Introduction
In December 2019, a series of diseases accompanied by pneumonia and death appeared first in Wuhan, China. The cause of this disease was announced to be related to the coronavirus family, namely, the coronavirus disease 2019 (COVID-19). This virus is now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 disease rapidly became the first cause of death globally and put the world into an emergent condition ever since (1, 2).

Evaluating the Effect of Smoking on COVID-19 Severity in Patients Admitted to Shahid Mohammadi Hospital in Bandar Abbas During 2021-2022

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Abstract
Background: The coronavirus disease 2019 (COVID-19) is a newborn virus that has become an emergency since December 2019. A severe form of this disease is accompanied by intensive care unit (ICU) admission and death. The COVID-19 pandemic is still occurring in several countries; however, few facts are available about the disease. Risk factors and protective factors of this disease are still unknown. We know that smoking is a risk factor for several respiratory infections. However, considering some previous studies and nicotine’s anti-inflammatory mechanism, a smoking paradox in COVID-19 still persists as an obscure issue. Thus, we decided to evaluate the association between smoking and COVID-19 disease.

Materials and Methods: In this study, sampling was performed simply and randomly from all admitted COVID-19 patients in 2020-2021. This is a retrograde case-control study, and 92 COVID-19 patients with a history of smoking were enrolled in the case group, and 92 COVID-19 patients without any smoking history were selected for the control group. Data were collected through a checklist. In this checklist, information such as the patient’s age, gender, and medical condition was recorded. In the end, collected data were analyzed by SPSS software version 26.0.

Results: In this study, we used a logistic regression test to indicate that smoking had a significant relationship with subsequent plasmapheresis (P=0.001). We also found a significant relationship between cigarette smoking and plasmapheresis (P<0.001). Furthermore, old age and diabetes were related to ICU admission (P=0.001 and P<0.000, respectively), and male gender and hypertension were related to plasmapheresis (P=0.007 and P=0.001, respectively). Moreover, only old age was related to mortality caused by COVID-19 infection (P=0.025).

Conclusion: Considering the issue of the smoking paradox in COVID-19, the association between smoking and COVID-19 disease was evaluated in this study. It was found that smoking is related to the need for plasmapheresis and was not related to ICU admission or death. Cigarette smoking had the same association. It should be noted that plasmapheresis had no significant relation with ICU admission and death. Moreover, hookah smoking had no relationship with plasmapheresis, ICU admission, and death. This study also evaluated other factors such as age, gender, and medical conditions such as hypertension, diabetes, and cardiovascular disease and their effect on COVID-19. We found that only old age was related to mortality caused by COVID-19.

Keywords: COVID-19, Smoking, ICU, Admission, Mortality

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in China, and the second was in 2012, imported from camels in the middle east which was called middle east respiratory syndrome. At this point, we cannot rule out more possible coronavirus outbreaks in the future (2). Compared to the human coronavirus, this zoonotic virus can cause severe respiratory symptoms and death (2). Since this virus has affected the world, smoking and its association with COVID-19 are in question (3).

The data from previous outbreaks of SARS-CoV-1 and middle east respiratory syndrome indicated unsubstantial conclusions (3). During the COVID-19 pandemic, primary evidence showed that patients with a smoking history had more complications, intensive care unit (ICU) admission, and death (3). Nevertheless, there is greater debate on this topic. In the following, different views regarding the role of smoking in COVID-19 is enumerated.

The first element supporting the idea that smoking is a risk factor for COVID-19 is gender. Many studies have demonstrated that the risk of complications and death is higher in male patients, and it is a well-known fact that smoking is more prevalent in men (3). Smokers are more prone to SARS-CoV-2 because of more hand-to-mouth movements and lesser uses of masks (4). Moreover, it is a fact that cigarette smoking can cause chronic obstructive pulmonary disease and lung cancers which have been shown to induce the severe form of COVID-19 (4). Biologically speaking, tobacco smoking can suppress the innate cells’ function, neutrophils, and T cells in the body, including the respiratory epithelium. Further, specific components of tobacco can disrupt the usual epithelial lining in the respiratory system, resulting in more oxidative injury and causing greater complications of COVID-19 such as pneumonia (4). The most important factor supporting this hypothesis is the angiotensin-converting enzyme 2 (ACE 2) since its gene expression can be increased by smoking. ACE2 is considered the receptor for SARS-CoV-2 and helps this virus enter the human body. However, it is still unclear whether this receptor has a role in COVID-19 complications and following mortalities (3).

Despite all the above-mentioned facts, there is no clear answer regarding the effects of smoking on COVID-19 disease. There are some other facts supporting the protective effect of smoking on COVID-19 disease. As opposed to the claim that the ACE2 receptor is over-expressed by smoking, it is established that the nicotine in cigarettes can decrease the ACE2 receptor gene expression (4). The severe form of COVID-19 disease results from the over-secretion of inflammatory cytokines, including interleukin-6 and TNF-alpha. It has been pointed out that due to chronic inflammation caused by smoking, the inflammatory response to COVID-19 is suppressed (4). Moreover, it has been observed that smokers are less socially active and more comfortable in quarantine (4).

Materials and Methods
This was a retrospective case-control study conducted in Bandar Abbas, Iran, in 2020-202. We evaluated two groups of COVID-19 patients. One group had a smoking history, whether the subject was a past smoker or a current smoker. Both cigarette smoking and hookah were considered to have a positive smoking history, and one group had no smoking history at all.

All the patients with a positive COVID-19 polymerase chain reaction test, over 18 years old, and without pregnancy referring to Shahid Mohammadi hospital were candidates for this study. Sampling was performed simply and randomly from the patients in the hospital, and the sample size was estimated to include 184 patients, with 92 patients in each group.

Collecting data was performed through a checklist containing information such as age, gender, exercise status, smoking habits, and medical disease, including hypertension, diabetes, myocardial infarcts, angina, hyperlipidemia, chronic obstructive disease, and cancers of the bladder, pancreatic, lung, and laryngeal. In this checklist, death, ICU admission, and plasmapheresis were also recorded as a variable for unsatisfactory outcomes of the disease.

After data collection, information was analyzed by SPSS software version 26.0 using descriptive statistics and tests such as logistic regression, and the significance level was set at 0.005. However, using the multiple logistic regression tests, the significance level was considered to be 0.2.

Results
This study consisted of 124 male patients (66.3%) and 60 female patients (32.1%). The case group comprised 81 (88.04%) male and 11 (11.95%) female patients, while the control group involved 43 (46.73%) males and 49 (53.26%) females. In the case group, the mean age of the group was 52.54, with a standard deviation of 16.32, while the control group’s mean age was 51.84, with a standard deviation of 18.68 years. Thirty-six (19.3%) patients in this study had hypertension, with 19 patients (20.65%) in the case group and 17 patients (18.47%) in the control group. Moreover, 32 (17.1%) patients had type 2 diabetes, with 18 patients (19.56%) in the case group and 14 patients (15.21%) in the control group. Thirty (16%) patients had cardiovascular disease, with 24 (26.08 %) patients in the case group and 6 (6.52%) patients in the control group. Furthermore, 8 (4.3%) patients had asthma, while 5 (5.43%) patients had asthma in case group, and 3 patients (3.26%) had asthma in the control group. Additionally, 8 (4.3%) patients and three (3.26%) patients had hyperlipidemia disease in the case group and in the control group, respectively, and 5 (5.43%) patients had hyperlipidemia. Overall in this study, 6 patients (3.2%) had chronic obstructive pulmonary disease, 5 of them (5.43%) were in the case group, and 1 (1.08%) of...
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At first, a univariate analysis was administered by using a logistic regression test to evaluate the association of plasmapheresis with ICU admission and mortality from COVID-19. As seen in Table 1, no significant relationship was found between plasmapheresis and mortality ($P = 0.787$) and ICU admission ($P = 0.157$).

The relationship between smoking (cigarettes and hookah) and plasmapheresis, ICU admission, and mortality has been evaluated. According to the univariate analysis by logistic regression in Table 2, smoking was not significantly related to ICU admission ($P = 0.238$) and mortality ($P = 0.413$). However, there was a significant relationship between the need for plasmapheresis and smoking ($P = 0.001$). Afterward, a multiple logistic regression was run, which indicated that the $P$ value reaches the significance level ($P = 0.002$).

The relations between cigarette smoking alone and plasmapheresis, ICU admission, and mortality were evaluated by logistic regression test. As depicted in Table 3, only plasmapheresis had significant relations with cigarette smoking ($P = 0.000$), but ICU admission and mortality from COVID-19 did not reach the significance level ($P = 0.476$ and $P = 0.943$). Then, multiple logistic regression was performed as the multivariate analysis between cigarette smoking and plasmapheresis, and the $P$ value was 0.000.

Further, the result of evaluating the hookah use and its relations with ICU admission, plasmapheresis, and mortality did not reach the significance level, and $P$ values were 0.837, 0.998, and 0.388, respectively, as illustrated in Table 4.

In this study, first, we evaluated the relationship between ICU admission and gender, age, diabetes, Hypertension, cardiovascular disease, and exercise by logistic regression test (univariate analysis). According to this test, age and diabetes were significantly related to ICU admission due to COVID-19 ($P = 0.000$ and $P = 0.001$, respectively). These results were supported by doing the multiple logistic regression test as multivariate analysis, which proved our previous results ($P = 0.005$ and $P = 0.023$, respectively). However, the other variables did not reach the significance level (Table 5).

The variables mentioned above were evaluated to determine their relations with the need for plasmapheresis. In the univariate analysis by logistic regression test, it was found that the male gender, hypertension, and cardiovascular disease had significant relations with the

### Table 1. Logistic Regression for Plasmapheresis

<table>
<thead>
<tr>
<th>Item</th>
<th>Plasmapheresis</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>Yes</td>
<td>23 (23.46%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>13 (15.11%)</td>
</tr>
<tr>
<td>Death</td>
<td>Yes</td>
<td>6 (21.42%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>30 (19.23%)</td>
</tr>
</tbody>
</table>

Note. ICU: Intensive care unit.

### Table 2. Logistic Regression for Smoking

<table>
<thead>
<tr>
<th>Item</th>
<th>Univariate Analysis (Unadjusted) Logistic Regression</th>
<th>Multivariate Analysis Multiple Logistic Regression Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>Smoking</td>
<td>$P$ Value</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>53 (57.60%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>39 (42.39%)</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Yes</td>
<td>27 (29.34%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>65 (70.66%)</td>
</tr>
<tr>
<td>Death</td>
<td>Yes</td>
<td>16 (17.39%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>76 (82.60%)</td>
</tr>
</tbody>
</table>

Note. CI: Confidence interval; ICU: Intensive care unit.

### Table 3. Logistic Regression for Cigarettes

<table>
<thead>
<tr>
<th>Item</th>
<th>Univariate Analysis (Unadjusted) Logistic Regression</th>
<th>Multivariate Analysis Multiple Logistic Regression Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>Cigarettes Smoking</td>
<td>$P$ Value</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>45 (56.25%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>35 (43.75%)</td>
</tr>
<tr>
<td>Plasmapheresis</td>
<td>Yes</td>
<td>27 (33.75%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>53 (66.25%)</td>
</tr>
<tr>
<td>Death</td>
<td>Yes</td>
<td>12 (15%)</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>68 (85%)</td>
</tr>
</tbody>
</table>

Note. CI: Confidence interval; ICU: Intensive care unit.
need for plasmapheresis (P value = 0.001, P value = 0.007, and P value = 0.003, respectively). Afterward, the multiple logistic regression as the multivariate analysis was run to support the obtained results, and it was observed that male gender (P value = 0.002) and hypertension (P value = 0.028) are related to the need for plasmapheresis in COVID-19 patients (Table 6).

Finally, we evaluated the variables and their relations with mortality from COVID-19. As indicated in Table 7, only old age (above 50 years old) had a significant relationship with mortality from COVID-19. The P values for univariate analysis (logistic regression) and multivariate analysis (multiple logistic regression) were 0.025 and 0.068, respectively.

### Discussion

COVID-19 remains a challenge in the world. We may have passed the emergent situation, but it is still crucial to learn about it since it still exists in the environment, and we probably will have more outbreaks in the future. This study strived to evaluate the factors related to adverse outcomes of COVID-19 disease, which was accompanied by ICU admission, plasmapheresis, and death variables. As mentioned before, the severe form of COVID-19 infection is caused by over secretion of different inflammatory factors such as interleukin-6 and TNF-alpha; hence, an effective way to manage the severe form of COVID-19 is plasmapheresis which is a method for evacuating these inflammatory factors (5).

It was reported in previous studies that doing the plasmapheresis improves the patient’s status strongly (6). Likewise, in some studies, it was reported that plasmapheresis improves the status of patients who are under mechanical ventilation (7).

In the current study, 98 patients were admitted to ICU, and 23 (23.46%) benefitted from plasmapheresis, of whom 15 people died and six were treated with plasmapheresis. Overall, 36 people benefitted from plasmapheresis. Due to the logistic regression test, no significant associations were observed between plasmapheresis and ICU admission and death from COVID-19. A significant relation was also found between the need for plasmapheresis and smoking in general (cigarettes and hookah) and cigarettes alone. Multiple
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logistic regression tests were used to support the results. However, no significant associations were detected between ICU admission and death from COVID-19 and smoking (cigarettes and hookah). Furthermore, there were no associations between cigarette smoking only and ICU admission and death from COVID-19.

Similar to the result of the present study, a study by Lippi et al found that active smoking is not associated with the progression of severe COVID-19 (8). Monteiro et al reported that smoking is related to the need for mechanical ventilation but found no association between smoking and mortality (9). The results of Uğur Chousein and colleagues’ study are consistent with ours. They reported that the rate of active smoking in patients hospitalized with COVID-19 is lower than that of the average population. They found no association between smoking status and this disease’s severity, prognosis, and mortality (10).

On the other hand, through one of the most significant meta-analyze studies, Reddy et al reported that current smokers are at greater risk of severe COVID-19, need for mechanical ventilation, ICU admission, and death (11). Simons et al found that smoking prevalence among people with COVID-19 is generally lower than the national prevalence. They observed that former smokers were at greater risk of mortality and severe form of COVID-19, and the results for current smokers were inconclusive (12). Mahabee-Gittens et al conducted a similar study and found that smoking status and intensity were associated with ICU admission, but the results for COVID-19 mortality and smoking were inconclusive as well (13).

The present study found that using a hookah is
unrelated to the severity of COVID-19 disease, ICU admission, plasmapheresis, and mortality. Shekhar et al reported in their study that hookah smoking is possibly related to SARS-CoV-2 due to sharing the pipes between users. However, its relation with the severity of the disease is unclear (14). In their study, Münzel et al detected that all sorts of smoking (e.g., electronic cigarettes and water pipes) are related to the severe form of COVID-19 (15). Ebrahimi Kalan et al came up with similar results (16).

In this study, age, gender, and medical conditions such as diabetes and hypertension were investigated to find their role in COVID-19’s unsatisfactory outcomes. The results indicated that age and diabetes are significantly related to ICU admission for COVID-19. It was also found that the male gender and hypertension are related to the need for plasmapheresis in COVID-19 patients. Moreover, only older age (above 50 years old) had a significant relation with mortality from COVID-19. The risk factors for these three variables with adverse outcomes were different except for age, which is a risk factor for ICU admission and mortality of COVID-19. Similar to our result, Levin et al reported that COVID-19 infection is more severe in elderly patients, and the risk of mortality is higher in these patients (17). O’Brien et al and Alizadehsani et al reported similar results (18,19). On the other hand, fewer studies were found with the opposite results; for example, Zhao et al reported that age is not statistically related to COVID-19 mortality (20).

**Conclusion**

Based on the obtained results in this study, it was found that the need for plasmapheresis is not related to ICU admission and mortality from COVID-19. Furthermore, smoking in general was found to be associated with the need for plasmapheresis. Additionally, cigarette smoking alone was related to the need for plasmapheresis. However, smoking in general or cigarettes alone was not related to ICU admission and mortality from COVID-19. Nevertheless, hookah smoking was not associated with the need for plasmapheresis or ICU admission and death. Furthermore, male gender, hypertension, and cardiovascular disease were associated with the need for plasmapheresis. Old age and diabetes were related to ICU admission due to COVID-19 disease. Likewise, age was reported as a risk factor for COVID-19 mortality. It is essential to further investigate the role of smoking in ICU admission and mortality from COVID-19 since smoking is considered an important risk factor for adverse outcomes of COVID-19 in numerous other studies.

**Acknowledgements**

We would like to thank the staff of Shahid Mohammadi Hospital in Bandar Abbas.

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**Methodology**: Maryam Sahafibandary.

**Project administration**: Maryam Sahafibandary.

**Resources**: Amir Hasan Asadi, Saeed Hayati.

**Supervision**: Amir Hasan Asadi-Saeed Hayati-Maryam Sahafibandary, Ali Massoudifar.

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**Competing Interests**

The authors declare no conflict of interests.

**Disclaimer**

The authors declare no discrete opinions from funding sources, organizations, or others.

**Ethical Approval**

The Ethical Committee of the Hormozgan University of Medical Sciences approved the study.

**Funding**

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**References**


