Trends
in Psychiatry and Psychotherapy

JOURNAL ARTICLE PRE-PROOF
(as accepted)

Original Article

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Fabrício Emanuel Soares de Oliveira, Daniella Reis Barbosa Martelli, Maria Christina L. Oliveira, Enrico A. Colosimo, Hercílio Martelli Júnior, Eduardo A. Oliveira

http://doi.org/10.47626/2237-6089-2024-1028

Original submitted Date: 01-Jan-2025

Accepted Date: 22-Feb-2025

Outcomes and risk factors of death among individuals with alcohol use disorder hospitalized with COVID-19: an observational Brazilian cohort study

Running title: Alcohol use disorder and COVID-19 outcomes

Fabrício Emanuel Soares de Oliveira[1], Daniella Reis Barbosa Martelli[2], Maria Christina L. Oliveira[3], Enrico A. Colosimo[4], Hercílio Martelli Júnior[1], Eduardo A. Oliveira[3,5]

[1]Postgraduate Program in Health Sciences, Unimontes, Montes Claros, MG, Brazil.
[2]Postgraduate Program in Primary Health Care, Unimontes, Montes Claros, MG, Brazil.
[3]Department of Pediatrics, Health Sciences Postgraduate Program, School of Medicine, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
[4]Department of Statistics, Federal University of Minas Gerais (UFMG), Belo Horizonte, MG, Brazil.
[5]Department of Pediatrics, Rady Children's Hospital, University of California, San Diego, USA.

Corresponding author:
Fabrício Emanuel Soares de Oliveira
State University of Montes Claros, UNIMONTES, Prof. Darcy Ribeiro University Campus, Prof. Rui Braga Avenue, Vila Mauricéia, Montes Claros, Minas Gerais, Brazil. Postal Code: 39401-089.
Phone number: +55(38)99997-6845
E-mail: fabricioemanuel1@hotmail.com

Abstract

Objective: This study aimed to investigate the clinical outcomes and mortality risk factors associated with alcohol use disorder (AUD) in hospitalized COVID-19 patients.
Methods: We analyzed a national database containing information on the clinical and sociodemographic aspects of patients hospitalized with severe acute respiratory

syndrome between February 2020 and February 2023 in Brazil, including those aged > 18 years with laboratory-confirmed COVID-19. The primary exposure of interest was a history of AUD before admission and the primary outcome was in-hospital mortality. **Results:** Among the 2,124,285 patients, 11,433 (0.53 %) had AUD. The in-hospital mortality rate was higher in the patients with AUD (46.2%) than in those without AUD (31.9%). After adjusting for confounding covariates, individuals with AUD had twice the risk of death (Odds Ratio [OR]= 1.94, 95% confidence interval [CI] 1.85-2.03) compared with non-AUD patients. Among individuals with AUD, the covariates independently associated with the primary outcome were age > 60 years, male sex, hospitalization in the Central-West, Northeast and North regions, symptoms of dyspnea and reduced oxygen saturation at admission, presence of comorbidities, and year of admission. **Conclusion:** In this population-based study, we found that patients with AUD had twice the risk of fatal outcomes than those without AUD.
Keywords: Alcoholism. COVID-19. Mental Health. Mortality. Pandemics.

Introduction

The emergence and subsequent spread of SARS-CoV-2 has resulted in a devastating coronavirus disease 2019 (COVID-19) pandemic. This public health crisis ranks among the most severe in recorded history, with over seven million deaths reported by August 2023. Large-scale vaccination programs implemented worldwide played a critical role in bringing the pandemic under control[1-3]. Several underlying chronic health conditions have been identified as significant risk factors for mortality in COVID-19 patients, including hypertension, obesity, and diabetes. Furthermore, studies have shown that the presence of multiple comorbidities poses an even higher risk[5,6].

Alcohol Use Disorder (AUD) is a globally prevalent public health concern characterized by uncontrolled and excessive alcohol consumption[10,11]. It disproportionately affects males and is associated with a wide range of health complications, with respiratory infections being a significant area of concern[10-14]. The emergence of the COVID-19 pandemic has underscored the heightened susceptibility of individuals with AUD to severe respiratory illnesses and mortality[15,16]. Despite this growing body of evidence, there is a significant knowledge gap regarding the specific mechanisms by

which SARS-CoV-2 infection affects individuals with AUD. This highlights the need for large-scale studies to comprehensively assess the impact of COVID-19 in this population. Such research will be instrumental in informing the development of targeted interventions aimed at improving the response to COVID-19 and other respiratory infections in this vulnerable group.

In this retrospective population-based cohort study of more than 2 million patients, we used the Brazilian National Epidemiological Surveillance System of Severe Acute Respiratory Infection to compare the clinical outcomes of SARS-CoV-2 infections among individuals with and without AUD and to identify the risk factors for mortality in a subsample of patients with AUD.

Methods

Study design

This is a population-based, retrospective cohort study. The primary data source was the SIVEP-Gripe database, a national surveillance system established by the Brazilian Ministry of Health to monitor severe acute respiratory syndrome (SARS) cases caused by diverse respiratory viruses, including SARS-CoV-2. This repository contains anonymized information on hospitalized patients, including demographics, clinical data, comorbidities, and clinical outcomes. Notifications of influenza-like illness (ILI) or SARS from all Brazilian hospitals, public and private, contribute to the SIVEP-Gripe database. The database is publicly accessible [Brazilian Ministry of Health, opendatasus.saude.gov.br/dataset] and ensures patient anonymity. All study procedures adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational cohort studies.

Participants and Case-Defining

The inclusion criterion was patients aged > 18 years registered in the database between February 2020 and February 2023 with laboratory-confirmed SARS-CoV-2 infections.

Exposure of interest

The primary exposure of interest was self-reported AUD. We identified AUD cases in the dataset by retrieving data from an open text field, which provides invaluable self-report information on chronic medical conditions and other relevant clinical issues.

Covariates

This study incorporated a range of demographic and clinical covariates to account for potential confounding variables. Demographic data included age, sex, ethnicity, educational attainment, and geographic macroregion. Age was categorized into four strata: 19-29 years, 30-59 years, 60-79 years, and greater than 80 years. Ethnicity data were based on the Brazilian Institute of Geography and Statistics (IBGE) classification system, encompassing White, Black, Brown, Asian, and Indigenous categories. Brazil's geopolitical macroregions (North, Northeast, Central-West, Southeast, and South) were included as covariates because of potential historical social, economic, and healthcare system variations.

Clinical covariates included the date of birth, symptom onset date, and admission date. Additionally, signs and symptoms at presentation (fever, cough, respiratory distress, gastrointestinal symptoms, and oxygen desaturation), nosocomial infections, and pre-existing comorbidities were documented. Comorbidities included asthma; diabetes; obesity; immune deficiencies; malignancies; and heart, lung, kidney, neurological, and hematological diseases. For analysis purposes, the presence of comorbidities was categorized into four levels based on the number of pre-existing conditions identified.

Outcome

The primary outcome measure of this investigation was in-hospital mortality. This binary variable was analyzed in the entire study cohort. Subsequently, a stratified analysis was conducted to evaluate in-hospital mortality, specifically within the subgroup of patients diagnosed with AUD.

Additionally, this study assessed healthcare resource utilization among hospitalized patients. This included the evaluation of intensive care unit (ICU) admission and the use

of respiratory support. Respiratory support was categorized as none, noninvasive, or invasive (e.g., mechanical ventilation).

Statistical analysis

The study cohort was stratified into two distinct groups for analysis: individuals with AUD and those without AUD (non-AUD). The analysis was implemented in three sequential stages. The first stage involved describing the demographic, clinical, and epidemiological characteristics of the two groups included in the analysis. Descriptive data for all eligible patients were presented as means and standard deviations, medians and interquartile ranges, or counts and proportions, as appropriate. For intergroup comparisons, Student's t-test and Pearson's chi-square test were used, where applicable. The second stage focused on estimating the odds ratio (OR) for the primary outcome variable using a binary logistic regression analysis. Subsequently, a multivariate binary logistic regression model was used to calculate the adjusted odds ratio (AOR). This model incorporates variables identified as statistically significant ($p < 0.20$) during the prior stage. All models were adjusted for potential confounders, including age, sex, ethnicity, region of admission, and signs and symptoms registered at admission (dyspnea and oxygen saturation). The final stage involved the assessment of the predictors of fatal outcomes, specifically within the subgroup of individuals diagnosed with AUD. This analysis mirrored the steps outlined above using binary logistic regression analysis. Multicollinearity diagnostics were performed to ensure independence of the variables within the model. Variance Inflation Factor (VIF) and tolerance values were analyzed to confirm this assumption. Additionally, goodness-of-fit tests, including the Hosmer-Lemeshow test and the Omnibus test of model coefficients, were employed to verify the suitability of the model.

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software version 27. Two-tailed statistical tests were employed throughout the analysis, with the significance level set at $p < 0.05$.

Ethical aspects

This study was exempted from ethics committee approval as it involved the analysis of anonymized public data that complied with the regulations of data protection legislation in Brazil.

Results

Baseline demographic and clinical characteristics

Table 1 presents the clinical and epidemiological characteristics of the cohort, based on the presence or absence of AUD. The cohort comprised 2,124,285 cases, of which 11,433 (0.54%) were identified as individuals with AUD. The average age of AUD cases (58.69 ± 13.77) was slightly lower than the average age of non-AUD patients and the overall average age. The majority of patients with AUD (51.3%) were concentrated in the 30–59-year-old age group, with fewer alcohol users in the younger and older age groups. We observed a very high prevalence of men (88.7%) among patients with AUD. Regarding ethnicity, 56.1% of patients with AUD were non-white, with a higher prevalence of comorbidities than those without AUD.

Table 1. Characterization of patients with laboratory-confirmed COVID-19 stratified according to the presence of Alcohol Use Disorder (AUD) (n= 2,124,285)

	Overall (%)	Non-AUD (%)	AUD (%)	*p*-value
	2,124,285 (100)	2,112,852 (99.5)	11,433 (0.5)	
Age (years)				
Mean (SD)	59.84 (17.43)	59.85 (17.45)	58. 69 (13.77)	<0.001
Age group (years)				
18.0 - 29.9	93,579 (4.4)	93,374 (4.4)	205 (1.8)	<0.001
30.0 - 59.9	961,467 (45.3)	955,604 (45.2)	5,863 (51.3)	
60.0 – 79.9	770,274 (36.3)	765,602 (36.2)	4,672 (40.9)	
≥ 80.0	298,965 (14.1)	298,272 (14.1)	693 (6.1)	
Gender (n = 2,124,042)				
Female	954,799 (45.0)	953,507 (45.1)	1,292 (11.3)	<0.001
Male	1,169,243 (55.0)	1,159,102 (54.9)	10,141 (88.7)	
Ethinicity (n = 1,733,847)				

White	906,249 (52.3)	901,978 (52.3)	4,271 (43.9)	<0.001
Non-white	827,598 (47.7)	822,129 (47.7)	5,469 (56.1)	
Region				
Southeast	1,049,801 (49.4)	1,045,461 (49.5)	4,340 (38.0)	<0.001
South	362,590 (17.1)	359,885 (17.0)	2,705 (23.7)	
Central-West	215,464 (10.1)	214,368 (10.1)	1,096 (9.6)	
Northeast	356,644 (16.8)	353,564 (16.7)	3,080 (26.9)	
North	139,786 (6.6)	139,574 (6.6)	212 (1.9)	
Signs and symptoms				
Dyspnea	1,479,577 (69.7)	1,471,528 (69.6)	8,049 (70.4)	0.080
Oxygen saturation <95% (n = 1,759,083)	1,322,729 (75.2)	1,315,275 (75.2)	7,454 (76.7)	0.001
Comorbidities				
None	1,040,959 (49.0)	1,036,202 (49.0)	4,757 (41.6)	<0.001
1	630,273 (29.7)	626,517 (29.7)	3,756 (32.9)	
2	342,699 (16.1)	340,615 (16.1)	2,084 (18.2)	
≥ 3	110,354 (5.2)	109,518 (5.2)	836 (7.3)	
Year admission (n = 2,115,110)				
2020	660,003 (31.2)	656,128 (31.2)	3,875 (34.2)	<0.001
2021	1,231,153 (58.2)	1,225,805 (58.3)	5,348 (47.2)	
2022	223,954 (10.6)	221,850 (10.5)	2,104 (18.6)	
ICU[a] admission (n = 1,831,937)				
No	1,143,845 (53.8)	1,138,682 (53.9)	5,163 (45.2)	<0.001
Yes	688,092 (32.4)	682,825 (32.3)	5,267 (46.1)	
Ventilatory support (n = 1,805,302)				
None	385,715 (18.2)	383,745 (18.2)	1,970 (17.2)	<0.001
Non-invasive	1,050,747 (49.5)	1,045,886 (49.5)	4,861 (42.5)	
Invasive	368,840 (17.4)	365,298 (17.3)	3,542 (31.0)	
Death rate (n = 2,080,899)				
Discharged	1,415,104 (68.0)	1,409,045 (68.1)	6.059 (53.8)	<0.001
In-hospital mortality	665,795 (32.0)	660,596 (31.9)	5.199 (46.2)	

[a] Intensive Care Unit

Clinical outcomes

Regarding clinical outcomes, the incidence of death was greater in individuals with AUD (46.2%) than in those without (31.9%). Moreover, ICU admissions were more prevalent in patients with AUD. It is noteworthy that the proportion of patients with AUD who required invasive ventilatory support was nearly double (31.0%) that of patients without AUD who required the same intervention (17.3%) (Table 1).

Risk factors of fatal outcome in entire cohort

Among 2,080,899 patients hospitalized with severe acute respiratory syndrome and confirmed COVID-19, 665,795 (32%) experienced fatal outcomes. The results of univariate logistic regression analysis for the risk of death are presented in Table 2. Patients over 80 years of age exhibited an OR nearly 10 times higher than that in the age group of 18–29.9 years. Furthermore, we observed higher ORs in male patients (OR 1.05; 95% CI 1.04-1.05) and in patients of non-white ethnicity (OR 1.08; 95% CI 1.08-1.09). Patients hospitalized in the Northeast and North regions demonstrated a greater chance of death, with ORs of 1.22 (95% CI 1.21-1.23) and 1.21 (95% CI 1.20-1.22) respectively. The presence of dyspnea and oxygen saturation <95% were associated with a higher chance of death, with ORs of 1.49 (95% CI 1.48-1.50) and 2.03 (95% CI 2.02-2.05) respectively. Notably, AUD patients presented twice the OR of death (OR 1.83; 95% CI 1.76-1.90).

Table 2. Univariate binary logistic regression of death in the entire cohort (n= 2,124,285)

	Discharged (%)	**Death (%)**	**OR (95%CI)**	***p*-value**
	1,415,104 (68.0)	**665,795 (32.0)**		
Age group (years)				
18.0 - 29.9	81,637 (89.6)	9,469 (10.4)	1.0	
30.0 - 59.9	746,585 (79.5)	192,823 (20.5)	2.22 (2.18-2.27)	<0.001
60.0 – 79.9	448,904 (59.4)	307,231 (40.6)	5.90 (5.77-6.03)	<0.001
≥ 80.0	137,978 (46.9)	156,272 (53.1)	9.76 (9.54-9.98)	<0.001
Gender				
Female	641,148 (68.6)	294.007 (31.4)	1.0	
Male	773.797 (67.5)	371,723 (32.5)	1.05 (1.04-1.05)	<0.001

Ethinicity				
White	604,896 (67.7)	288,253 (32.3)	1.0	
Non-white	533,425 (65.9)	276,348 (34.1)	1.08 (1.08-1.09)	<0.001
Region				
Southeast	702,543 (68.2)	327,318 (31.8)	1.0	
South	252,027 (70.7)	104,658 (29.3)	0.89 (0.88-0.90)	<0.001
Central-West	154,514 (72.1)	59,788 (27.9)	0.83 (0.82-0.84)	<0.001
Northeast	218,096 (63.7)	124,384 (36.3)	1.22 (1.21-1.23)	<0.001
North	87,924 (63.9)	49,647 (36.1)	1.21 (1.20-1.22)	<0.001
Signs and symptoms				
Dyspnea	950,769 (65.5)	501,538 (34.5)	1.49 (1.48-1.50)	<0.001
Oxygen saturation <95%	833,310 (64.1)	465,997 (35.9)	2,03 (2,02-2,05)	<0.001
Number of associated comorbidities				
None	766,689 (75.5)	249,238 (24.5)	1.0	
1	399,116 (64.5)	219,736 (35.5)	1.69 (1.68-1.70)	<0.001
2	194,569 (57.7)	142,561 (42.3)	2.25 (2.23-2.27)	<0.001
≥ 3	54,730 (50.2)	54,260 (49.8)	3.05 (3.01-3.09)	<0.001
Year				
2020	449,810 (68.9)	202,900 (31.1)	1.0	
2021	807,269 (67.3)	392,539 (32.7)	1.08 (1.07-1.08)	<0.001
2022	152,783 (69.2)	68,033 (30.8)	0.98 (0.97-0.99)	0.015
AUD				
No	1,409,045 (68.1)	660,596 (31.9)	1.0	<0.001
Yes	6,059 (53.8)	5,199 (46.2)	1.83 (1.76-1.90)	

Table 3. Odds ratio of death in patients with Alcohol Use Disorder (AUD) and laboratory-confirmed COVID-19 (n = 11,433)

	Discharged (%) 15,765 (69.2)	**Death (%) 7,021 (30.8)**	**OR (95%CI)**	***p*-value**
Age group (years)				
18.0 - 29.9	132 (65.3)	70 (34.7)	1.0	
30.0 - 59.9	3,479 (60.3)	2,291 (39.7)	1.24 (0.92-1.66)	0.150
60.0 – 79.9	2,191 (47.7)	2,406 (52.3)	2,07 (1.54-2.78)	<0.001

≥ 80.0	257 (37.3)	432 (62.7)	3,17 (2.28-4.40)	<0.001
Gender				
Female	718 (56.4)	556 (43.6)	1.0	
Male	5,341 (53.5)	4,643 (46.50	1.12 (0.99-1.26)	0.054
Ethnicity				
White	2,311 (54.6)	1,918 (45.4)	1.0	
Non-white	2,786 (51.9)	2,584 (48.1)	1.11 (1.03-1.21)	0.007
Region				
Southeast	2,437 (56.8)	1,857 (43.2)	1.0	
South	1,469 (54.8)	1,210 (45.2)	1.08 (0.98-1.91)	0.116
Central-West	599 (54.9)	492 (45.1)	1.07 (0.94-1.23)	0.271
Northeast	1,463 (49.0)	1,522 (51.0)	1.36 (1.24-1.50)	<0.001
North	91 (43.5)	118 (56.5)	1.70 (1.28-2.25)	<0.001
Signs and symptoms				
Dyspnea	4,020 (50.6)	3,919 (49.4)	1.55 (1.43-1.68)	<0.001
Oxygen saturation <95%	3,695 (50.3)	3,650 (49.7)	1.82 (1.65-2.01)	<0.001
Comorbidities				
None	2,775 (59.4)	1,895 (40.6)	1.0	
1	1,945 (52.6)	1,752 (47.4)	1.31 (1.20-1.43)	<0.001
2	998 (48,3)	1,069 (51.7)	1.57 (1.41-1.74)	<0.001
≥ 3	341 (41.4)	483 (58.6)	2.07 (1.78-2.41)	<0.001
Year (n = 2,115,110)				
2020	2,128 (55.4)	1,711 (44.6)	1.0	
2021	2,726 (51.9)	2,526 (48.1)	1.15 (1.06-1.25)	0.001
2022	1,162 (55.9)	918 (44.1)	0.98 (0.88-1.09)	0.748

The findings of the multivariate binary logistic regression analysis of the entire cohort are shown in Figure 1. Following adjustment for potential confounding factors, the risk of death was nearly doubled in individuals with AUD compared to the non-AUD group and was even greater than in the univariate analysis (aOR 1.94; 95% CI 1.85-2.03). Moreover, age (30-59, 60-79, >80 years), male sex, non-white ethnicity, hospitalizations in the Northeast and North regions, dyspnea and reduced oxygen saturation at admission, presence of comorbidities, and admission in 2021 remained significantly associated with death. In contrast, hospitalization in the southern region and admission in 2022 were associated with a significantly lower risk of death.

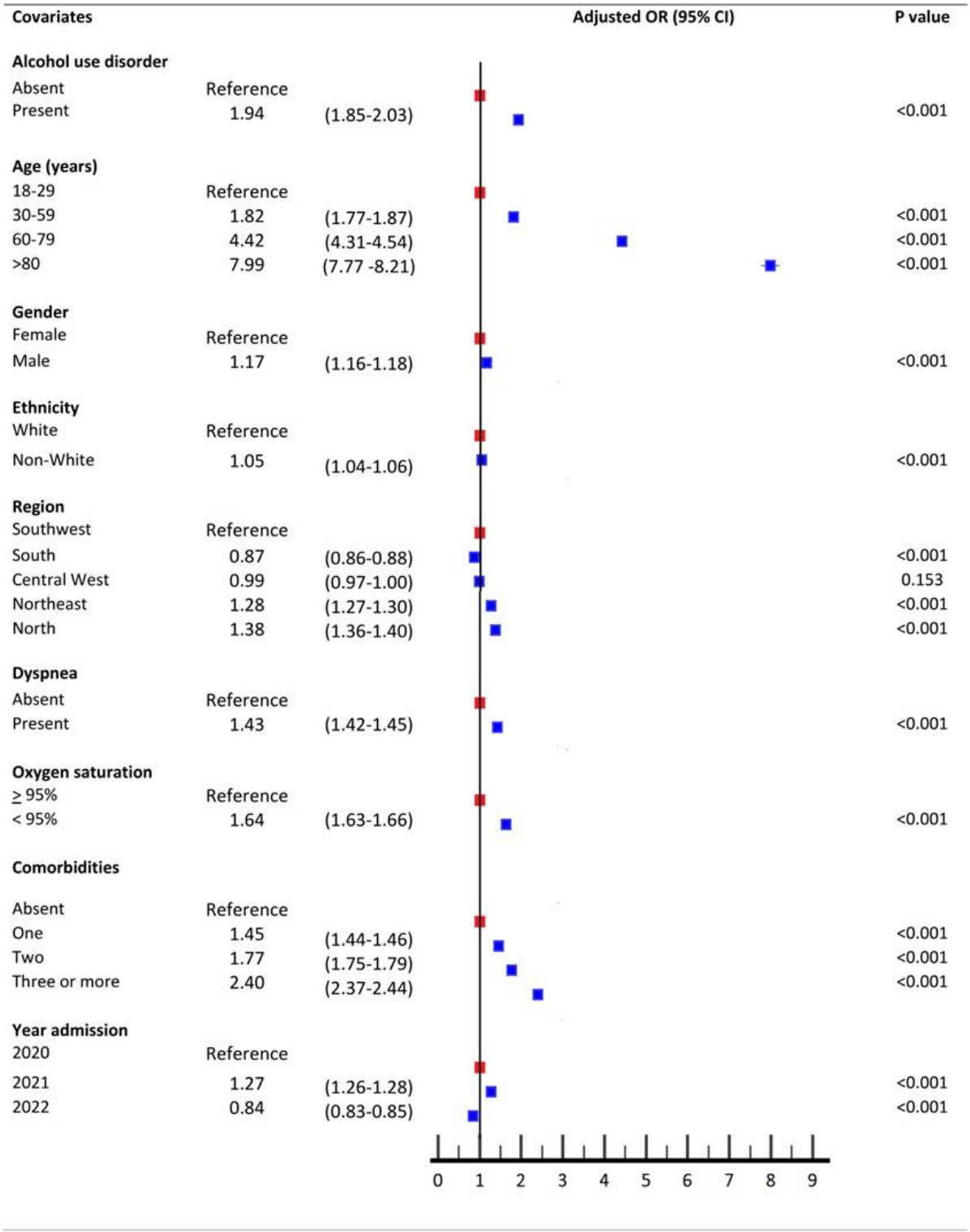

Figure 1. Adjusted odds of death in the entire cohort according to the presence of alcohol use disorder and other clinical covariates. Red markers correspond to the reference categories (n= 2,124,285, Teste de Omnibus: P<0.001, Teste de Hosmer-Lemeshow: p-valor <0,001).

Risk factors of fatal outcome in AUD cohort

Among 11,433 individuals with AUD who were hospitalized with COVID-19, 5,199 (45.5%) had fatal outcomes. The results of the multivariate logistic regression analysis of the risk of death among individuals with AUD are shown in Figure 2. After adjustment, the analysis revealed that the following covariates were significantly associated with a higher risk of death in the AUD cohort: age (60-79, > 80 years), male sex, hospitalization in the Central-West, Northeast and North regions, dyspnea and reduced oxygen saturation at admission, and presence of comorbidities. It was also observed that admissions in 2021 and 2022 were associated with a higher OR for death.

Covariates			Adjusted OR (95% CI)	P value
Age (years)				
18-29	Reference			
30-59	1.32	(0.92-1.90)		0.129
60-79	2.00	(1.39-2.88)		<0.001
>80	2.96	(1.98 -4.43)		<0.001
Gender				
Female	Reference			
Male	1.19	(1.04-1.38)		0.014
Region				
Southwest	Reference			
South	0.92	(0.82-1.03)		0.162
Central West	1.25	(1.06-1.49)		0.008
Northeast	1.34	(1.19-1.51)		<0.001
North	1.69	(1.21-2.35)		0.002
Dyspnea				
Absent	Reference			
Present	1.39	(1.25-1.56)		<0.001
Oxygen saturation				
≥ 95%	Reference			
< 95%	1.58	(1.40-1.77)		<0.001
Comorbidities				
Absent	Reference			
One	1.30	(1.17-1.45)		<0.001
Two	1.47	(1.30-1.67)		<0.001
Three or more	2.03	(1.70-2.43)		<0.001
Year admission				
2020	Reference			
2021	1.26	(1.14-1.39)		<0.001
2022	1.17	(1.03-1.34)		0.015

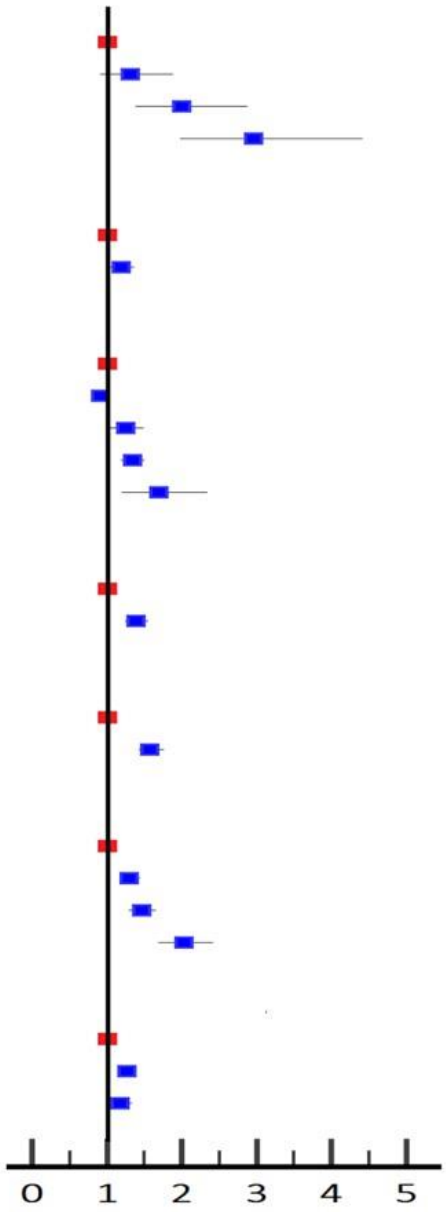

Figure 2. Adjusted odds of death among individuals with alcohol use disorder. Red markers correspond to the reference categories (n = 11,433, Teste de Omnibus: P<0.001, Teste de Hosmer-Lemeshow: P=0.176)

Figure 2. Adjusted odds of death among individuals with alcohol use disorder. Red markers correspond to the reference categories (n = 11,433, Teste de Omnibus: P<0.001, Teste de Hosmer-Lemeshow: P=0.176)

Discussion

In a population-based study, we evaluated the outcomes of individuals with a history of AUD who were hospitalized for COVID-19 during the three years of the COVID-19 pandemic in Brazil. After adjusting for clinical and epidemiological confounders, individuals with AUD had twice the risk of death than those without AUD. Among individuals with AUD, the covariates independently associated with death were older age, male sex, presence of comorbidities, hospitalization in the Northeast and North regions, symptoms of dyspnea and reduced oxygen saturation on admission, and year of hospitalization.

The findings of our cohort's demographic characteristics revealed a noteworthy prevalence of AUD among individuals aged 30–59 years, which aligns with previous studies conducted in Brazil[17], China[18], and the United States[19]. In our cohort, males comprised approximately 90% of those diagnosed with AUD. This observation is consistent with prior research and may be influenced by cultural factors such as societal expectations of masculinity, stigmatization of alcohol consumption in women, and advertising campaigns targeting men. Additionally, studies have found that men tend to consume more alcohol than women[18,19,20,21]. Our cohort also showed a higher prevalence of AUD among non-white individuals, consistent with previous research[22-24.] However, some studies have reported higher rates of alcohol-related disorders among white individuals[18,21]. The disparity in AUD prevalence among different racial/ethnic groups may be attributed to various factors including historical experiences of discrimination, socioeconomic disadvantages, risky drinking behaviors, immigration experiences, and genetic factors that affect alcohol metabolism[25,26]. Our study found a higher proportion of alcohol users in the Southeast and Northeast regions, which is consistent with research conducted among Brazilian health professionals during the

pandemic[27]. These regions are the most populous and urbanized in Brazil, and higher rates of AUD are generally associated with more urbanized and populated areas[28,29]. AUD is a major public health concern that has numerous detrimental consequences on multiple organ systems, including the respiratory system[30]. AUD is commonly associated with several health problems such as liver cirrhosis, pancreatitis, cardiomyopathy, neuropathy, and dementia[31]. Furthermore, AUD also negatively affects lung function by interfering with both adaptive and innate immunity, increasing susceptibility to viral infections, and increasing the risk of developing acute respiratory distress syndrome[32,33]. In the context of the COVID-19 pandemic, several studies have investigated the correlation between AUD and disease susceptibility. For example, Bhalla et al.[34]. used a machine learning classifier to study the effect of AUD on COVID-19 severity and concluded that AUD is an independent risk factor for severe COVID-19. Our analysis also revealed that patients with AUD had twice the risk of death than those without AUD after adjusting for clinical and epidemiological confounders. These findings are consistent with previous studies that have reported mortality risk ranging from 1.15 (95% CI 1.12-1.19) to 2.58 (95% CI 1.33-5.04)[15,16,20,35]. Notably, Bailey et al.[18] reported in a large retrospective cohort study of inpatients and outpatients at the National COVID Cohort Collaborative (USA) that after adjustment for age, sex, race/ethnicity, smoking status, body mass index, and comorbidities, individuals with AUD were more likely to require hospitalization (aOR, 1.51; CI, 1.46 to 1.56) and had higher odds of all-cause mortality (aOR 1.55, CI 1.46, 1.65). Taken together, these findings indicate the heightened susceptibility of individuals with AUD to severe COVID-19 outcomes. It is important to acknowledge that in addition to compromised immune function, which is essential for combating viral infections such as COVID-19, individuals with AUD frequently grapple with various other issues that increase exposure to the virus and contribute to poorer results. These include pre-existing chronic health conditions, socioeconomic challenges, limited access to healthcare, and a propensity towards risky behaviors, coupled with poor adherence to public health guidelines.

In the second part of our analysis, we investigated specific risk factors for in-hospital mortality in patients with a history of AUD. After conducting binary logistic regression analysis, we found that the risk factors for death in individuals with AUD were similar to

those identified in the general population, with minor variations. These risk factors included age (60-79 years and > 80 years), male sex, hospitalization in more vulnerable regions, respiratory symptoms at onset, and the presence and number of comorbidities. Additionally, we observed that admissions in 2021 and 2022 were associated with a higher odds of death. Few studies have examined the relationship between AUD and COVID-19, or the potential predictors of worse outcomes in these patients. The increased risk of death with age observed in our study is consistent with the results of a previous study involving hospitalized patients with AUD[35]. Several factors, such as age-related remodeling of the immune system, immunosenescence, increased susceptibility to respiratory infections, impaired immune responses to vaccination, and a higher prevalence of comorbidities may explain the high mortality among older patients with COVID-19. In our analysis, male patients with AUD had a 19% higher risk of death than did female patients. This finding aligns with that of another investigation conducted in China that examined 367,120 patients and revealed a 20% higher risk of all-cause mortality in individuals with AUD[19]. Additionally, a study carried out in the Bologna metropolitan area of Italy analyzed mortality in 4,996 alcoholic patients during the COVID-19 pandemic and found an even more concerning outcome for male alcoholic patients, with a standardized mortality rate of 6.49 (95% CI 3.84-10.26)[15]. Notably, a stepped gradient effect was observed in the multivariate analysis regarding the risk of death, which increased in accordance with the number of pre-existing medical conditions. This is consistent with other studies that have reported an elevated risk of death in patients with AUD and comorbidities as well as COVID-19. However, it is important to recognize that approximately 40% of the AUD participants in this study had no comorbidities and one-third had only one comorbidity. Despite this, nearly half of AUD patients with COVID-19 died.

The strength of this study lies in the large cohort size, which enabled a comparison of the clinical characteristics, outcomes, and risk factors of death in individuals with and without AUD. However, this study has several limitations that are primarily related to the administrative nature of the SIVEP-Gripe database. First, one of the major limitations of the SIVEP-Gripe database is that information on pre-existing clinical conditions is self-reported, which means that there is no information regarding the characteristics of

patients' previous admissions or in-hospital management. Therefore, some important information, including data on AUD severity, could not be included in the analysis. Additionally, AUDs have been underreported in medical records, suggesting that the study may have focused on patients with a more severe disease spectrum[39]. Furthermore, the "non-AUD" group may have included individuals with AUD that has not yet been reported. Finally, large databases, such as SIVEP-Gripe, may have inconsistencies, typographical errors, and missing, incomplete, or inaccurate data, which could affect the interpretation of the results.

In conclusion, our study, which analyzed data from a nationwide multicenter registry of adults hospitalized with COVID-19, revealed that individuals with AUD had a higher in-hospital mortality rate. After taking into account confounding factors such as comorbidities, our findings indicated that those with AUD were twice as likely to die as those without AUD. These results suggest that AUD is an independent risk factor of severe COVID-19. Given the potential for SARS-CoV-2 to become an endemic seasonal pathogen in the coming years, addressing AUD and its associated health complications is crucial for mitigating the impact of respiratory infections.

Acknowledgements

To the Minas Gerais Research Support Foundation (FAPEMIG), to the National Council for Scientific and Technological Development (CNPq), to the Coordination for the Improvement of Higher Education Personnel (CAPES).

Conflict of Interest

No conflict declared

Author contributions: CRediT TaxonomyFabrício Emanuel OliveiraConceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Investigation-Equal, Methodology-Equal, Writing - original draft-Equal, Writing - review & editing-EqualDaniella MartelliConceptualization-Equal, Methodology-Equal, Project administration-Equal, Validation-Equal, Visualization-Equal, Writing - review & editing-EqualMaria Christina OliveiraConceptualization-Equal, Methodology-Equal, Project administration-Equal,

Validation-Equal, Visualization-Equal, Writing - review & editing-EqualEnrico ColosimoData curation-Equal, Formal analysis-Equal, Methodology-Equal, Supervision-Equal, Writing - review & editing-EqualHercílio Martelli JúniorConceptualization-Equal, Investigation-Equal, Project administration-Equal, Supervision-Equal, Validation-Equal, Visualization-Equal, Writing - review & editing-EqualEduardo OliveiraConceptualization-Equal, Data curation-Equal, Formal analysis-Equal, Project administration-Equal, Supervision-Equal, Validation-Equal, Writing - original draft-Equal, Writing - review & editing-Equal

Handling Editor: Dr. Thiago Roza

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