5.55 (3.66–8.42)	< 0.01
Age (per 10-yr interval)	1.37 (1.25–1.50)	< 0.01
Male sex	1.23 (0.94–1.60)	0.13
Body mass index	0.98 (0.96–1.00)	0.04
ICU admission	3.49 (2.70–4.51)	< 0.01
Diabetes mellitus	1.06 (0.81–1.39)	0.67
Liver disease	1.20 (0.74–1.95)	0.46
D) In-hospital death		
Alcohol misuse	1.46 (0.93–2.28)	0.10
Age (per 10-yr interval)	1.76 (1.64–1.88)	< 0.01
Male sex	1.70 (1.42–2.04)	< 0.01
Body mass index	1.01 (1.00–1.02)	0.10
Diabetes mellitus	1.10 (0.92–1.33)	0.30
Liver disease	1.60 (1.11–2.31)	0.01

OR = odds ratio.

Several factors may explain the increased need for intensive care utilization and initiation of mechanical ventilation among those with alcohol misuse in our cohort, including the higher frequency of delirium in this subgroup. For example, sedating medications used to address delirium may have led to a need for ICU-level monitoring and even prompted initiation of mechanical ventilation. Further, in patients with alcohol misuse and liver disease, superimposed hepatic encephalopathy or delayed clearance of medications prescribed for delirium may have further increased requirements for ICU care, as has been previously noted in studies of patients with chronic liver disease revealed (34). Alternatively, the observation that patients with alcohol misuse had on average lower BMIs raises the possibility of metabolic derangements driving delirium in this subgroup. Addressing risk factors for delirium early in hospitalization can reduce short-and long-term morbidity (22). Our work suggests that specific actions and interventions to mitigate delirium, such as standardized protocols to identify and control alcohol withdrawal delirium, avoidance of benzodiazepines in patients having delirium unrelated to alcohol withdrawal, providing early nutritional assessment and intervention, and treatment of hepatic encephalopathy could reduce requirements for ICU care.

Our results highlighted a more than two-fold increase in in-hospital death among patients with alcohol misuse who were diagnosed with delirium. For comparison, in a study involving U.S. patients hospitalized for COVID-19 early in the pandemic, a history of myocardial infarction was similarly associated with a more than two-fold increased odds for mortality, while development of acute kidney failure increased odds for mortality over five-fold (35). We posit that delirium may be in the causal pathway between alcohol misuse and in-hospital death and that alcohol misuse is synergistic with delirium in increasing risk for mortality. Along with addressing delirium as described, early identification of alcohol misuse in hospitalized patients may represent a modifiable care opportunity to improve patient outcomes. Unfortunately, systematic identification of alcohol misuse among hospitalized patients remains challenging for several reasons, including the stigmatization surrounding alcohol misuse influencing patient self-report; the severity of present illness that can limit obtaining alcohol use history; and deprioritization in obtaining substance use history by patient care providers during the busy pandemic (and in ICU settings more generally). Notably, the prevalence of alcohol misuse was relatively low (4%) in our cohort raising the possibility for underrecognition of alcohol misuse in the inpatient setting.
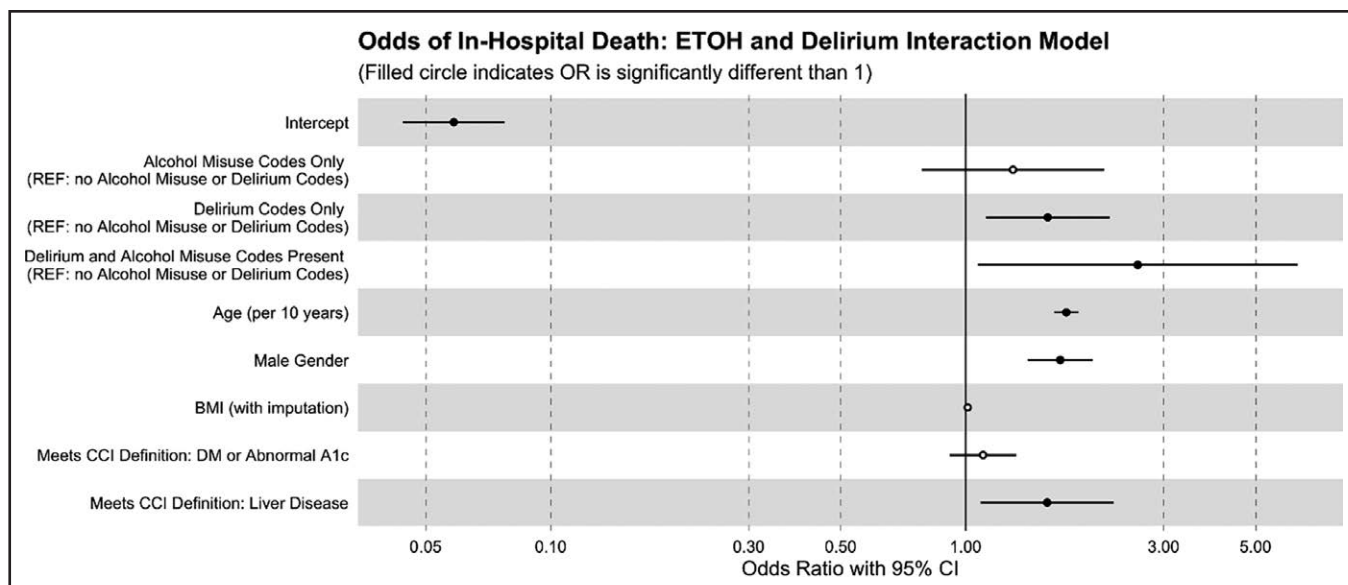
Figure 2. *Forest plot* illustrating model of alcohol misuse and delirium interaction on the odds of in-hospital death. BMI = body mass index, CCI = Charlson Comorbidity Index, DM = diabetes mellitus, ETOH = alcohol misuse present, OR = odds ratio, REF = reference.

Furthermore, existing screening tools such as the alcohol use disorders identification test (AUDIT) are challenging to use in patients who lack capacity. Given the associations we observed between alcohol misuse and healthcare utilization in the setting of COVID-19, further studies should aim to validate universal alcohol misuse screening tools in this population.

We did not observe an independent association between alcohol misuse and in-hospital mortality in our cohort, which contrasts with prior community-acquired pneumonia investigations (7, 36, 37). Similarly, multiple studies show that ICU patients with AUDs admitted for illnesses including respiratory infections and ARDS experience a more severe disease course (4–6, 8–10). In contrast, hospitalized patients with alcohol misuse in our cohort were not more likely to develop ARDS, had a shorter ICU length of stay, and exhibited a similar need for vasopressor therapy. In the subgroup of patients who required ICU care (~26% of the total cohort), a relatively larger percentage of patients with alcohol misuse required initiation of mechanical ventilation, but the number of days on mechanical ventilation remained substantially shorter in this subgroup. Although it is possible that patients with alcohol misuse had mechanical ventilation initiated to manage delirium (as mentioned above), our inclusion criteria and the time frame of data collection make it unlikely that patients had delirium but not COVID-19 pneumonia. Rather, it remains possible that residual confounding by illness severity drove differences in our results compared with prior studies. Since patients with alcohol misuse in our cohort were young and had substantially lower BMIs, their COVID-19 infection may have resolved more quickly than in the nonmisuse group, diminishing requirements for mechanical ventilation. It is also possible that our study was underpowered to adequately examine differences in secondary outcomes. Finally, given that patients with alcohol misuse were more often uninsured or insured via Medicaid, socioeconomic status may also be implicated as another potential contributor to poorer outcomes in this subset of patients.

Our study features certain strengths and limitations. We leveraged a large, regional EHR database to examine the impact of alcohol misuse over the course of pandemic. The size and robustness of these data helped to overcome challenges faced by prior studies with inadequate power to investigate alcohol misuse in this context. We acknowledge that EHR investigations can be impacted by misclassification. To enhance the likelihood of patients in the cohort having true COVID-19 pneumonia, we included patients with a primary diagnosis of COVID-19 who also had a positive PCR test and included data only from their initial hospitalization. The timing of our investigation early in the pandemic also increases the likelihood of patients having COVID-19 pneumonia. Further, we used a previously validated EHR-based definition to identify patients with alcohol misuse, and the percentage of patients in our

cohort classified as having alcohol misuse was consistent with prior studies involving EHR or claims data. Furthermore, demographics of patients with alcohol misuse in our cohort (e.g., age, gender, insurance status) reflect reports from prior investigators (1, 23, 24). Although our dataset was limited to only selected parts of the EHR, future studies could incorporate elements such as prior admissions for alcohol-related conditions, or medications prescribed for alcohol withdrawal, to improve sensitivity to detect alcohol misuse. Additionally, measurements of biomarkers such as RBC phosphatidylethanol could be used to identify recent (past month) alcohol use (38) and perhaps the severity of alcohol misuse (39), but is not predictive of alcohol withdrawal. Since our definition for alcohol misuse was unlikely to identify patients with less risky consumption habits, it is unclear if patients with less severe alcohol misuse would have similar outcomes. Delirium diagnoses may also have been subject to misclassification, and it is unclear if patients classified with "unspecified" delirium, in fact, had alcohol-related delirium (delirium tremens), which is known to influence outcomes adversely. Operationalizing a delirium definition to include administration of anti-psychotic medications could improve specificity (40). Given these and other constraints in conducting research with EHR or claims data, we anticipate further prospective cohort studies utilizing multiple methods to classify alcohol misuse and delirium will be necessary to fully appreciate these relationships.

Other confounders may have also influenced our results. For example, disorders such as asthma or prior vaccination may have influenced severity of the COVID-19 disease course but were not specifically assessed. Underlying dementia, or administration of medications to treat presumed alcohol withdrawal (e.g., benzodiazepines) might have increased likelihood for delirium, leading to downstream effects on outcomes. We attempted to address likely confounders by adjusting for severity of illness in a number of ways that included accounting for specific organ failure (e.g., liver disease) and using the CCI to quantify baseline health risk; however, some unmeasured confounders were likely still present. Additionally, our analysis was comprised of data from 12 Colorado hospitals in a singular healthcare network, using data collected earlier in the pandemic. These factors limit its generalizability in other populations outside of Colorado infected with emerging severe acute respiratory syndrome coronavirus 2 variants. Future studies should aim to expand our findings to include national and international data to ensure generalizability of our findings.

Depending on the hospital setting, alcohol misuse is estimated to be present in 20–40% of hospitalized patients (41, 42). Single center studies have reported that alcohol-related ICU hospitalizations are responsible for up to 10% of all ICU admissions (43, 44). As such, clinicians should strive to identify and address alcohol misuse in hospitalized patients, which frequently coexists with other illnesses that are more apparent, given its potential impact on outcomes. Systematic utilization of AUDIT-concise as a validated, efficient method of determining alcohol consumption habits could be useful in this context (45), although results could still be affected by patient willingness, or capacity, to report alcohol use. Future investigations in this area could include more granular exploration of the frequency and quantity of alcohol misuse to better understand the epidemiology of specific alcohol use habits (e.g., acute intoxication, binge consumption) in COVID-19, and the pathobiology of alcohol exposure on short- and long-term outcomes after COVID-19. Additionally, understanding the impact of alcohol misuse along with other substances, including tobacco, cannabis, or other illicit would help to establish if other modifiable factors alter outcomes in COVID-19 pneumonia (46).

CONCLUSIONS

In this study of nearly 6,000 patients hospitalized across a regional healthcare system with COVID-19, alcohol misuse was associated with increased need for critical care services including ICU admission and initiation of mechanical ventilation. Further, patients with a history of alcohol misuse were over five times more likely to develop delirium, and the combination of alcohol misuse and delirium generated a more than two-fold greater odds of in-hospital death. Healthcare providers should recognize patients admitted with COVID-19 pneumonia with a history of alcohol misuse may be at increased risk for a more morbid disease course and consider implementation of strategies aimed at preventing delirium in order to promote better clinical outcomes.

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