

**Mahdi Afshari,
Iraj Shahramian,
Morteza Salarzaei,
Hadi Mirzaie,
Fateme Parooie ***

OPIUM USE AND COVID-19 INFECTION, A RETROSPECTIVE STUDY IN IRAN

Zabol University of Medical Sciences
Pediatric Gastroenterology and Hepatology Research Center
Zabol, Iran

Університет медичних наук, Заболь
Дослідницький центр дитячої гастроентерології та гепатології
Заболь, Іран

*e-mail: FatemeParooie@gmail.com

Цитування: Медичні перспективи. 2022. Т. 27, № 3. С. 122-127

Cited: *Medicni perspektivi*. 2022;27(3):122- 127

Key words: *opium, addiction, Covid-19*

Ключові слова: *опіум, залежність, Covid-19*

Abstract. **Opium use and COVID-19 infection, a retrospective study in Iran. Mahdi Afshari, Iraj Shahramian, Morteza Salarzaei, Hadi Mirzaie, Fateme Parooie.** *The situation of Covid-19 patients with opium consumption has not been comprehensively investigated especially in Iran. This study is aimed to investigate the effect of current opium addiction on the severity and outcome of the Covid-19 infection. During a retrospective cohort study, clinical, demographic and all variables related to the severity and death due to the Corona virus infection were collected from the medical records of patients hospitalized from February 2020 to June 2021 in the study area. The role of current addiction in the severity and outcome of the disease was investigated using Cox, logistic and linear regression models. Of 939 confirmed Covid-19 cases admitted during the study period, 70 (7.5%) patients were currently addicted. Multivariate regression models showed that current opium addiction significantly increased the chance of endotracheal intubation ($OR=2.96, p=0.005$) and reduced the mean length of stay in hospital (beta coefficient $=-0.42, p<0.0001$). However, opium addiction did not change the risk of death ($HR=1.54, p=0.063$) or O_2 saturation ($OR=1, p>0.99$). Opium addiction can be associated with the severity of Covid-19 infection, but does not play a considerable role in the mortality of the patients.*

Реферат. **Вживання опіуму та інфекція COVID-19, ретроспективне дослідження в Ірані. Махді Афшарі, Ірадж Шахрамیان, Мортеза Саларзаї, Хаді Мірзаї, Фатеме Паруї.** *Стан пацієнтів з Covid-19, які вживають опіум, не була всебічно досліджена, зокрема в Ірані. Це дослідження мало на меті дослідити вплив поточної залежності від опіуму на тяжкість і результат інфекції Covid-19. Під час ретроспективного когортного дослідження клінічні, демографічні та всі змінні, пов'язані зі ступенем тяжкості та смертю внаслідок зараження вірусом Корона, були зібрані з медичних карт пацієнтів, госпіталізованих з лютого 2020 року до червня 2021 року в досліджуваному регіоні. Роль поточної залежності на тяжкість і результат захворювання досліджували за допомогою моделей Кокса, логістичної та лінійної регресії. З 939 хворих з підтвердженням Covid-19, які госпіталізовані протягом періоду дослідження, 70 (7,5%) пацієнтів були залежними. Багатофакторні регресійні моделі показали, що поточна залежність від опіуму значно збільшила ймовірність ендотрахеальної інтубації ($OR=2,96, p=0,005$) і зменшила середню тривалість перебування в лікарні (бета-коефіцієнт $=-0,42, p<0,0001$). Однак залежність від опію не змінила ризик смерті ($HR=1,54, p=0,063$) або насичення O_2 ($OR=1, p>0,99$). Опіумна залежність може бути пов'язана з тяжкістю інфекції Covid-19, але не відіграє istotної ролі в смертності пацієнтів.*

Covid-19 infection originated from SARS COV-2 family viruses reported for the first time in Wuhan China has led to a pandemic [1]. It has been frequently reported that some individuals are more susceptible to the virus. For example, patients with cardiac and respiratory diseases as well as older people and substance addicts are at higher risk of developing infection and death [2]. Recent study carried out by Saeedi et al. showed that mortality

among Covid-19 cases with opium addiction was much more than that among non-addicts [3]. Substance addiction is one of the social problems involving the health systems in all parts of the world. World Health Organization (WHO) has introduced the substance addiction as one of the main social determinants of health (SDH) [4]. Opium is one of these drugs which has been widely used by the Iranian during the last centuries. Opium addiction can cause

different behavioral and psychological consequences in the individual and social levels [5].

According to the recent literature, approximately 2.8%-9% of the Iranian adults are consuming opium which reaches 22% in some areas. The main concern of the opium addiction in the community is related to the changes in the life situation of the addict persons and also the increased susceptibility of them to different diseases [6]. It should be noted that there are some non-scientific evidences regarding the protective effects of opium consumption against Covid-19 infection [3] which can encourage people to continue such behaviors. While, opium consumption can be a risk factor for developing viral infections due to mucosal tissue dysfunction, immunodeficiency, inadequate access to health and welfare services. In addition, co-morbidities in the addicted people increase the risk of developing viral disease [7, 8]. Although the exact mechanisms of the pathogenicity of the SARS COV2 virus among opium addicts are still unknown, Nabawi et al. showed that plasma Interleukin-6 increase in these patients can lead to cytokine storm syndrome which is the main cause of death following Covid-19 infection [9]. Considering the limited original studies regarding the effect of opium consumption on developing Covid-19 infection, this study was carried out to investigate the association between opium use and severity of the Covid-19 disease in a highly prevalent opium use area [6] in the east of Iran.

MATERIALS AND METHODS OF RESEARCH

This retrospective cohort study was carried out among COVID-19 confirmed patients admitted from February 2020 to June 2021 in Sina hospital of respiratory diseases in Sistan area located in the eastern part of Iran. Patients were defined as Covid-19 confirmed cases if they had a positive result of real time PCR test for SARS COV2 antigen. Required information was provided from the patients' electronic databases. In the case of any deficiencies in the recorded data, relevant physicians or patients/families were interviewed by the researchers.

Study protocol was approved by the ethical committee of Zabol University of Medical Sciences, Zabol, Iran (ethical code: IR.ZBMU.REC.1400.039), all patients filled informed consent forms. The research was conducted in accordance with the principles of bioethics set out in the WMA Declaration of Helsinki – “Ethical principles for medical research involving human subjects” and “Universal Declaration on Bioethics and Human Rights” (UNESCO).

The main independent variable was current opium use defined as consuming opium at least one time per day for at least six months prior to the hospitalization. Dependent factors were death following the Covid-19

infection as the outcome variable and also O₂ saturation and endotracheal intubation as severity characteristics. Patients were classified into low O₂ saturation when PO₂ was lower than 93%.

All statistical analyses were performed by Stata version 14 software (Stata Corp., College Station, TX). Categorical variables were compared between Addicted/non-addict patients using Chi square test. Comparing the quantitative variables between the two groups was conducted using Independent t test as well as Mann Whitney U test. Cox regression models (considering the proportional hazard assumption) were applied to assess the association between current addiction and death following Covid-19 infection. Logistic regression models were applied for assessment the impact of opium addiction on the severity of the Covid-19 infection. The role of the opium addiction on the length of stay (LOS) in hospital was investigated using linear regression models. Since the LOS variable was positively skewed, the normal logarithmic scale of the variable was used for the model. All models were designed as crude and adjusted. All variables with significant associations in the univariate analysis were entered into the multivariate models for adjustment. P value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

During the study period, 4070 patients suspected to Covid-19 infection were admitted, 939 of which were diagnosed as confirmed Covid-19 cases. Of them, 2146 (53.73%) were women and 211 (5.18%) were foreigners. Mean(SD) age of the confirmed cases was 53.50 (18.78) years varied between 6 months and 99 years. They were admitted in average for 5.75 (SD=5.22) days ranged between one and 57 days. Among these patients, 171 (18.21%) were admitted in the intensive care units and 373(39.72%) patients had at least one chronic underline co-morbidity.

Out of the Covid-19 confirmed cases, 70 patients (7.45%) had current opium consumption with at least one time per day for at least the recent six months prior to the admission.

As presented in Table 1, there was no difference between patients with and without opium use regarding gender (p=0.397) and nationality (p=0.590). While addicted cases had significantly higher median age (p=0.0001) and at least one co-morbidity (p=0.004) than non-addict patients.

Frequency of intubation status (p<0.0001) and death (p=0.007) among patients with opium addiction was significantly higher than that among those without. On the other hand, mean duration of admission was significantly shorter among addicted patients than the others (p=0.0006). No difference

was observed between the two groups regarding low O₂ saturation during the admission (p=0.106).

Results of the Cox regression models showed a significant crude hazard ratio for death following

opium use (HR=2.01, p=0.002). Having adjusted for age and co-morbidities, the corresponding hazard ratio was not statistically significant (HR= 1.54, p=0.063).

Table 1

Baseline characteristics and outcomes of the Covid-19 confirmed cases

Baseline and outcome factors			Addiction status		p value
			no addiction	current addiction	
gender	male	no	443	32	0.397
		%	50.98	45.71	
	female	no	426	38	
		%	49.02	54.29	
nationality	Iranian	no	842	67	0.59
		%	96.89	95.71	
	foreigner	no	27	3	
		%	3.11	4.29	
intubation	No	no	831	60	<0.0001
		%	95.63	85.71	
	Yea	no	38	10	
		%	4.37	14.29	
O ₂ Sat	normal	no	484	32	0.106
		%	55.7	45.71	
	high	no	385	38	
		%	44.3	54.29	
death	alive	no	711	48	0.007
		%	81.82	68.57	
	dead	no	158	22	
		%	18.18	31.43	
co-morbidity	no	no	535	31	0.004
		%	61.57	44.29	
	At least one disease	no	334	39	
		%	38.43	55.71	
age	Median (IQ range)		53(39, 66)	65,5(56, 75)	0.0001
Length of stay	Median (IQ range)		5 (3, 7)	3 (1, 6)	0.0006

In addition, logistic regression models showed no significant association between opium use and low O₂ saturation at the time of admission in crude (OR=1.49, p=0.108) and adjusted (OR=1, p>0.99) models.

On the other hand, patients with opium use compared to those without, had approximately three times higher chance of experiencing endotracheal intubation during admission (adjusted OR=2.96, p=0.005).

Linear regression models showed that opium users had shorter length of stay in hospital compared to non-addict cases (beta coefficient=-1.04, p=0.109). Controlling the effect of the potential confounders,

the corresponding coefficient remained significant (beta coefficient =-0.42, p<0.0001) (Table 2).

In the present study, a relatively large number of Covid-19 infected patients admitted in the eastern part of Iran were investigated. Since the beginning of the pandemic, just limited information has been released regarding the association between opium use and the Covid-19 situation [10, 11]. Unfortunately, some misconceptions about the resistance of the addicted people against this infection were reported in the community.

Table 2

Crude and adjusted associations for opium addiction and different outcomes of the Covid-19 infection

outcomes	Crude estimates	95% confidence intervals	Adjusted* estimates	95% confidence intervals
Death (HR)	2.01	1.28, 3.15	1.54	0.98, 2.43
O ₂ Sat (OR)	1.49	0.91, 2.43	1	0.60, 1.68
Intubation (OR)	3.64	1.73, 7.67	2.96	1.39, 6.32
log LOS (beta coefficient)	-1.04	-2.31, -0.23	-0.42	-0.62, -0.21

Notes. Controlling for the effect of age and co-morbidities. HR=hazard ratio, OR= odds ratio, LOS: length of stay.

According to the results of the current study, although having history of opium consumption caused 50% increased risk of death among Covid-19 patients, controlling the role of potential confounders showed no effect of this drug on mortality. However, Saeedi et al reported 3.6 times higher risk of mortality among Covid-19 opium addicted cases [3]. In addition, Wang et al in a larger study in the United States reported that opium, tobacco and other similar substances increased the risk of developing Covid-19 infection especially among African-American groups [12]. They also showed that opium was more associated with mortality so that caused more than 10 times higher chance of death. It seems that controlling the effect of various factors which play as confounders in different studies can be one of the main reasons for these controversies. For example, in the Wang study, variables such as age, type of insurance and race had been adjusted in the multivariate analyses, while in the current study, effect of chronic co-morbidities were also controlled in the final estimates and as shown in the results, crude and adjusted associations between opium addiction and death were completely different indicating that opium consumption leads to death from different pathways such as aging, co-morbidities and so on. The different definitions of the opium addiction might be another

explanation for these controversies. Moreover, our statistical analyses were performed based on survival analysis considering the time to death as a major variable. It should be noted that the present study population contained a single ethnicity and the primary analyses showed no difference between Iranian and foreigners (Afghan people) regarding the rate of opium use.

We found that opium consumption in Covid-19 patients can independently cause about three times higher risk of receiving mechanical ventilation. Dolati et al reported different reasons for severity of the Covid-19 infection among opium addicted patients including their personal hygiene and life style as well as the impact of opium use on the immune system, respiratory tissue and other factors. They concluded that early treatment with interferon can be effective in prevention of relapse and mortality. In addition, due to the socioeconomic situations such as lack of access to health and welfare facilities, inappropriate housing and mass consumption of opium in the dense places, opium addicted patients cannot follow physical and social distancing and other protective measures. All of these factors can increase the susceptibility of the opium addicted people to severe Covid-19 infection and death [13, 14]. Moreover, opium addicted patients compared to the

others had poor nutritional status making them more susceptible to immunodeficiency [13].

Although we did not find any effect of opium use on the O₂ saturation of the Covid-19 patients, it seems that opium addiction can be considered as a risk factor in Covid-19 patients. It can cause adverse consequences in the addicted patients independently or via other factors such as co-morbidities and poor social, economical and health conditions during the Covid-19 infection. It should be noted that the shorter length of stay in hospital among addicted patients can be explained by their higher mortality and also their persistence on early discharge after admission.

Our study was prone to some limitations. Due to the delayed beginning of mass vaccination in Iran, many studied cases had not received Covid-19 vaccine, therefore, the effect of vaccination was not considered in the statistical analyses. In addition, cigarette smoking was a relatively rare behavior in the study population so that it was not considered in the analyses as a potential confounder.

CONCLUSION

In conclusion, our study revealed that opium addiction can be associated with the severity of Covid-19 infection and its duration of admission. To be able to assess the exact effects of opium use on more consequences of the Covid-19 infection, further prospective studies with larger sample sizes among different ethnicities are recommended.

Contributors:

Mahdi Afshari, Fateme Parooie – conceptualization, methodology, resources, data curation, writing – review & editing, project administration;

Iraj Shahramian, Morteza Salarzaei, Hadi Mirzaie – investigation, methodology, resources, writing – original draft.

Funding. This research received no external funding.

Conflict of interests. The authors declare no conflict of interest.

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Стаття надійшла до редакції
30.01.2022

