A Retrospective Cohort Study of SARS-CoV-2 Mortality Rate in Individuals with Opioid Use Disorder in Ilam (Southwest of Iran)

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ABSTRACT

Background & Objective: Individuals with opioid use disorder are a marginalized population in any society. They commonly have a weaker immune system, greater stress vulnerability, poorer health, more high-risk behaviors, and less access to healthcare services compared to the general population, which can expose them to a risk of severe COVID-19 complications. This study aimed to evaluate the effects of opioid use disorder on mortality in patients with SARS-CoV-2.

Materials & Methods: This registry-based retrospective cohort study was conducted on 2362 consecutive inpatients with a confirmed diagnosis of SARS-CoV-2 between March 5, 2020 and March 21, 2021, presenting to a university hospital in Ilam in the southwest of Iran. Forty-five patients with opioid use disorder were identified in this study and matched to 100 patients without opium addiction. All patients with a history of opium addiction were included in the study group, and age- and sex-matched patients without opioid use disorder were randomly recruited as the controls. After adjusting for the effects of age and comorbidities, data were analyzed in STATA version 10, using logistic regression models.

Results: The mortality of patients with opioid use disorder increased following COVID-19 (adjusted OR: 6.59; 95% CI: 1.84–23.59; P=0.004). Hypertension (adjusted OR: 8.17; 95% CI: 2.21–30.15; P=0.002) and advancing age (OR: 1.06; 95% CI: 1.01–1.11; P=0.01) were significantly associated with increased COVID-19 mortality.

Conclusion: Based on the present findings, opioid use disorder is a possible risk factor for mortality following COVID-19. The findings of the present study can be applied in the implementation of preventive measures and policies and prioritization of COVID-19 vaccination. However, further relevant research is recommended.

Keywords: COVID-19, Opioid use disorder, Opioids, Mortality

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new member of the coronavirus family, which can infect humans (1). Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 was first reported in November 2019 in Wuhan, China (2). By March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic (3). Individuals older than 55 years and those with an underlying medical condition, such as cardiovascular disease (CVD), chronic respiratory disease, diabetes, and immune system defects, are generally at a higher risk of hospitalization and mortality due to COVID-19 (4, 5).

On the other hand, the health burden of opioids is considerable around the world, involving hospitalization due to diseases, drug overdose, and mortality (6). Opioids comprise a group of drugs, including heroin, fentanyl, and pain medications, such as morphine, codeine, and methadone (7). These drugs are highly addictive and can lead to opioid use disorder (OUD) (7). OUD is a serious problem in Iran (8), with an estimated prevalence of more than 3% in the general population (9). The majority of individuals with OUD experience many problems, which can expose them to a high risk of infections, such as COVID-19 (10).

Individuals with OUD are usually a marginalized group in any society, with limited access to healthcare services (11). They commonly have a poorer health status and immune functions compared to the general population and suffer from chronic infections, respiratory disease, CVD, metabolic disorders, and various psychiatric disorders. Evidence suggests that the prevalence of these disorders is usually three to five times higher in the OUD population compared to the general population (10).

In many Asian countries, it is believed that opium use has protective and therapeutic effects against various diseases, such as CVD, diabetes, and hypertension **(9)**. Recently, during the COVID-19 pandemic, some misconceptions have spread about the protective effects of opioid use against COVID-19, leading to increasing demands for these substances and consequently, an increase in health and social problems **(8)**. The adverse effects of OUD have been reported in patients suffering from diseases, such as CVD **(12)**. Due to the decreased lung function in patients with COVID-19, OUD may also increase the risk of mortality associated with chronic respiratory diseases **(13)**. Besides, low ventilation and severe hypoxia due to opioid overdose and abuse can lead to cardiac arrest, pulmonary complications, brain damage, and death **(13)**. Therefore, the present study aimed to investigate the effects of OUD on COVID-19 mortality.

Materials and Methods

This retrospective cohort study was conducted on patients with COVID-19, who were hospitalized in the infection ward of Mostafa Khomeini Hospital in Ilam Province in the southwest of Iran between March 5, 2020 and March 21, 2021. A total of 2,362 laboratory-confirmed SARS-CoV infections were recorded in the registry of COVID-19. Data were collected from the health records of the university hospital. Overall, 45 patients with a current OUD were identified. A random sample of 100 age- and sex-matched patients without previous or current OUD was also recruited from the registry of COVID-19 patients for comparison (Table 1).

Table 1. The demographic data of patients with SARS-CoV-2 infection. Data are shown as n (%) or mean (standard error).

Characteristics	OUD	Non-OUD	P-value
Total	45	100	-
Age (years) (mean±SE)	55.8 (2.5)	55.5 (1.7)	0.92
Sex			0.41
Male	39 (86.7%)	81 (81%)	-
Female	6 (13.3%)	19 (19%)	-
BMI (kg/m^2) (mean±SE)	26.1 (0.6)	26.7 (0.5)	0.48
Marital status			0.53
Single	4 (8.9%)	6 (6%)	-
Married	41 (91.1%)	94 (94%)	-
Cigarette smoking status			<0.001
Lifetime non-smoker	17 (37.8%)	97 (97%)	
Ex-smoker	1 (2.2%	0 (0)	-
Smoker	26 (57.7%)	1 (1%)	-
Unknown	1 (2.2%)	2 (2%)	-
Comorbidities			
Diabetes	9 (20%)	23 (23%)	0.69
Cardiovascular disease	15 (33.3%)	21 (21%)	0.11
Hypertension	8 (18.8%)	25 (25%)	0.34
Chronic lung disease	4 (8.9%)	4 (4%)	0.23
Chronic kidney disease	4 (8.9%)	5 (5%)	0.37
Cancer	2 (4.5%)	1 (1%)	0.18

BMI: Body mass index.
Ex-married: Divorced or separated.
Ex-smoker: An individual who has given up cigarette and/or tobacco smoking.
Chronic lung diseases: asthma and COPD.

Differences in the demographic and background variables between addicted and non-addicted cohorts were examined using *t*-test and Chi-square test for continuous and categorical variables, respectively. The effect of opium addiction on mortality was investigated in this cohort, and the mortality rate was compared between the opium-addict and control groups. Logistic regression models were used to identify the effect of OUD on

mortality in patients with COVID-19 (Table 2). All significant variables in the univariate analysis were

exported to the multivariate logistic regression model using STATA version 10 (StataCorp, TX, USA).

Table 2. The univariate logistic regression models for factors associated with mortality in COVID-19

Characteristics	Crude odds ratio (95% CI)	P-value
Age (years)	1.05 (1.02–1.09)	0.003*
Sex		
Female	1**	-
Male (%)	1.21 (0.323–4.49)	0.76
BMI	1.03 (0.95–1.13)	0.46
Marital status		
Single	1	-
Married	1.01 (0.81–2.85)	0.56
Cigarette smoking status		
Non-smoker	1	-
Ex-smoker	1.23 (1.01–8.06)	0.61
Smoker	2.04 (0.70–5.92)	0.23
OUD		
No	1	-
Yes	3.27 (1.25–8.59)	0.02*
Cardiovascular disease		
No	-	-
Yes	2.97 (1.12–7.90)	0.03*
Hypertension		
No	1	-
Yes	7.43 (2.71–20.39)	<0.001*
Chronic lung disease		
No	1	-
Yes	2.20 (0.41–11.77)	0.36
Diabetes		
No	-	-
Yes	3.63 (1.35–9.77)	0.01*
Chronic kidney disease		
No	1	-
Yes	3.50 (0.80–15.32)	0.05*
Cancer		
No	1	-
Yes	3.24 (0.28–37.46)	0.35

*Significant   **Reference category
BMI: Body mass index.
Ex-married: Divorced or separated.
Ex-smoker: An individual who has given up cigarette and/or tobacco smoking.
Chronic lung diseases: Asthma and COPD.

Results

Based on the results of data analysis, 45 (1.9%) patients had self-reported OUD. Besides, 100 age- and sex-matched patients were randomly selected as the control group. Table 1 presents the demographic and background characteristics of addicted and non-addicted cohorts. Differences in these variables between the cohorts were examined using *t*-test and Chi-square test for continuous and categorical variables, respectively. Based on the results, 34% of OUD patients had a history of CVD, and 9% had a history of a chronic lung disease.

Regarding active cigarette smoking, there was a significant difference between addicts and non-addicts (57.7 vs. 1%; P<0.001). However, there were no significant differences between the two cohorts regarding other variables. The mean age of the deceased due to COVID-19 was 66.3 years, and the mean age of recovered patients was 53.9 years. The rate of mortality was estimated at 24.4% and 9% in OUD and non-OUD patients, respectively. According to the univariate analysis, the variables of age, OUD, CVD, hypertension, diabetes, and chronic kidney disease were associated with COVID-19 mortality.

In the univariate analysis, the odds ratio (OR) of mortality was 3.27 (95% CI: 1.25–8.59) times higher in OUD patients compared to non-addicts (Table 2). By entering all significant variables of the univariate analysis to the multivariate logistic regression model, hypertension, age, diabetes, and OUD were identified as independent predictors of COVID-19 mortality. OUD was associated with a higher risk of COVID-19 mortality in the adjusted model, with an adjusted OR of 6.59 (95% CI: 1.84–23.59) and a P-value of 0.004; this relationship was statistically significant (Table 3).

Table 3. Adjusted multivariate logistic regression models for the effect of OUD on COVID-19 mortality

Risk factors	Adjusted odds ratio (95% CI)	SE for aOR	P-value
Age	1.06 (1.01–1.11)	0.02	0.01*
Cardiovascular disease			
No	1**	-	-
Yes	0.43 (0.11–1.84)	0.32	0.26
Hypertension			
No	1	-	-
Yes	8.17 (2.21–30.15)	5.44	0.002*
Chronic kidney disease			
No	1	-	-
Yes	2.72 (0.36–20.51)	2.81	0.33
Diabetes			
No	1	-	-
Yes	3.29 (0.85–12.66)	2.26	0.08
OUD			
No	1	-	-
Yes	6.59 (1.84–23.59)	4.29	0.004*

*Significant.
**Reference category.

Discussion

The present study aimed to evaluate the effect of OUD on mortality in patients with SARS-CoV-2 infection. COVID-19 was a global health crisis, affecting all populations around the world **(14)**. Many vulnerable groups are exposed to a higher risk of COVID-19 mortality **(15)**. The present results indicated a significant relationship between OUD and COVID-19 mortality in the univariate model. The risk of mortality was also higher among COVID-19 patients with diabetes, cancer, and respiratory disease.

Individuals with OUD generally comprise a vulnerable group with weaker immune responses, high-risk behaviors, and inadequate access to healthcare services, which expose them to many diseases, including COVID-19 **(10)**. According to

some reports, opioids have complex effects on the immune system (16, 17). Some opioids, such as morphine, suppress the immune system and increase the risk of infectious diseases, such as pneumonia (13, 16, 18). Although the short-term use of these substances can stimulate the immune system, it is clinically established that chronic and long-term use of opioids is associated with an increased risk of infections, especially pulmonary infections (16, 18, 19). In some epidemiological studies, opioid use has been associated with a higher risk of mortality in COVID-19 patients, and the mortality has been mostly attributed to the immunosuppressive and respiratory depressive effects of infection (19).

In this study, some OUD patients had a history of cardiovascular and chronic lung diseases. People with OUD, such as heroin addicts, may develop asthma and chronic obstructive pulmonary disease (20). Previous studies have revealed that patients with COVID-19 and comorbid cardiovascular and pulmonary diseases had poorer outcomes and an increased mortality risk (21). The OUD patients commonly have chronic health conditions, associated with a higher disease burden, which increases the risk of mortality from infectious diseases, such as COVID-19 (22). Chronic lung disease is known to increase the risk of opioid mortality (23), and the reduced lung function due to COVID-19 may also endanger OUD patients (24).

Based on the current results, 44% of patients with OUD were admitted to the ICU, 23% underwent intubation due to severe acute respiratory failure, and 18% underwent mechanical ventilation; the corresponding values were 19%, 10%, and 9% in the control group, respectively. These results can be interpreted as the physiological and immunological effects of OUD, as the co-occurrence of OUD with COVID-19 exacerbates the disease.

Limitations

A limitation of this study was the relatively small number of samples in the groups. Therefore, caution must be exercised, as the findings may not be generalizable to other populations.

Conclusion

OUD is a possible risk factor for mortality following COVID-19 infection. Early identification and timely treatment of COVID-19 can decrease the rate of mortality in OUD patients. Opioid addicts with an underlying medical condition, such as CVD, chronic obstructive pulmonary disease, diabetes, and kidney disease, should be considered as a high-risk group of mortality and morbidity. The findings of this study can be considered in the implementation of preventive measures and policies, including the prioritization of COVID-19 vaccination; further relevant research is also recommended.

Acknowledgments

Conflict of Interest

The authors declare that they have no conflicts of interest.

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