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The Association of Opium Abuse with Mortality Amongst Hospitalized COVID-19 Patients in Iranian Population

Alireza Mirahmadizadeh[1] · **Alireza Heiran**[1] · **Amineh Dadvar**[2] ·
Mohammad Javad Moradian[3] · **Mohammad Hossein Sharifi**[1] ·
Roya Sahebi[4]

Abstract

Opioid abuse is a serious problem in the society. Since the first months of COVID-19 pandemic, several myths, rumors and misconceptions have been spread about the benefits of opium consumption for COVID-19 outcome. In addition, data are limited on the relationship between opium abuse and COVID-19 mortality amongst hospitalized COVID-19 patients. In this historical cohort study, we assessed the risks of several variables for mortality amongst all hospitalized COVID-19 patients from the beginning of COVID-19 pandemic in South of Iran from March 15th, 2021 to October 14th, 2021. Data was acquired from the Medical Care Monitoring Center (MCMC), affiliated to Shiraz University of Medical Sciences. A total of 64,427 hospitalized COVID-19 patients were included into the analysis. The mortality rate was 10.59% ($n = 6756$). Of all, 2030 (3.15%) patients—1702 males and 328 females—reported the positive history of opium abuse with a mean age of 57 ± 17.21 years. The results of multivariable risk showed that the positive history of opium abuse had a significant association with mortality (adjusted RR: 1.173; $p = 0.007$). Other significant predictive risk factors were male gender, elder ages, and comorbidities such as pulmonary diseases, cardiovascular disease, cancer, nephrological diseases, neurological diseases, and diabetes. However, being a health care worker and having thyroid gland diseases were protective factors amongst hospitalized COVID-19 patients (adjusted RR: 0.650 and 0.642; $p = 0.040$ and $< .0001$, respectively). Opium abuse is a risk factor for mortality amongst hospitalized COVID-19 patients. It is vital to educate societies about the consequences of unauthorized opium consumption.

Keywords COVID-19 · Opium abuse · Mortality · Retrospective cohort · Iran

✉ Mohammad Hossein Sharifi
  mhsharifi1350@gmail.com

Extended author information available on the last page of the article

Introduction

Opium abuse is a serious global problem. According to the latest World Drug Report in 2018, approximately 269 million people suffer from drug use disorders (substances such as opium, alcohol, marijuana, nicotine, cocaine, and heroin),worldwide, which was 30% more than the 2009 estimates (Mahdavi & Aliramezany, 2021). Also, it is estimated that 2.8–9.0% of Iranians are opium abusers (Ignaszewski, 2021). Misconceptions are prevalent in the society regarding the befits and risks of opium consumption in human health and COVID-19 infection (Mahdavi & Aliramezany, 2021). There are plenty of studies about the association between comorbidities and COVID-19 mortality (Sanyaolu et al., 2020; Zaki et al., 2020). Diabetes, hypertension, cardiovascular disease, and higher cholesterol levels are associated with higher COVID-19 severity and mortality (Yang et al., 2020). Based on a systematic review of a total of 54 articles, the links between COVID-19 and some comorbidities such as cancer, kidney disease, and stroke are unclear and need further evaluation (Zaki et al., 2020). Moreover, smoking appears to be associated with a worse prognosis (Patanavanich & Glantz, 2020; Zaki et al., 2020).. Since the effect of opium abuse on COVID-19 prognosis is not well understood, this study was conducted to investigate the association between opium abuse and mortality among hospitalized COVID-19 patients. Due to the lack of a data base for gathering data in the general population, this investigation was performed on hospitalized patients.

The scientific evidence on the impact of opioid abuse on health and disease is conflicting (Ignaszewski, 2021; Mahdavi & Aliramezany, 2021). Besides the insufficient scientific evidence, some myths and rumours have been spread by social media in the community which claimed that opium consumption has protective effects against COVID-19 infection and COVID-19 infection less affect the people with the mild COVID-19 infection (Mahdavi & Aliramezany, 2021). In addition, opium abuse, according to traditional beliefs and studies, has therapeutic effects in cases of headache, toothache, earache, and sexual impotence. It also has analgesic, hypnagogic, antitussive, and antidiarrheal effects (Karam et al., 2004; Farahani et al., 2015; Hasandokht et al., 2018). A recent systematic review found no evidence that opium use protects against cardiovascular disease (Hasandokht et al., 2018; Adib et al., 2020; Riahi et al., 2021). Several studies with small sample sizes have shown that subjects with substance use disorders (SUDs) are at a higher risk of contracting COVID-19 infection (Pirnia et al., 2020; Riahi et al., 2021), as well as poor outcomes (Dubey et al., 2020). Since identification of factors linked to COVID-19 mortality can help in risk reduction and can cause appropriates interventions (Zaki et al., 2020), more studies are needed to better determine the relationship between opium abuse and mortality amongst COVID-19 patients. The main aim of this study was to investigate the association between opium abuse and mortality amongst hospitalized COVID-19 patients in an Iranian population during 2021.

Methods

In this historical cohort study, we assessed the risk of mortality for several variables amongst all hospitalized COVID-19 patients from the early months of COVID-19 pandemic in Fars province, South of Iran, from March 15th, 2021 to October 14th, 2021. This study was approved by Shiraz University of Medical Sciences (SUMS) Local Ethics Committee by the code: IR.SUMS.REC.1399.1165.

According to legal and regulatory framework, demographic, medical history, and clinical data for any suspected or confirmed COVID-19 hospital admission or transfer have to be registered by an ER physician. Therefore, for our research purpose, we used an administrative data repository, the "Medical Care Monitoring Center" (MCMC). By announcing COVID-19 pandemic, this system was updated by the Vice-Chancellor of Treatment Affairs of SUMS to record data in a separate database about all suspected COVID-19 hospitalizations (Gray Zones admissions) in all 31 counties under cover of the SUMS, which includes 47 hospitals (https://sums.ac.ir/page-Main/fa/0/form/pId770).

The inclusion criteria were as followed: age ≥ 18 years—since opium abuse is rare at younger ages—and confirmed COVID-19 disease. While, opium abuse defines as any compulsive urge to use opioid (or opioid derivative) drugs, the definition would be different in the regions that opium abuse is a tradition, which is consumed to alleviate acute and chronic pain, mostly by old people. That is, in Iran, the most common type of opium abuse is to inhale on smoke of the burning dark crude material retrieved from *Papaver somniferum* (Nakhaee et al., 2020). Therefore, in this study, we considered the recent definition.

An individual was excluded if data was not available for any of the studied variables or a patient had more than one admission. Moreover, since the endpoint of study was the hospital outcome of each patient (deceased or discharged), those who were still hospitalized or transferred to another ward or hospital were excluded. For this purpose, MCMC has a feature that shows if a hospitalized COVID-19 patient is (Mahdavi & Aliramezany, 2021) deceased due to COVID-19, (Ignaszewski, 2021) cured of the COVID-19 and discharged from the hospital, (DRUGS UNOO, LABOR, 2021) transferred to another ward (non-Gray Zone) in the same hospital for other medical complaints, or (Sanyaolu et al., 2020) transferred to another hospital to manage for other medical complaints. The reason for excluding the second two conditions was the uncertainty about outlook of COVID-19 and if a patient cured of the COVID-19 or not, since our repository did not contain data after the transfers.

The acquired dataset includes admission date, demographic variables (gender, age), medical history (being health care worker, smoking, opium abusing) and underlying medical condition (HIV or immunodeficiency, pulmonary diseases, cancer, thyroid diseases, hematological diseases, hepatic diseases, nephrological disease, neurological diseases, hyperlipidemia, diabetes, cardiovascular diseases, and hypertension), as well as outcome and its' date. Data access request was sent to the Vice-Chancellor of Treatment Affairs; upon accepting, the Information Technology (IT) unit of SUMS retrieved our target variables using SQL (Structured Query Language).

For statistical analysis we used 'GLM' [denoting Generalized Linear Model], 'Sandwich' and 'lmtest' packages, implemented in R programing language (version 4.0.4 for MacOS). Hospital outlook of each patients was the outcome (dependent) variable, opium abusing was the exposure variable, and all of the remaining variables considered as the confounding (independent variables). Initially, univariate odds ratio (OR) was calculated for each independent variable. Variables with p value < 0.25 were selected for the multivariable analysis (Bursac et al., 2008). Since OR always overestimates the risk ratio in cohort studies, the single variable relative risk (RR) and adjusted RR were calculated; hence, we used the Poisson single univariable and multivariable regression with robust standard errors, instead of logistic regression (Knol et al., 2012). The null hypothesis was that the coefficient for the association between each independent variable and the outlook of hospitalization due to the COVID-19 was equal to zero. A p value < 0.05 was considered statistically significant. Furthermore, to compare opium-user and non-user hospitalized COVID-19 patients, we used ‡ Pearson's Chi-square test (or Fisher's exact test) and independent t-test for qualitative and quantitative variables, respectively. The R codes are yielded in appendix 1.

Results

A total of 64,427 hospitalized COVID-19 patients were included into the analysis (Fig. 1). The mortality rate was 10.59% ($n = 6756$). Of all, 2030 (3.15%) patients—1702 male and 328 female—reported the positive history of opium abuse with a mean age of 57 ± 17.21 years, ranging 18–96 years old. Opium abuser patients were significantly older and male, and had higher rates of positive history of cigarette smoking, numbers of comorbidities, and mortality ($p = 0.032, < 0.0001, < 0.0001, < 0.0001, < 0.0001, 0.001$) (Table 1).

Table 2 depicts the univariate ORs. positive history of opium abuse was statistically associated with death amongst hospitalized adult COVID-19 patients (OR: 1.264; $p = 0.001$). Positive history of smoking, immunodeficiency/HIV and hematological diseases were not significant risk factors (OR: 1.030, 1.115 and 1.182; $p = 0.706, 0.290$ and 0.194, respectively). The first two variables had a P value > 0.25, so these were excluded from multivariate analysis.

The results of univariable and multivariable risk analysis using Poisson regression with robust standard errors are shown in Table 3. According to the multivariable analysis, we found that the positive history of opium abuse was significantly an independent risk factor for mortality amongst hospitalized adult COVID-19 patients (adjusted RR: 1.173; $p = 0.007$). In addition, controlling the confounding variables, male or elder patients had higher risk of mortality (adjusted RR: 1.036, 1.218; $p < 0.0001, < 0.0001$). Considering comorbidities, pulmonary diseases, cancer, hepatic diseases, nephrological diseases, neurological diseases, diabetes, and cardiovascular disease were significantly associated with mortality (Table 3). Of note, hepatic diseases had the highest, more than 120%, increase in risk of mortality amongst hospitalized patients (adjusted RR: 2.211; $p = 0.007$). Interestingly, being a health care worker or have a thyroid gland disease were protective factors
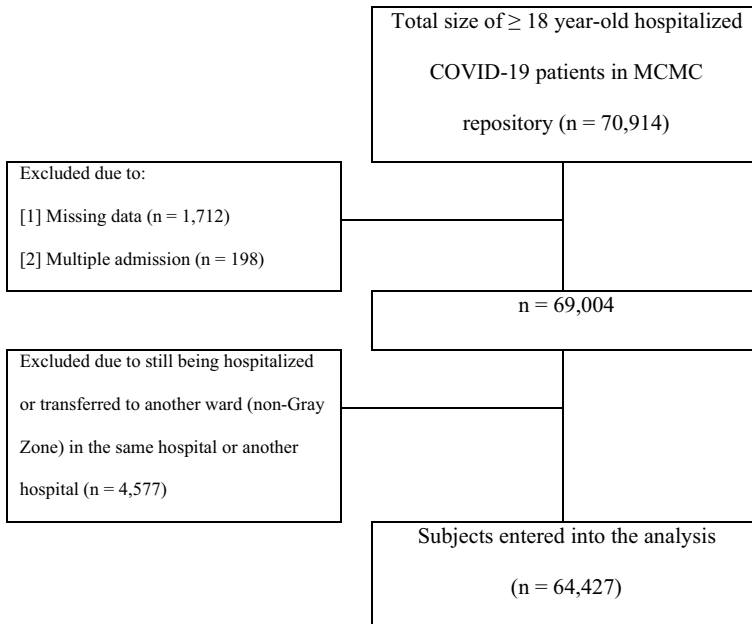
Fig. 1 Flowchart of the included subjects into the analysis from MCMC repository

for mortality (adjusted RR: 0.650, 0.642; $p = 0.040, < 0.0001$). Furthermore, while hyperlipidemia and hypertension were associated with mortality in univariable analysis (RR: 1.315, 1.801; $p = 0.001, < 0.0001$), they were not independent predictive variable for mortality in multivariable analysis (adjusted RR: 0.925, 1.048; $p = 0.343, 0.073$).

Discussion

Following the COVID-19 pandemic, research on the impact of drug abuse/smoking or other substance abuse on the outcome of COVID-19 infection outlook has been an area of interest for the research groups. The current study examined the relationship between opium abuse and mortality amongst 64,427 COVID-19 hospitalized patients. According to the findings, opium abuser patients had a 17% higher risk for mortality. In addition, male gender, higher ages and the underlying diseases such as cardiovascular disease, diabetes, cancer, hepatic disease, were significant risk factors for mortality; but hyperlipidemia and hypertension were not found to be significant risk factors.

While the reasons of just-mentioned 17% increase in risk of mortality amongst hospitalized COVID-19 patients who were opium abuser is not clear, it might have something to do with immune system, serum factors and inflammatory biomarkers. Opium contains approximately 20 alkaloids and over 70 other components that can suppress the immune system and increase inflammation (Karam

Table 1 Comparison of hospitalized COVID-19 patients who were opium abuser and opium non-abuser

Variable	Opium abusers ($n=2030$)	Opium non-abusers ($n=62,397$)	p^a
Age	57.00 ± 17.21	56.11 ± 18.46	0.032^b
Gender			
Male	1702 (83.8%)	31,875 (51.1%)	<0.0001
Female	328 (16.2%)	30,522 (48.9%)	
History of smoking			
Positive	750 (36.9%)	1035 (1.07%)	<0.0001
Negative	1280 (63.1%)	61,362 (98.3%)	
Number of comorbidities			
0	0 (0)	3805 (6.1%)	<0.0001
1	13 (0.6%)	14,374 (23.0%)	
2	222 (10.9%)	19,886 (31.9%)	
3	526 (25.9%)	13,469 (21.6%)	
4	585 (28.8%)	7016 (11.2%)	
5	389 (19.2%)	2808 (4.5%)	
≥ 6	295 (14.5%)	1039 (1.7%)	
Mean number of comorbidities	4.05 ± 1.38	2.29 ± 1.32	$<0.0001^b$
Outcome			
Deceased	260 (12.8%)	6496 (10.4%)	0.001
Discharged	1770 (87.2%)	55,901 (89.6%)	

[a]Pearson's Chi-square test or Fisher's exact test

[b]Independent t-test

et al., 2004). In this respect, previous studies showed that the levels of most cytokines were changed in opium users—lower levels of IL-4 and higher levels of IL-6 compared to the controls (Nabati et al., 2013; Pirnia et al., 2020). In addition, it has been shown that mortality in COVID-19 patients is linked to the cytokine storm, driven by high levels of interleukin-6 (IL-6) (Nabati et al., 2013; Mahdavi & Aliramezany, 2021). Another possible explanation is about the effect of opium on some serum factors, i.e., HDL, potassium, Fe^{2+} and TIBC (Total Iron Binding Capacity), which may increase mortality, indirectly (Karam et al., 2004). It is sophisticated to explain this result, but Asadi Karam and colleagues showed that opium decreases HDL, which increases the risk for atherosclerosis. Opium increases serum potassium, which may interfere with water regulation and blood pressure. Furthermore, in males, Fe2 + is shown to be higher in diabetic addicts than non-addicted diabetics ($p=0.0141$), but TIBC was lower in diabetic addicts than diabetic non-addicts ($p=0.0098$). A previous study found that having a high serum iron level was associated with an increased risk of mortality (Corti et al., 1997; Lan et al., 2018). Furthermore, serum CRP (C-Reactive Protein) levels in opium abusers were shown to be 12-fold greater than controls (Ghazavi et al., 2013). As a result, opium may exacerbate inflammatory responses. However, to

Table 2 Descriptive data and univariable derived odds ratio of different variables for mortality amongst hospitalized COVID-19 patients (n = 64,427; deceased = 6756, discharged = 57,671)

Variable	N	% of death		OR	95% CI	P^a
		+	−			
Gender						
Male	33,577	11.56%	88.44%	1.273	1.210–1.340	**< 0.0001**
Female (reference)	30,850	9.31%	90.69%			
Age	–	68.27 ± 15.72	54.71 ± 18.19	1.045	1.044–1.047	**< 0.0001**
Health care worker						
Positive	564	3.55%	96.45%	0.312	0.199–0.487	**< 0.0001**
Negative	63,863	10.55%	89.45%			
History of smoking						
Positive	1787	10.76%	89.24%	1.030	0.885–1.199	0.706
Negative	62,642	10.48%	89.52%			
History of opium abuse						
Positive	**2030**	**12.81%**	**87.19%**	**1.264**	**1.107–1.443**	**0.001**
Negative	**62,397**	**10.41%**	**89.59%**			
HIV or immunodeficiency						
Positive	521	11.90%	88.10%	1.155	0.885–1.507	0.290
Negative	63,906	10.47%	89.53%			
Pulmonary diseases						
Positive	3079	13.54%	86.46%	1.359	1.222–1.512	**< 0.0001**
Negative	61,348	10.33%	89.67%			
Cancer						
Positive	2355	17.92%	82.08%	1.921	1.724–2.141	**< 0.0001**
Negative	62,072	10.20%	89.80%			
Thyroid diseases						
Positive	23,595	6.87%	93.13%	0.513	0.484–0.544	**< 0.0001**
Negative	40,832	12.58%	87.42%			
Hematological diseases						
Positive	568	12.15%	87.85%	1.182	0.918–1.523	0.194
Negative	63,859	10.47%	89.53%			
Hepatic diseases						
Positive	676	21.30%	79.70%	2.339	1.942 -2.817	**< 0.0001**
Negative	63,751	10.37%	89.63%			
Nephrological diseases						
Positive	2478	18.20%	81.80%	1.964	1.767–2.182	**< 0.0001**
Negative	61,949	10.18%	89.82%			
Neurological diseases						
Positive	1866	20.10%	79.90%	2.214	1.972–2.487	**< 0.0001**
Negative	62,561	10.20%	89.80%			
Hyperlipidemia						
Positive	940	13.72%	86.28%	1.365	1.131–1.646	**0.001**
Negative	63,487	10.44%	89.56%			

Table 2 (continued)

Variable	N	% of death		OR	95% CI	P^a
		+	−			
Diabetes						
Positive	10,208	16.17%	83.83%	1.856	1.748–1.971	**< 0.0001**
Negative	54,219	9.42%	90.58%			
Cardiovascular disease						
Positive	9142	17.52%	82.48%	2.065	1.942–2.195	**< 0.0001**
Negative	55,285	9.32%	90.68%			
Hypertension						
Positive	14,425	16.01%	83.99%	1.954	1.851–2.062	**< 0.0001**
Negative	50,002	8.89%	91.11%			

Bold values indicate statistically significant

[a]Univariate logistic regression

Table 3 Relative risks (RR) of different variables for mortality amongst hospitalized COVID-19 patients ($n = 64,427$; deceased $= 6756$, discharged $= 57,671$) using Poisson regression with robust standard errors

Variable	Univariate analysis			Multivariate analysis		
	RR	95% CI	P^a	RR	95% CI	P^a
Age	1.039	1.038–1.041	<0.0001	1.036	1.035–1.038	**< 0.0001**
Gender [reference = female]	1.242	1.186–1.300	<0.0001	1.218	1.164–1.274	**< 0.0001**
Health care worker	0.336	0.218–0.517	<0.0001	0.650	0.431–0.981	**0.040**
History of opium abuse	**1.230**	**1.096–1.381**	**< 0.001**	**1.173**	**1.044–1.312**	**0.007**
Pulmonary diseases	1.311	1.195–1.437	<0.0001	1.162	1.062–1.272	**0.001**
Cancer	1.756	1.606–1.921	<0.0001	1.742	1.590–1.908	**< 0.0001**
Thyroid diseases	0.545	0.518–0.576	<0.0001	0.642	0.609–0.677	**< 0.0001**
Hematological diseases	1.160	0.929–1.449	0.191	1.093	0.873–1.368	0.436
Hepatic diseases	2.054	1.774 -2.378	<0.0001	2.211	1.902–2.570	**< 0.0001**
Nephrological diseases	1.788	1.640–1.950	<0.0001	1.431	1.312–1.562	**< 0.0001**
Neurological diseases	1.970	1.795–2.163	<0.0001	1.343	1.222–1.476	**< 0.0001**
Hyperlipidemia	1.315	1.118–1.546	0.001	0.925	0.789–1.086	0.343
Diabetes	1.718	1.632–1.808	<0.0001	1.311	1.242–1.384	**< 0.0001**
Cardiovascular disease	1.878	1.784–1.977	<0.0001	1.138	1.078–1.202	**< 0.0001**
Hypertension	1.801	1.719–1.887	<0.0001	1.048	0.999–1.103	**0.073**
Intercept	–	–	–	0.010	0.009–0.011	**< 0.0001**

Bold values indicate statistically significant

[a]Poisson regression with robust standard errors

draw the full picture of opium abuse and morality in COVID-19 infection, more studies are warranted.

Such risk factors, independent of opium abuse, may increase the risk of COVID-19 mortality. The current study showed that underlying diseases such as cardiovascular disease, diabetes, cancer, and hepatic disease, were significant risk factors for COVID-19 mortality. In this regard, hepatic and neurological diseases had highest odds ratios (OR: 2.3 and OR: 2.2). This finding could be explained by the fact that some patients with hepatic and neurological diseases had poor prognoses due to malnutrition and lack of appropriate treatment. According to a meta-analysiss, the pooled odds ratios for hypertension, respiratory system disease, and cardiovascular diseases in severe COVID-19 were 2.36, 2.46, and 3.42, respectively, when compared to non-severe patients (Yang et al., 2020b). What is surprising is that hypertension and hyperlipidemia were not significant independent predictive factors for COVID-19 mortality in multivariate analysis. However, in the univariate analysis, hypertension and hyperlipidemia were significant risk factors for COVID-19 mortality. Previous research has linked hypertension by a 2.5-fold increase with the risk of COVID-19 mortality, particularly in elderly (Lippi et al., 2020; Escobedo-de la Peña et al., 2021). This discrepancy result is difficult to explain; it could be attributed to a variety of mechanisms, including angioplasty-converting enzyme 2 (ACE2) receptors, the NADH/NADPH oxidase system, and the inflammatory response and cytokine storm affected by COVID-19 and hypertension. Further biologic and clinical researches are needed to determine the exact mechanisms by which hypertension is linked to the risk of COVID-19 infection and mortality outcomes. Hence, these results should be interpreted with caution. Moreover, male gender was a risk factor for COVID-19 mortality, which is consistent with previous studies (Nguyen et al., 2021). It should be noticed that the age distribution of opium abuser COVID-19 hospitalized patients was bell-shaped, with a mean of 57 ± 17.21 years; that is higher than that of the general population (33.9 years) (Ahmadi et al., 2007). This result might be explained by the fact that the rate of hospitalization due to COVID-19 infection increases with age In addition, the current study found that elderly was a significant risk factor for COVID-19 mortality. One possible explanation for this is that elder patients had other comorbidities at the time of the infection.

Being a health care worker or having a thyroid gland disease was a protective factor amongst hospitalized COVID-19 patients in current study. It appears that these findings are the result of higher health literacy among health care worker than in the general population. According to a systematic review and meta-analysis, the Iranian population's, health literacy was inadequate and borderline. However, the overall level of health literacy among all health care worker was good to moderate (Dadipoor et al., 2018). Despite the findings of the current

study, previous research has shown that thyroid gland diseases increased the risk of COVID-19 poor outcomes and were influenced by the patient's age (Damara et al., 2021). This is a difficult finding to explain, but it could be related to the current study's lack of detailed data collection. Hypothyroidism, hyperthyroidism, and other conditions are not distinguished in this regard.

Although the large sample size might be the most important strength of the present study, this historical cohort study is inherently limited by absence of data on independent variables such as education level, socio economic status, BMI, etc. that potentially could influence the interpretation of the findings.

Conclusion

Despite a part of community belief that opium use is beneficial in preventing COVID-19 infection, we found that opium abuse is a risk factor for mortality amongst hospitalized COVID-19 patients. Opium use is illegal and a major issue in society and government policy, but there was no clear response to the community's belief. In clinical practice, expert opinion and health workers' opinion about the benefits and drawbacks of opium use, as a primary role group in society, can have a significant influence on public belief. We strongly suggest to educate the general population for the risks of unauthorized opium consumption, especially during COVID-19 pandemic. As part of the strategy to control the pandemic in access to healthcare support, it is necessary to highlight the need to screen and treat individuals who abuse opium.

Appendix 1

R codes for univariate logistic regression and univariate and multivariate Poisson regression model with robust standard errors

```
> data <—read.csv("…/data.csv")
> attach(data)
> library(sandwich)
> library(lmtest)
> fit_log_1 = glm(outlook ~ var.1, family = binomial(link = 'logit')) ### Iterating univariate logistic
  regression for each variable
```

```
> log2prob = function(log_){return(exp(log_))} ### Returning logs of estimated coefficients
> summary(fit_log_1)
> log2prob(coef(fit_log_1)) ### Returning ORs
> exp(coefci(fit_log_1)) ### Returning 95% Cis
> fit_poi_1 = glm(outlook ~ var.1, family = poisson(link = 'log')) ### Iterating univariate Poisson
  regression model for each variable with P < 0.25 in univariate logistic regression
> fit_robust_1 = coeftest(fit_poi_1, vcov = sandwich) ### Iterating univariate Poisson regression
  model with robust standard errors for each variable with P < 0.25 in univariate logistic regres-
  sion
> fit_robust_1
> log2prob(fit_robust_1)
> log2prob(coef(fit_robust_1))
> log2prob(confint(fit_robust_1))
> fit_poi_n = glm(outlook ~ age + gender + health_staff + hx_opium + respiratory_dx + cancer + thy-
  roid_dx + blood_dx + liver_dx + kidney_dx + neuro_dx + hyperlipidemia + diabetes + CVD + HTN,
  family = poisson(link = 'log')) ### Fitting multivariate Poisson regression model on variables with
  P < 0.25 in univariate logistic regression
fit_robust_n = coeftest(fit_poi_n, vcov = sandwich)
> fit_robust_n
> log2prob(fit_robust_n)
> log2prob(coef(fit_robust_n))
> log2prob(confint(fit_robust_n))
```

Declarations

Conflict of Interest The Authors declare that there is no competing interest.

Ethical Approval This study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. This study was approved by Shiraz University of Medical Sciences Local Ethics Committee by the code: IR.SUMS.REC.1399.1165.

Consent to Participate Written informed consent forms were obtained from each participant.

Consent for Publication All of the authors have approved the contents of this paper and have agreed to the submission policies. Also, each of the authors confirms that this manuscript has not been previously published and is not currently under consideration by any other journal.

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Authors and Affiliations

Alireza Mirahmadizadeh[1] · **Alireza Heiran[1]** · **Amineh Dadvar[2]** ·
Mohammad Javad Moradian[3] · **Mohammad Hossein Sharifi[1]** ·
Roya Sahebi[4]

  Alireza Mirahmadizadeh
  mirahmadia@sums.ac.ir

  Alireza Heiran
  heiran.alireza@gmail.com

  Amineh Dadvar
  dadvara@sums.ac.ir

  Mohammad Javad Moradian
  drmoradian@sums.ac.ir

  Roya Sahebi
  rasahebi@yahoo.com

[1]   Non-communicable Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

[2]   Shiraz University of Medical Sciences, Shiraz, Iran

[3]   Trauma Research Center, Shahid Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

[4]   Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran