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THE EFFECT OF SMOKING AND OPIOID CONSUMPTION ON THE SEVERITY OF THE DISEASE AND DURATION OF HOSPITALIZATION IN COVID-19 PATIENTS

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Abstract. Objective: *In the Coronavirus 2019 (COVID-19) global pandemic, various studies on the target communities of this virus were widely started and rapidly progressed. Smokers and opioid consumers are one of the virus targets since they have a vulnerable respiratory system. Due to the contradictory results in previous studies and the lack of similar investigations in this area, we aimed to perform this study to investigate the effect of smoking and opioid consumption on the consequences of the COVID-19 disease.* ***Materials and Methods:*** *In this retrospective study, the required information was collected and analyzed from the archives of Razi Hospital, Rasht, Iran. Study variables included age, sex, the need for intubation, hospital length of stay, history of current smoking or opioid consumption, and intensive care unit (ICU) admission, ICU length of stay, admission oxygen saturation, disease severity, and the outcome of death or recovery. Data were collected and divided into the case (including current cigarette smokers, opioid consumers, and cigarette-opioid consumers) and control (non-smokers and non-opioid-consumers) groups. Out of 986 patients, 489 patients met the criteria for inclusion and subsequent analysis. The average age was 69.79 ± 16.06, and 294 (60.1%) patients were male. The median age of the case group (65.15 ± 42.41) was older than the control group (57.45 ± 15.71, P = 0.001). The case group consisted of more male patients than the control group (P = 0.001).* ***Results:*** *The adjusted regression models demonstrated that current cigarette smoking, opioid, and cigarette-opioid consumption did not significantly predict hospital and ICU length of stay, ICU admission, disease severity, and mortality outcomes (P > 0.05). Current cigarette smoking and opioid consumption could not be an independent predictor for the consequences of ICU admission, hospital and ICU length of stay, the need for intubation, disease severity, and mortality in COVID-19 patients.*

Key words: *COVID-19, SARS-CoV-2, opioid abuse, smoking, opioid*

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INTRODUCTION

A new infectious disease caused by the Coronavirus 2019 (COVID-19) first appeared in China in December 2019 and spread worldwide as the World Health Organization (WHO) described it as an epidemic in March 2020 announced. The magnitude of the crisis has made the COVID-19 epidemic the worst health disaster of the century [1]. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded RNA-enveloped virus, which codes structural and nonstructural proteins [2]. The most important receptor in human host cells is the angiotensin-converting enzyme 2 (ACE2) receptor that provides the entry for SARS-CoV-2 [3]. Both immune impairment and excessive immune response to SARS-CoV-2 result in severe conditions in patients [4].

Clinical manifestations of SARS-CoV-2 infection are diverse, ranging from asymptomatic infection to severe viral pneumonia with respiratory failure and death [5]. Older age, male gender, hypertension, diabetes, cardiovascular disease, and respiratory disease were reported as the COVID-19 risk factors and are associated with a poor outcome in these patients [6, 7]. Although there is general agreement that severe COVID-19 infection is related to the comorbidities listed above, the link between tobacco use and the severity of COVID-19 disease is still debated [8-13]. Smokers and opioid consumers are one of the virus targets since they have a vulnerable respiratory system. It is estimated that there are about 1 billion smokers worldwide, accounting for about 30% of men and 7% of women [14]. Exposure to tobacco leads to pneumonia, increased permeability of epithelial cells, and damage to the mucosal defense barrier [15]. Disorders of mucous secretions are a side effect of smoking, and the risk of underlying diseases such as diabetes and vascular disease is more common among smokers [16].

Additionally, due to frequent hand-to-mouth motions and sharing of tobacco products, smokers are more vulnerable to COVID-19 disease and more likely to become infected [17]. There is concern among the WHO and the USA Food and Drug Administration (FDA) that cigarette smoking may raise the risk of COVID-19 [18]. Although many studies have assessed the effects of smoking on the severity of COVID-19 disease, the results have not been the same; and there are generally controversies in this area [18, 19]. Usman et al. contributed some of these controversies among studies to the lack of distinction between current and former smokers and unadjusted analysis [20].

In this regard, we performed this retrospective adjusted study to evaluate the effects of current smoking and opioid consumption on the COVID-19 patient's outcomes, including intensive care unit (ICU) admission, hospital and ICU length of stay, and duration of intensive mechanical ventilation (IMV), disease severity and mortality.

PATIENTS AND METHODS

Data, Inclusion, and Exclusion criteria

The Ethics Committee of Guilan University of Medical Sciences approved this retrospective research project (IR.GUMS.REC.1399.377). The data of this retrospective study were obtained from the archives of Razi Hospital, Rasht, Iran. All consecutive adult patients (≥ 18 years of age) included in the study presented to the Razi Hospital between March 20th to September 21th, 2020, with a SARS-CoV-2 diagnosis confirmed by positive reverse transcriptase polymerase-chain-reaction (RT-PCR). Patients with a definitive clinical outcome (being discharged to outpatient setting, cured or dead) were included for further study. Patients younger than 18 years of age, without complete history information, or patients who didn't complete their hospital course and ex-smokers were excluded from the analysis. Informed consent was obtained from all individual participants included in the study.

Clinical variables

Demographical data and clinical characteristics of patients including age, gender, history of current cigarette smoking, opioid consumption, and underlying disease (diabetes, hypertension, cardiovascular disease, liver or kidney disorders, asthma, chronic obstructive pulmonary disease (COPD), and cancer), the need for intubation, duration of invasive mechanical ventilation, admission oxygen saturation, ICU admission, hospital and ICU length of stay, lab test results and the discharge outcome (death or recovery) were collected. Patients were categorized into two groups, including case (n = 205) (smokers, opioid consumers, smoker-opioid consumers) and control group (n = 284) (non-smokers and non-opioid-consumers). Severe COVID-19 was defined as the occurrence of each of the consequences of ICU admission, the need for intubation, organ failure, severe hypoxia (O_2sat < 90%), and DIC in patients during the hospitalization.

Statistical Analysis

Categorical variables are described as frequency and percentage, while continuous variables are as median and interquartile ranges. Chi-square test or exact Fisher test were applied to evaluate the association between two categorical variables, while a non-parametric Wilcoxon Mann-Whitney test was used to study differences between two groups of a categorical variable on a continuous variable. The Kaplan-Meier survival curves were used to analyze overall survival, along with 95% confidence intervals (CIs). The Cox proportional hazard models were checked to simultaneously evaluate the effect of independent variables on patient survival and ICU admission. Statistical calculations were performed using the IBM SPSS Statistics for Windows (version 22) and statistical significance was evaluated at the level of 0.05.

RESULTS

Out of 986 patients, 489 patients met the criteria for inclusion and subsequent analysis. A total of 324 patients didn't meet the selection criteria, and 173 did not complete their hospital course. The demographic and clinical characteristics of these patients are summarized in Table 1. The average age was 69.79 ± 16.06, and 294 (60.1%) patients were male. The case group consisted of 205 patients, including fifty-six current smokers, ninety-nine opioid consumers, and fifty cigarette-opioid consumers. The median age of the case group (65.15 ± 42.41) was older than the control group (57.45 ± 15.71, P = 0.001). The case group consisted of more male patients compared to the control group (P = 0.001). Multiple linear regression models analysis adjusted with age, gender, underlying disease revealed that hospital and ICU length of stay outcomes could not be predicted significantly by current smoking ([ß = 0.052, P = 0.959], [β = -0.134, P = 0.867]), opioid consumption ([β = -1.036, P = 0.207], [ß = -0.065, P = 0.920]) and cigarette-opioid consumption ([ß = -0.599, P = 0.559], [β = 0.454, P = 0.575]), respectively (Table 2). Binominal logistic regression models adjusted for age, gender, underlying disease showed that disease severity and the need for intubation consequences could not significantly be predicted by current smoking ([β = 0.212, CI = 0.62-2.44], [ß = -0.021, CI = 0.40-2.39]), opioid consumption ([β = 0.076, P = 0.62-1.85], [β = 0.187, CI = 0.59-2.44]) and cigarette-opioid consumption ([β = 0.142, CI = 0.58-2.27], [β = 0.570, CI = 0.75-4.15]), respectively (Table 3). The Cox regression model after adjustment for confounding factors demonstrated that the risks of death outcome in current smokers (HR = 1.19, 95%CI = 0.65-2.18), opioid consumers (HR = 1.56, 95%CI = 0.97-2.51), and cigarette-opioid consumers (HR = 1.61, 95%CI = 0.89-2.92) were 1.19, 1.56 and 1.61 fold higher than the control group, respectively, although they were not statistically significant (Table 4). Also, the risks of ICU hospitalization in current smokers (HR = 0.63, 95%CI = 0.25-1.59), opioid consumers (HR = 1.05, 95% CI = 0.54-2.05), and cigarette-opioid consumers (HR = 0.66, 95%CI = 0.27-1.61) were 0.63, 1.05 and 0.66 folds higher than the control group, respectively, although they were not statistically significant (Table 4).

Table 1. Baseline characteristics and outcomes of the participants according to case and control groups

Variable	Case (n = 205)	Control (n = 284)	P-value
Age (Year)	65.15 ± 42.41	57.45 ± 15.71	0.001
Gender (Male)	155 (75.6%)	139 (48.9%)	0.001
Underlying disease	129 (62.9%)	84 (64.8%)	0.703
Hospital length of stay (Day)	7.68 ± 5.18	8.33 ± 6.79	0.584
ICU admission	30 (22.6%)	37 (13.3%)	0.022
ICU length of stay (Day)	8.97 ± 7.23	10.11 ± 10.92	0.934
The need for Intubation	39 (19.0%)	37 (13.0%)	0.077
Duration of IMV* (Day)	6.92 ± 8.39	8.70 ± 11.02	0.448
SpO2 (%)**	91.27 ± 7.45	92.74 ± 6.42	0.024
Severely ill patients	124 (66.0%)	139 (56.0%)	0.038
Hospital outcome (Death)	65 (31.7%)	53 (18.7%)	0.001

*IMV = Intensive mechanical ventilation, **SpO_2 = Peripheral oxygen saturation. P-value < 0.05 is statistically significant.

Table 2. Multiple linear regression analysis for predicting hospital and ICU length of stay consequences based on age, gender, underlying disease, case and control groups

Variables		Unstandardized Coefficients β	Unstandardized Coefficients SE**	Standardized Coefficients Beta	t	P-value
Hospital length of stay	Age	0.001	0.022	0.003	0.054	0.957
	Female gender	1.698	0.679	0.131	2.502	0.013
	Underlying disease	0.418	0.695	0.031	0.601	0.548
	Current smoker	0.052	1.010	0.003	0.051	0.959
	Opioid consumer	-1.036	0.820	-0.065	-1.264	0.207
	Cigarette/Opioid consumer	-0.599	1.025	-0.030	-0.584	0.559
	Severe COVID-19	2.059	0.632	0.158	3.258	0.001
ICU length of stay*	Age	-0.024	0.017	-0.076	-1.418	0.157
	Female gender	0.507	0.536	0.050	0.946	0.345
	Underlying disease	-0.140	0.549	-0.013	-0.256	0.798
	Current smoker	-0.134	0.798	-0.009	-0.167	0.867
	Opioid consumer	-0.065	0.648	-0.005	-0.100	0.920
	Cigarette/Opioid consumer	0.454	0.810	0.029	0.561	0.575
	Severe COVID-19	2.229	0.499	0.217	4.463	< 0.001

*ICU = Intensive care unit, **SE = Standard error. P-value < 0.05 is statistically significant

Table 3. Logistic regression for predicting severe COVID-19 and the need for intubation consequences based on age, gender, underlying disease, smoking, and opioid consumption

Variable		B	SE*	Wald	Odds Ratio (OR)	P-value	95%CI for OR** Lower	95%CI for OR** Upper
Severe COVID-19	Age	0.023	0.007	9.684	1.023	0.002	1.00	1.03
	Female gender	-0.483	0.227	4.548	0.617	0.033	0.39	0.96
	Underlying disease	0.336	0.232	2.102	1.399	0.147	0.88	2.20
	Control group	-	-	0.454	-	0.929	-	-
	Current smoker	0.212	0.348	0.370	1.236	0.543	0.62	2.44
	Opioid consumer	0.076	0.277	0.075	1.079	0.785	0.62	1.85
	Cigarette/Opioid consumer	0.142	0.347	0.167	1.152	0.683	0.58	2.27
Need for intubation	Age	0.007	0.10	0.542	1.007	0.462	0.98	1.02
	Female gender	0.171	0.319	0.288	1.187	0.591	0.63	2.21
	Underlying disease	-0.151	0.322	0.219	0.860	0.640	0.45	1.61
	Control group	-	-	1.986	-	0.575	-	-
	Current smoker	-0.021	0.456	0.002	0.979	0.963	0.40	2.39
	Opioid consumer	0.187	0.360	0.268	1.205	0.605	0.59	2.44
	Cigarette/Opioid consumer	0.570	0.435	1.718	1.769	0.190	0.75	4.15

*SE = Standard error, **CI = Confidence interval, OR = Odds ratio. P-value < 0.05 is statistically significant

Table 4. Cox regression analysis for predicting ICU admission and patient's survival based on age, gender, underlying disease, smoking, and opioid consumption

Variable		SE*	Hazard ratio	z	P > | z |	95% CI**	
						Lower	Upper
ICU admission	Age	0.009	1.009	0.95	0.341	0.99	1.02
	Female gender	0.193	0.653	-1.43	0.152	0.36	1.16
	Underlying disease	0.330	1.086	0.27	0.786	0.59	1.97
	Current smoker	0.297	0.630	-0.98	0.329	0.25	1.59
	Opioid consumer	0.357	1.057	0.17	0.867	0.54	2.05
	Cigarette/Opioid consumer	0.301	0.667	-0.90	0.371	0.27	1.61
Patients Survival	Age	0.007	1.013	1.85	0.065	0.99	1.02
	Female gender	0.167	0.709	-1.45	0.147	0.44	1.12
	Underlying disease	0.223	1.016	0.07	0.942	0.66	1.56
	Current smoker	0.366	1.195	0.58	0.561	0.65	2.18
	Opioid consumer	0.378	1.567	1.86	0.062	0.97	2.51
	Cigarette/Opioid consumer	0.489	1.616	1.59	0.113	0.89	2.92
	Severe COVID-19	2.148	5.804	4.75	< 0.001	2.81	11.98

*SE = Standard error, **CI = Confidence interval, P-value < 0.05 is statistically significant

DISCUSSION

In our study, the mean age in the case group was significantly higher than the control group and the majority of patients in the case group were males. According to the culture and conditions in society, it was expected to see more smoking in men and more opium consumption in the elderly. In this regard, in a study by Khalili et al., it was found that the highest number of opium consumers was in the age range of 55-64 years old, and the rate of opium consumption in males was significantly higher than in females [21]. Also, in the study by Mehrabi et al., it was reported that the prevalence of smoking in females is more prone to old age [22]. This present study showed that ICU admission, the need for intubation, and hospital and ICU length of stay didn't differ in the two study groups. Similar to our study, Huang et al. reported that smokers required less hospitalization in ICU [23]. The study by Ho et al. also found that current smoking was not associated with the consequences of intubation, ICU, mortality, and hospitalization [18]. The other finding of our study was the lack of association between current smoking, opioid, and cigarette-opioid consumption with disease severity and survival outcomes. Although our study initially manifested a significant relationship between these groups with disease severity and survival outcome, after adjusting regression models with age, gender, and underlying disease, it became interestingly non-significant. Before our study, Reddy et al. and Ho et al. studies demonstrated that current smoking was not associated with the consequences of intubation, ICU, mortality and hospitalization risk [7, 18]. Our study is consistent with previous studies that found no association between active smoking and disease severity [11, 13, 24] and mortality [18, 19, 25]. However, some studies, such as Alqahtani et al., showed that the severity and mortality of the COVID-19 disease were higher in people who smoked [26]. In addition, Gulsen et al. study stated that the severity of the disease in smokers is 1.5-2 times higher than in non-smokers [12]. However, many studies have been conducted to investigate the consequences of the COVID-19 in smokers, but the results have not been conclusive. The study by Simons et al. revealed that the outcomes of hospitalization, disease severity, and mortality in current smokers were inconclusive, but generally, smoking increased the risk of more severe disease slightly [19]. Theoretically, smokers are expected to have a higher risk of developing the COVID-19 disease due to impaired pulmonary mucociliary clearance system, increased permeability of the airway epithelial membrane, and increased respiratory system inflammation [27]. Yet, a systematic review reported a lower frequency of smokers in COVID-19 patients than in the general population [28]. One mechanism that justifies this disagreement is a higher expression level of ACE2 in the smokers. Nicotine alone can increase ACE2 gene expression [29]. Several studies have shown the opposite effect of nicotine, with nicotine or smoking reducing ACE-2 receptor expression [30-32]. Moreover, nicotine, with its cholinergic agonist properties, in cigarettes exerts anti-inflammatory effects and inhibits the expression of inflammatory cytokines such as IL-1, IL-6, and TNF5, which are activated in the cytokine

storm in COVID-19 patients. Therefore, although smokers are expected to have a greater risk of developing the disease since ACE2 receptors are the only way the COVID-19 virus enters the body, the simultaneous protective effect of ACE2 and the anti-inflammatory effect of nicotine may reduce the potential consequences of the COVID-19 disease. This reason can justify the controversies among studies. In this study, opioid consumption and concomitant use of cigarettes and opioids were evaluated on the consequences of the hospital and ICU length of stay, the need for intubation, disease severity, and survival in COVID-19 patients, which represented no significant relationship. So far, few studies have assessed the relationship between opioid consumption and the COVID-19 outcomes. Consistent with our research, Qeadan et al. found no higher mortality rate among patients taking opioids, although patients were more likely to require ICU care [33]. However, Riahi et al.'s unadjusted study demonstrated that opium consumers experience higher mortality and severity of the COVID-19 disease [34]. According to studies, opium exerts anti-inflammatory properties by suppressing bone marrow leukocyte migration [35]. The immune system can also be dangerously suppressed by high levels of opium [36]. However, some studies have indicated that although opioids like morphine reduce the production of inflammatory cytokines such as IFN- α and IFN-Y, they weaken the immune system and consequently increase virus entry into the body and lungs damage. From another point of view, smokers and opium users have a lower level of socio-economic status and access to health care than other members of society [37]. Concurrent comorbidities such as COPD and cardiovascular diseases, which are associated with higher severity of COVID-19, have been reported more frequently in these patients [12, 38, 39]. Generally, it seems that concomitant factors such as age, gender, and underlying diseases play an important role in worsening the outcomes of these patients.

Our study had some limitations. First, although the Razi hospital was the primary referral center in the Guilan province, Iran, for the COVID-19 patients, due to being a single center, the results may differ in a larger population with different ethnicity. Secondly, according to the COVID-19 pandemic and top referral of the COVID-19 patients, the hospital ICU capacity for patient admission was limited, and therefore, this limitation could affect the comparison of numbers of ICU admission between study groups. Thus, further multi-center studies with a more diverse population are recommended.

CONCLUSION

Current cigarette smoking and opioid consumption could not be an independent predictor of the consequences of ICU admission, hospital and ICU length of stay, the need for intubation, disease severity, and mortality in COVID-19 patients.

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Ethical Approval: *The Ethics Committee of Guilan University of Medical Sciences approved this retrospective research project (IR.GUMS.REC.1399.377).*

Informed Consent: *The authors affirm that human research participants provided informed consent for the publication of the study.*

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Authors Contribution

All authors contributed to study conception and design. Material preparation, data collection, and analysis were performed by Haniyeh Sadat Fayazi, Maryam Yaseri, Arvin Naeimi, and Seyyedeh Sahereh Mortazavi Khatibani. The first draft of the manuscript was written by Haniyeh Sadat Fayazi, Arvin Naeimi, and Seyyedeh Sahereh Mortazavi Khatibani and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

Disclosure Summary: *The authors have nothing to disclose.*

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