



# Assessment of Risk Factors for Severe Coronavirus Disease 2019 among Iranian Patients

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## Abstract

**Background:** The outbreak of Coronavirus Disease 2019 (COVID-19) has led to a major concern for those who are more vulnerable to infections.

**Objectives:** This study aimed to evaluate the most important risk factors for severe COVID-19 pneumonia.

**Methods:** This retrospective study included information on clinical and epidemiological features of 105 patients with severe COVID-19 pneumonia hospitalized in Tajrish Hospital, Tehran, Iran. Initially, the medical records of the patients were investigated, and an interview was conducted based on an already established checklist to seek information about symptoms, past medical history, medication history, and behavior before hospitalization.

**Results:** Out of 105 participants, 76 (72.5%) cases were male, and 54 (51.4%) patients were older than 54 years old. The majority of the patients (n=18; 17.1%) had both hypertension and diabetes (n=12; 11.4%). Metformin (n=36; 34.3%) was the most used medication amongst the studied patient. In addition, 24 (22.9%) patients were recreational hookah smokers, and the majority (75%) of them were under the age of 46 years old. Eventually, 19 patients died, of whom 11 individuals had diabetes, and 10 cases were using metformin.

**Conclusion:** Hookah smoking played a critical role in the spread of COVID-19 in Iran and has made younger people more susceptible. In addition to older age, the immunosuppressive effects of Metformin seem to make diabetic patients with an impaired immune system more vulnerable to severe COVID-19 pneumonia. More studies on the immune system of vulnerable individuals by identifying their differences can help to protect them.

**Keywords:** COVID-19, Coronavirus disease 2019, Pneumonia, SARS-Cov-2, Vulnerable

## 1. Background

For the first time, highly contagious Coronavirus Disease 2019 (COVID-19) pneumonia was reported in Wuhan, Hubei Province, China, in December 2019 (1), which continued to spread rapidly across other parts of the country, followed by an outbreak in many other nations (2-5). The COVID-19 is an infectious disease and the World Health Organization (WHO) has declared it as a global public health emergency. The WHO Director-General characterized COVID-19 as a pandemic on March 11, 2020 (6). According to WHO reports, Iran is one of the countries with the most rapid growth of COVID-19 cases (1). From February 20, 2020, when the first confirmed case of COVID-19 was reported in Iran, the number of

confirmed cases surged rapidly to 27017 on March 26, 2020, followed by the death of 2077 patients (7). Although information about local epidemiological features of patients suffering from COVID-19 is highly important in facing this outbreak, to the best of our knowledge, no study has been conducted on this issue in Iran.

## 2. Objectives

This retrospective study aimed to focus on the risk factors for COVID-19 and severe pneumonia among a group of suspected patients hospitalized in Tehran, Iran. It is worth mentioning that some clinical features of these patients were explored in this study at the time of their admission.

### 3. Methods

#### 3.1. Study design and setting

This retrospective study was designed to evaluate the risk factors of COVID-19 among patients with acute respiratory illness who were hospitalized for at least 48 h in Tajrish Hospital, Tehran, Iran, from March 1 to 18, 2020. The follow-up was continued until March 26, 2020.

#### 3.2. Participants and data collection

Shahid Beheshti University of Medical Sciences designated Tajrish hospital as one of the centers for confirmed and suspected cases of COVID-19 from February 29, 2020. This retrospective study included 105 in-patients who were suspect of COVID-19 and hospitalized to receive medical aid for at least 48 h. Accordingly, in-patients with typical chest computed tomography (CT) findings (i.e., distributed multifocal ground-glass opacities and patchy consolidations) were included in this study. It is evident that the chest CT has much higher sensitivity for the diagnosis of COVID-19, compared to RT-PCR, and therefore, it would help in the early detection of infection (8-11). After obtaining some demographic and clinical information from the medical records of the patients, those who were willing to take part in the study were interviewed based on a checklist prepared before to collect their demographic information, past medical history, medication history, and some information about risk factors for respiratory diseases. After this initial visit, they were followed-up during their hospitalization. It should be noted that outpatients and in-patients who were not able to participate in the interview, those in critical condition, and cases with aphasia or other communication problems were excluded from the study, except for five individuals whose family members were available and consented to take part in the study.

#### 3.3. Data analysis

Data were analyzed in SPSS software (version 19) through categorical (numbers and percentages) and continuous (mean and median) (maximum-minimum) measurements.

#### 3.4. Ethical consideration

All participants were informed about the research objective, and they were assured that their information would be kept confidential. Moreover, written informed consent was obtained from each individual, and they were allowed to withdraw from the study at any time.

### 4. Results

In total, 105 patients with severe COVID-19 pneumonia who required medical attention were included in this study. In total, 81 (77.1%) cases were

discharged until March 26, 2020, and 19 (18.1%) individuals with developed acute respiratory distress syndrome (ARDS) died, and 5 (4.8%) patients were still hospitalized.

#### 4.1. Demographic characteristics of the patients

The mean age of the participants was 59.84±17.20 years (age range: 25-90 years). Out of 105 studied patients, 76 (72.5%) cases were male. The majority of the patients were retired (n=37; 35.2%) or housewife (n=25; 23.8%), and 21 cases (20%) were shopkeepers or salespersons. Although Tajrish hospital is located in the northern Tehran, most of the patients (n=47; 44.8%) were the residents of the eastern part of the city, of whom 17 (36%) individuals were from Tehranpars region that is one of the most crowded regions in Tehran, Iran (Table 1).

#### 4.2. Clinical features of the patients

Shortness of breath was the most frequent chief complaint (n=60; 57.1%), followed by annoying coughs (n=28; 26.7%). Even though most patients had referred to the hospital with signs of acute respiratory diseases, two (1.9%) cases were hospitalized by the diagnosis of multiple trauma after car accidents and further medical examinations

**Table 1.** Demographic characteristics of the patients

Variables	Number (%)
<b>Age</b>	
20-39	18 (17.1)
40-59	33 (31.4)
60-79	42 (40.0)
80-100	12 (11.4)
<b>Gender</b>	
Male	76 (72.4)
Female	29 (27.6)
<b>Occupation</b>	
Retired	37 (35.2)
Housewife	25 (23.8)
Shopkeeper or salesperson	21 (20)
Construction worker or engineer	7 (6.7)
Taxi driver	4 (3.8)
Others	11 (10.5)
<b>Residential area in Tehran</b>	
Eastern part	47 (44.8)
Northern part	24 (22.9)
Southern part	13 (12.4)
Western part	9 (8.6)
Central part	5 (4.8)
Travelers	7 (6.7)
<b>Recent traveling destination</b>	
None	81 (77.1)
Mashhad	7 (6.7)
Rasht	6 (5.7)
Qom	2 (1.9)
Other cities	9 (8.6)
<b>History of regular activity</b>	
Yes	11 (10.5)
No	94 (89.5)
<b>Working/resting before hospitalization</b>	
Working	12 (11.4)
Resting	94 (88.6)
<b>Using facemask before hospitalization</b>	
Yes	15 (14.3)
No	90 (85.7)

including chest CT revealed that they were suffering from COVID-19 pneumonia. Since one of them was in critical condition and could not answer our questions, an interview was conducted with one of his family members who mentioned that his brother had signs of respiratory disease before the car accident.

Overall, it is true that shortness of breath was the most frequent reason that forced patients to refer to the hospital. The majority of the patients regarded fever as the first symptom (n=52, 49.5%), followed by coughing (n=25, 23.8%). Furthermore, most patients had felt the initial signs of respiratory illness within the first week (n=55, 52.4%) or two weeks (n=36, 34.2%) before referring to the hospital; however, 14 (13.4%) participants mentioned that they had felt initial signs of their illness more than 14 days before referring to the hospital. All patients had experienced multiple signs before the time of interview; nonetheless, coughing was the most prevalent sign (n=87; 82.9%) along with fever (n=82; 78.1%), shortness of breath (n=76; 72.4%), and myalgia (n=51; 48.6%). Out of 87 patients who complained of coughing, 43 (49.4%) cases regarded it as permanent and non-productive, and 42 (48.2%) individuals stated that it was temporary and non-productive. Moreover, two patients reported that their coughing was productive (Table 2).

After checking the patient's vital signs upon admission, 31 (29.5%), 18 (17.1%), and 36 (34.3%) cases had a fever (body temperature more than

38°C), tachycardia (pulse rate more than 100 times per minute), and tachypnea (respiratory rate more than 20 breaths per minute), respectively. Furthermore, the majority of the patients had oxygen (O<sub>2</sub>) saturation between 80%-90% (n=55.2, 58%). Table 2 tabulates the information about the initial vital signs of the patients.

As shown in Table 3, the majority of the patients (n=54; 51.4%) had normal white-cell count (between 5000 and 10000 per µl); however, 47.6% (n=50) of the cases had lymphopenia (lymphocytes under 1100 per µl), which was more severe in 42 cases (lymphocytes under 1000 per µl). Although most patients (n=71; 67.7%) had normal neutrophil count (2500-7500 per µl), 19% (n=20) and 13.3% (n=14) of them had neutrophilia (more than 7500 neutrophil count per µl) and neutrophilopenia (under 2500 neutrophil count per µl), respectively. Unexpectedly, 52.2% (n=52) of the studied patients had a serum creatinine of more than 1.2 mg/dL. Last but not the least, according to our result, the majority of the patients (n=84; 80%) had C-reacting protein more than 10 mg/L.

Due to the low O<sub>2</sub> saturation, the majority of the patients required oxygen therapy mostly by reservoir face mask (n=39, 37.1%), followed by a face mask (n=21, 20%). A total of 16 patients continued breathing ambient air under respiratory and cardiac monitoring. One self-referred patient had a history of heart disease, lost his consciousness in the examination room of the emergency ward, got intubated immediately, and was hospitalized in a general ward. Further examinations revealed that he had COVID-19 pneumonia, and he was included in this study because his family member was available. Until March 26, 2020, in addition to two patients who had multiple trauma, 17 patients developed ARDS and got intubated (n=19; 18.1%). Table 2 gives more

**Table 2.** Clinical features, vital signs, and kind of oxygen therapy

Sings and symptoms	Number (%)
Coughing	87 (82.9)
Fever	82 (78.1)
Shortness of breath	76 (72.4)
Myalgia	51 (48.6)
Fatigue and weakness	29 (27.6)
Headache	23 (21.9)
Excessive sweating	23 (21.9)
Diarrhea	17 (16.2)
Nausea	15 (14.3)
Vomiting	7 (6.7)
Sour through	3 (2.9)
<b>Initial vital signs</b>	
vTachycardia (HB>100)	18 (17.1)
Fever (Central temperature >38°)	31 (29.5)
Tachypnea (RR>20)	36 (34.3)
<b>Initial O<sub>2</sub> saturation</b>	
60-69	3 (2.9)
70-79	12 (11.4)
80-89	58 (55.2)
90-94	30 (28.6)
95-100	2 (1.9)
<b>First kind of oxygen therapy</b>	
Non-Rebreathing oxygen face mask	39 (37.1)
Simple face mask	21 (20.0)
Nasal cannula	16 (15.2)
Breathing ambient air	16 (15.2)
Venture mask	6 (5.7)
BiPAP machine	6 (5.7)
Ventilator	1 (1.0)

**Table 3.** Clinical laboratory results

Measures	Number (%)
<b>White-cell count (per µl)</b>	
Under 5000	35 (33.3)
5000-10000	54 (51.4)
More than 10000	16 (15.2)
<b>Absolute neutrophil count (per µl)</b>	
Under 2500	14 (13.3)
Between 2500-7500	71 (67.7)
More than 7500	20 (19.0)
<b>Absolute lymphocyte count (per µl)</b>	
Under 1000	42 (40.0)
Between 1000-1100	8 (7.6)
More than 1100	55 (52.4)
<b>Serum creatinine (mg/dL)</b>	
Under 0.6	1 (1.0)
Between 0.6-1.2	46 (43.8)
More than 1.2	58 (52.2)
<b>C-reactive protein (mg/L)</b>	
Under 3	7 (6.7)
Between 3 to 10	12 (11.4)
More than 10	84 (80.0)
Missing	2 (1.9)

**Table 4.** First venous blood gas results of patients after oxygen therapy

	Number (%)
<b>pH</b>	
< 7.31	13 (12.4)
7.31-7.41	73 (69.5)
>7.41	19 (18.1)
<b>pO2 (mmHg)</b>	
<30	60 (57.1)
30-40	28 (26.7)
>40	17 (16.2)
<b>pCO2 (mmHg)</b>	
<41	44 (41.9)
41-51	47 (44.8)
>51	14 (13.3)
<b>Bicarbonate (mmol/L)</b>	
<22	22 (21.0)
22-28	73 (69.5)
>28	10 (9.5)
<b>O2 saturation (%)</b>	
<65	83 (79.0)
65-75	11 (10.5)
>75	11 (10.5)

detailed information about the type of initial oxygen therapy.

Table 4 summarizes the results of venous blood gas (VBGs) which was taken from patients after being hospitalized. As it is shown in Table 4, after being hospitalized and receiving oxygen therapy, 84 (80%) patients still had O2 saturation under 65%. Furthermore, 22 (20.95%) cases had HCO3 under 22 mEq/L, whereas only 11 (10.47%) individuals had partial pressure of carbon dioxide (PCO2) over 52 mm Hg.

#### 4.3. Underlying diseases and medication history

Regarding risk factors and past medical history, 18 patients had diabetes and hypertension (n=18; 17.1%), and 12 (11.4%) cases had only diabetes. In general, hypertension was the most prevalent underlying disease (n=39; 37.14%), followed by diabetes in 37 patients (35.2%) as the second most prevalent underlying disease. Furthermore, six patients (5.7%) mentioned that they had a history of respiratory disease, and 65 (61.9%) patients had a history of using medications for their underlying diseases. Further exploration revealed that Metformin was the most prevalent medication used amongst patients (n=36; 34.3%), followed by Atorvastatin (n=27; 25.7%) (Table 5).

In this study, out of 19 patients who expired, 11 cases had diabetes, and 10 individuals were taking Metformin (Table 6).

With respect to patients' smoking habits, 24 (22.9%) cases were occasional hookah smokers, of which 18 individuals (75%) were no more than 46 years old, and only two patients had underlying diseases.

## 5. Discussion

This descriptive retrospective study investigated

**Table 5.** Coexisting diseases, medication history, and other risk factors

	Number (%)
<b>Coexisting disease</b>	
None	37 (35.2)
Diabetes Mellitus and hypertension	18 (17.1)
Diabetes Mellitus	12 (11.4)
Hypertension	11 (10.5)
Diabetes Mellitus, hypertension, and heart disease	5 (4.8)
Hypertension and heart disease	5 (4.8)
Diabetes Mellitus and heart disease	4 (3.8)
Heart disease	2 (1.9)
Diabetes Mellitus and other diseases	2 (1.9)
Pregnancy	1 (1.0)
Other diseases	8 (7.6)
<b>Respiratory disease</b>	
Yes	6 (5.7)
No	99 (94.3)
<b>Smoking history</b>	
None	75 (71.4)
Occasional hookah smoking	24 (22.9)
Cigarette smoking	6 (5.7)
<b>Medication history</b>	
Metformin	36 (34.3)
Atorvastatin	27 (25.7)
Losartan	23 (21.9)
ASA	22 (21.0)
Metoprolol	14 (13.30)
<b>Family members with COVID-19</b>	
Yes	10 (9.5)
No	95 (90.5)

**Table 6.** Risk factors among 19 patients who died because of COVID-19 pneumonia

Variables	Number (%)
<b>Age</b>	
20-39	1 (5.3)
40-59	4 (21.1)
60-79	11 (57.9)
80-100	3 (15.8)
<b>Gender</b>	
Male	14 (73.7)
Female	5 (26.3)
<b>Coexisting disease</b>	
None	4 (21.1)
Diabetes Mellitus and hypertension	5 (26.3)
Diabetes Mellitus	4 (21.1)
Hypertension	1 (5.3)
Diabetes Mellitus, hypertension, and heart disease	1 (5.3)
Hypertension and heart disease	1 (5.3)
Diabetes Mellitus and other diseases	1 (5.3)
Pregnancy	1 (5.3)
Other diseases	1 (5.3)
<b>Medication history</b>	
Metformin	10 (52.6)
Atorvastatin	6 (31.6)
Losartan	4 (21.1)
ASA	5 (26.3)
Metoprolol	4 (21.1)
<b>Smoking history</b>	
None	15 (78.5)
Occasional hookah smoking	3 (15.8)
Cigarette smoking	1 (5.3)

105 suspected patients with developed COVID-19 pneumonia. The results showed that more than two-thirds of the patients were male, and half of them were elderly people over 60 years. Although the

majority of the patients referred to the hospital due to the shortness of breath, most of them stated fever as the first symptom. Amongst the elderly patients, individuals with a history of hypertension and diabetes as well as those who consumed Metformin were the most vulnerable groups. On the other hand, amongst the younger patients, hookah smoking was the main risk factor for COVID-19.

According to the results, most patients with COVID-19 were male and senior citizens whose mortality rate was also higher. According to the studies performed in China, elderly males are more susceptible to develop COVID-19 (12-14). One probable reason for this issue is rooted in the prevalence of chronic diseases among this group of population. The prevalence of chronic diseases varies by both gender and age. Generally, females are more vulnerable to hypertension, asthma, chronic bronchitis, and arthritic symptoms, compared to males. On the other hand, males report higher levels of other diseases, such as cancer, diabetes mellitus, and emphysema. Although males have higher levels of cardiovascular disease than females, cardiovascular disease is more prevalent among females, compared to males by age 75 (15). Higher expression of angiotensin-converting enzyme 2 (major receptor for the SARS-Cov-2) among males has been announced as the other possible reason for this discrepancy of COVID-19 prevalence between males and females (5).

In this study, according to the patients' statements, non-productive coughing was the most prevalent sign (82.9%), followed by fever (78.1%). However, upon admission, under one-third of the patients had a fever, which is a very important symptom for diagnosis; nonetheless, it was temporary and it did not exist at the time of admission in most cases.

Several studies have also shown that coughing and fever are the most common symptoms among patients (1). Although only 43% of the patients had a fever at the time of admission, about 88.7% of them developed a fever during their hospitalization (16). According to our findings, fever was the first symptom that patients had encountered; nevertheless, most patients ignored it until they develop dyspnea, which was the most frequent chief complaint. There is still a lack of tangible evidence about this issue; however, according to our observations, weakness and fatigue announced by a quarter of the patients are important signs that sometimes accompanied with confusion in some cases. Moreover, they build up the risk of trauma, which was observed in several cases that had referred to the hospital due to trauma as the result of falling or other incidents. Since these patients were treated as normal trauma patients, the risk of the transition of infection to medical staff was high.

Several studies reported hypertension as the most

prevalent underlying disease among patients with COVID-19 (14, 16, 17), whereas other reported cardiac disease as the most prevalent underlying disease (18).

According to the aforementioned results, most patients with COVID-19 were elderly patients who mainly had several coexisting diseases, and the prevalence of disease was probably misleading among them. Therefore, they were classified according to their diseases, and it was found that although hypertension was the most prevalent disease among the study population, "hypertension and diabetes" was the most prevalent combination, followed by just diabetes. Based on the result, out of 19 COVID-19 patients who expired, 5 individuals had "hypertension and diabetes" and 4 cases had only diabetes, whereas just one person had hypertension. It is evident that diabetic patients are more susceptible to lower respiratory tract infections due to impaired immune response (19). Previous studies have shown that diabetes increases the risk of hospitalization after other viral pneumonia, such as influenza A, which also increases the risk of ICU admission (20). Accordingly, it is advisable to protect diabetic patients during the current emergency crises.

In this study, Metformin was the most prevalent medication consumed by the patients, followed by Atorvastatin. Among 37 patients who had diabetes, 36 cases consumed Metformin as home medication, and finally, 10 of whom died of severe COVID-19 pneumonia. Several studies showed that Metformin had an anti-inflammatory or immunosuppressive effect by reducing NF- $\kappa$ B activation with a concomitant reduction in the secretion of inflammatory cytokines (21). The anti-apoptotic activity of NF- $\kappa$ B is linked to its ability to stimulate and orchestrate both innate and adaptive immune responses (22). Moreover, studies have revealed that Metformin decreases serum interleukin-6 (23), which is involved in both inflammation and infection responses (24). The difference between the patients who overcame COVID-19 and those who were defeated regarding the immune system is of significant importance; however, there has been no reliable evidence in this regard so far. Although there is a need for more studies to investigate the effects of Metformin in such patients, this finding probably can pave the way for future studies on the immune system of COVID-19 patients.

Hookah smoking not only has made the investigated patients more vulnerable to develop severe pneumonia but also played probably a crucial role in the spread of COVID-19 in Iran. Hookah smokers usually use the same water-pipe mouthpieces, which helps the spread of infectious agents as well (25). According to the results, hookah is considered a risk factor for many diseases, including chronic obstructive pulmonary disease. It

has been shown that there is a significant difference between hookah smokers and non-smokers in terms of free radical levels in neutrophils of the blood samples which damages the lung parenchyma (26).

Identification and scrutinization of the risk factors for severe COVID-19 pneumonia can pave the path for researchers to find ways to protect vulnerable individuals. To the best of our knowledge, this study is the first in Iran investigating the patients with severe COVID-19 pneumonia focusing on their risk factors, such as underlying diseases, smoking habits, and consumption of home medication. The study revealed unusual fever as the first important sign of the disease, which is ignored by most patients until they develop other signs, such as coughing and shortness of breath. This information can be used for future studies to identify differences between people developing severe COVID-19 pneumonia and those who overcome it during the first stages regarding their immune and respiratory systems.

## 6. Conclusion

Hookah smoking probably plays a crucial role in the spread of COVID-19 in Iran which made younger people more susceptible. In addition to higher age, the immunosuppressive effects of Metformin probably made diabetic patients, who have an impaired immune system, more vulnerable to severe COVID-19 pneumonia. More studies on the immune system of vulnerable individuals can help protect them by identifying their differences.

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## Footnotes

**Authors' Contribution:** Seyedreza Mirsoleymani, Seyyed Mojtaba Nekooghadam, Mahnaz Ahmadi, Mahmoudreza Peyravi, Ahmad Soltani, Rita Rezaee, Simintaj Sharififar, Hossein Akbarialiabad, and Milad Ahmadi Marzaleh designed this study together and did the literature review. Seyyed Mojtaba Nekooghadam was responsible for diagnosis. Seyedreza Mirsoleymani, Mahnaz Ahmadi, and Milad Ahmadi Marzaleh were responsible for collecting information. Seyedreza Mirsoleymani, Seyyed Mojtaba Nekooghadam, Mahnaz Ahmadi, Mahmoudreza Peyravi, Ahmad Soltani, Rita Rezaee, Simintaj Sharififar, Hossein Akbarialiabad, and Milad Ahmadi Marzaleh analyzed data and wrote the manuscript together.

**Conflict of Interests:** The authors have no conflict of interest to declare.

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