

Hematological and Biochemical Parameters Associated with Mortality in COVID-19 Infection and Their Correlation with Smoking

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ARTICLE INFO	ABSTRACT
<p>Article type: Original Article</p>	<p>Introduction: Coronavirus disease 2019 (COVID-19) initially appeared in China, in December 2019 and has already evolved into a pandemic spreading rapidly throughout the world. The present study aimed to determine the relationship between hematologic and biochemical parameters associated with the mortality rate in COVID-19 infection and their correlation with smoking.</p> <p>Materials and Methods: This study was performed on 388 patients affected by COVID-19 who were admitted to Imam Reza Hospital in Mashhad, Iran from February 20, 2020, to May 21, 2020.</p> <p>Results: The patients were within the age range of 18-94 years old, and 341 of them were nonsmokers, while 47 of them were smokers. Moreover, chronic obstructive pulmonary diseases were more frequent among smokers. The mean of initial (on admission) white blood cell (WBC) count in smokers was significantly higher than nonsmokers (P=0.015). Males were more prone to death due to COVID-19 infection than females (P=0.035). In total, 60 (15.46%) out of 388 patients died because of COVID-19, while 84.5% of them survived.</p> <p>Conclusion: The results indicated a higher WBC count among smokers. Moreover, a higher WBC count on admission was associated with higher mortality. However, hospitalization duration was not different among smokers and nonsmokers groups. It was found that higher CRP levels and hospitalization periods were associated with an increased risk of death. The COVID-19 mortality rate was higher in men, compared to women. Eventually, no significant correlation was found between smoking and the mortality of patients with COVID-19.</p>
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Introduction

Coronavirus disease 2019 (COVID-19) outbreak initially appeared in China, in December 2019 and has already evolved into a pandemic (1). The presence of COVID-19 in Iran was detected in February 2020; afterward, Iran became one of the most infected countries worldwide (2-4).

Clinicians and public health professionals should consider that COVID-19 can cause a wide spectrum of symptoms. In more severe cases, it can cause severe acute respiratory syndrome, renal failure, and even death (5, 6). COVID-19 and influenza viruses have some indistinguishable symptoms, such as fever, dry cough, dyspnea, and bilateral ground-glass opacities on chest computed tomography (CT) scans (7). However, COVID-19 cases showed some unique clinical manifestations, including the lower airway targeting, as evidenced by upper respiratory tract symptoms, like rhinorrhea, sneezing, and sore throat (8).

At the beginning of the pandemic, it was believed that youngsters are immune to COVID-19 infection; however, recent studies have shown that the virus has the power to infect people of any age. Nevertheless, evidence to date shows that two groups of people are at higher risk for severe COVID-19 disease, including the elderly (over 60) and individuals who have special medical conditions, such as chronic obstructive pulmonary diseases (COPD) and smoking habits (9,10).

There are about 1.3 billion smokers in the world, and about one-third of them live in China (10). In Iran, it is estimated that approximately 20 million people have smoking habits (11). Numerous studies have shown the impact of cigarette smoking on lung cancer prevalence, cardiovascular disease, and reproductive system issues (12). Furthermore, smoking has profound effects on the immune system and its responsiveness to infections, making smokers more vulnerable to infectious diseases (13).

To date, smoking has been assumed to be possibly associated with poorer disease prognosis, as evidence has highlighted the negative impact of tobacco use on lung

health and its causal association with a variety of respiratory diseases (14). Previous studies have shown that smokers are twice more likely to be affected by influenza and have more severe symptoms, compared to nonsmokers. Moreover, the mortality rate of smokers was higher than others during the previous MERS-CoV outbreak (15,16).

Considering the gap in the evidence and the high prevalence of coronavirus and smokers in Iran, this study aimed to determine the relationship between smoking and COVID-19 disease prognosis.

Materials and Methods

Patients and Data Collection

All the patients affected by COVID-19 admitted to Imam Reza Hospital in Mashhad, Iran from February 20, 2020, to May 21, 2020, were enrolled in this study. The COVID-19 infection of the participants was proved by lung high-resolution computed tomography (HRCT) results and/or PCR test, as instructed in Iran national guidelines. The patient outcome was defined as their status at the time of discharge and was divided into categories of alive or dead. Smoking was defined as at least six months of inhalation of tobacco products.

All participants were diagnosed with COVID-19 using polymerase chain reaction (n=205) or lung high-resolution computed tomography (n=183). All the patients were admitted due to moderate to severe degrees of the disease (i.e., involvement of more than 40% of the lung parenchyma or instability of vital signs, such as hypoxemia and hypotension or severe leukopenia).

All the patients were interviewed in the first hours of admission. All the past medical history, previous medication consumption, and related hospitalization data, as well as laboratory tests, were recorded in the COVID-19 registry of Imam Reza Hospital. Patients were treated according to the national and universal COVID-19 management guidelines. Data were retrieved from the Imam Reza Hospital registry system.

Ethical consideration

Research Hospital Ethics Committee of Mashhad University of Medical Sciences

approved the current study (IR.MUMS.REC.1399.185). The study was done under the principles of the Declaration of Helsinki and written informed consent was taken from all participants.

Statistical analysis

Categorical variables were expressed as frequency and percentage, and continuous variables were expressed as mean±standard deviation. The chi-squared and Fisher exact, were used for parametric analysis and Student t-test and Wilcoxon tests were used for non-parametric analysis. Binomial logistic regression was conducted to assess the association of study parameters with the patient outcome. All study tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed in SPSS software (version 18).

Results

In total, 388 patients were included in this study, 47 (12.11%) of whom were smokers.

They were within the age range of 18-94 years. General characteristics of the patients are summarized in Table 1. Based on the comparisons of the characteristics of smoker and nonsmoker patients with COVID-19 infection, there was no statistically significant difference between the mean age of patients in smoker and nonsmoker groups. The results revealed that the smoker and nonsmoker groups had a significant difference in terms of gender ($P=0.006$). Mean of initial (on admission) WBC count in smokers was significantly higher than that in nonsmokers (10.41 ± 4.32 vs. 8.57 ± 5.38 , $P=0.015$). Besides, the frequency of COPD was statistically higher in smokers than in the nonsmoker group ($P<0.001$). In addition, there was no statistically significant difference between the two groups regarding initial C-reactive protein (CRP), initial erythrocyte sedimentation rate (ESR), and age. Furthermore, groups were not statistically different in terms of chronic renal disease ($P=0.52$) (Table 1).

Table1: comparison of characteristics of COVID-19 alive and death subjects disease

Variable *	Total (N=388)	Status		P value
		Alive N=328 (84.536)	Death N=60 (15.464)	
Patients age (year)	60.477 ±17.827	59.494±18.156	65.85±14.932	0.013*
Gender				0.035*
Female	171 (44.072)	152 (46.341)	19 (31.667)	
Male	217 (55.928)	176 (53.659)	41 (68.333)	
Smoker				0.108
Yes	47 (12.113)	36 (10.976)	11 (18.333)	
No	341 (87.887)	292 (89.024)	49 (81.667)	
InitialWBC	8.794±5.297	8.237±4.511	11.670±7.672	<0.001*
InitialCRP	90.130±77.737	78.864±66.802	140.941±100.927	<0.001*
InitialESR	51.340±32.336	50.079±32.342	57.038±32.007	0.141
Hospitalization Length	9.363±9.664	8.034±6.874	16.633±16.945	<0.001*
COPD				0.192
Yes	19 (4.897)	14 (4.268)	5 (8.333)	
No	369 (95.103)	314 (95.732)	55 (91.667)	
CKD				0.249
Yes	25 (6.443)	19 (5.793)	6 (10)	
No	363 (93.557)	309 (94.207)	54 (90)	
CLD				0.596
Yes	6 (1.546)	6 (1.829)	0	
No	391 (98.454)	322 (98.171)	60 (100)	

At the end of the study, 328 (84.54%) patients were alive, while 60 (15.46%) of them died during the hospitalization period. Regarding patient outcome, the difference between the mean age of alive patients and dead patients was statistically significant (59.49 ± 18.15 vs. 65.85 ± 14.93 , $P=0.013$).

There was a remarkable difference between the outcome of the disease (alive or dead) regarding gender ($P=0.035$). As shown in our analysis, men were more prone to death due to COVID-19 infection than women ($P=0.035$). Initial WBC and CRP count were significantly different between alive and

dead patients ($P<0.001$). Hospitalization length was significantly different between

alive and dead patients (8.03 ± 6.87 vs. 16.63 ± 16.94 , $P< 0.001$) (Table 2).

Table2: Comparison of characteristics of current smokers and current non- smokers with COVID-19 pneumonia

Variable ^a	Smoking			P value
	Total (N=388)	Smoker N= 47 (12.113)	Non-Smoker N= 341 (87.887)	
Patients age (year)	60.477 ± 17.827	60.149 ± 15.049	60.522 ± 18.196	0.690
Gender				0.006*
Female	171 (44.072)	12 (25.532)	159 (46.628)	
Male	217 (55.928)	35 (74.468)	182 (53.372)	
InitialWBC	8.794 ± 5.297	10.411 ± 4.323	8.574 ± 5.385	0.015*
InitialCRP	90.130 ± 77.737	112.931 ± 101.811	86.886 ± 73.370	0.259
InitialESR	51.340 ± 32.336	53.853 ± 40.044	51.010 ± 31.270	0.884
Hospitalization Length	9.363 ± 9.664	11.575 ± 13.749	9.059 ± 8.942	0.314
COPD				<0.001*
Yes	19 (4.897)	9 (19.149)	10 (2.933)	
No	369 (95.103)	39 (80.851)	331 (97.067)	
CKD				0.525
Yes	25 (6.443)	4 (8.511)	21 (6.158)	
No	363 (93.557)	43 (91.489)	320 (93.842)	
CLD				0.157
Yes	6 (1.546)	2 (4.255)	4 (1.173)	
No	391 (98.454)	45 (97.745)	337 (98.827)	

Effects of age, gender, smoking habits, initial WBC, initial ESR, initial CRP, and hospitalization length on the survival were examined by binomial logistic regression analysis. Table 3 summarizes the results of logistic regression. According to the analysis, the variables that are significantly associated with death were age (odds ratio [OR]=1.02, confidence interval [CI]=1.00-1.05), initial WBC (OR=1.16, CI=1.05-1.28), initial CRP (OR=1.01, CI=1.00-1.01), and hospitalization length (OR=1.04, CI=1.01-1.08). It must be noted that COPD and smoking habits were not associated with the death rate of patients affected by COVID-19.

Discussion

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is no curative treatment for this disease, and the effectiveness of vaccination is in doubt. There are many dilemmas present in its management, specifically in more severe

cases. It is crucial to understand the basic pathophysiology and aggravating factors of the disease thoroughly to be able to introduce treatment strategies. Smoking is an established risk factor for various kinds of lung diseases the most known of which is COPD.

We analyzed the relationship of smoking (i.e., at least six months of regular tobacco inhalation) with the associated features of COVID-19 and disease outcomes in this study. The results showed no statistical difference between the smokers and nonsmokers in terms of age in the study population. This was predictable since our study population was a valid sample of the community.

It was found that there is a difference between smokers and nonsmokers with COVID-19 in terms of gender; accordingly, the majority of smokers were male. It is believed that this fact may be related to social factors in Iranian society. This gender predisposition has also been reported in China before (17). In the aforementioned

study, it was found that COVID-19 is more likely to affect males than females, and even smoking is more common in males in China. These results are in line with those of the present study (17). In the present study, the information of 388 hospitalized, including 217 males and 171 females were collected. Furthermore, the initial laboratory data of hospitalized smoker and nonsmoker COVID-19 patients were compared. It was found that smoker patients had a higher WBC count ($P=0.015$); however, no such relationship was confirmed when the CRP and ESR levels were compared. It must be mentioned that this was also the case with the other blood cell counts. Chuanqin et al. and Singhal et al. also found immune response dysregulation in patients affected by COVID-19; however, they did not compare the leukocyte count in smokers and nonsmokers (18,19). To the best of our knowledge, such a comparison has not been reported in the literature yet. Nevertheless, higher WBC counts have been manifested in the previous studies in smokers, compared to nonsmokers (20,21). According to the results, smoker and nonsmoker groups were not different in terms of hospitalization length ($P=0.314$). The COPD was significantly more common in the smoker group. This fact was thoroughly confirmed in the literature, and smoking is known as one of the major risk factors of COPD (22,23). Frequency of chronic kidney disease (CKD) was not different in smoker and nonsmoker groups. Although smoking is a known risk factor for CKD and its progression (24), the results of this study did not show a statistically significant relationship between these factors. This may be due to the small number of smokers in this study (25).

Conclusion

In conclusion, the results indicated a higher WBC count among smokers. Moreover, a higher WBC count on admission was associated with a higher mortality rate. However, hospitalization duration was not different among smokers and nonsmokers groups. It was also found that higher CRP levels and hospitalization periods were associated with an elevated risk of death. The COVID-19 mortality rate was higher in males, compared to females. Finally, no

significant correlation was found between smoking and death by COVID-19 infection. Considering the results of the current study, it seems essential to be more conservative regarding patients who have increased levels of CRP and WBC in emergency wards.

Conflict of Interest

The authors declare that there was no conflict of interest in this study.

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