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ORIGINAL ARTICLE

Impact of Smoking on Disease Severity and Mortality of Hospitalized Patients with Confirmed COVID-19

Yusuf Taha Güllü[1], Ebru Kulucan[1], Nazmiye Tibel Tuna[1], Nurhan Köksal[1], Nizameddin Koca[2]

[1]Department of Pulmonary Medicine, Ondokuz Mayıs University School of Medicine, Samsun, Turkey
[2]Department of Internal Medicine, University of Health Sciences, Bursa Şehir Training and Research Hospital, Bursa, Turkey

ORCID iDs of the authors: Y.T.G. 0000-0001-8165-234X, E.K. 0000-0001-9869-0772, N.T.T. 0000-0003-4386-8259, N.K. 0000-0001-9833-0304, N.K. 0000-0003-1457-4366.

Main Points

- Smoker patients had more severe coronavirus disease 2019 disease course than non-smokers.
- In smokers, inflammatory markers such as C-reactive protein, D-dimer, and ferritin except procalcitonin levels were significantly higher.
- Smokers need respiratory support devices more, and the disease results in more deaths.
- The clinical outcome of smokers and non-smokers in severe/critical patients was similar.
- To be affected by the pandemic at a minimum level, it was advised that smokers should quit smoking urgently.

Abstract

COVID-19 is a newly defined pandemic agent. Exposure to cigarette smoke causes increased mucosal inflammation, expression of inflammatory cytokines, impaired mucociliary clearance, and excessive mucus production. Changes in the lungs due to smoking can directly affect the outcome of the disease. In this study, we evaluated the relationship between smoking and the clinical severity of COVID-19. The charts of the patients with positive real-time polymerase chain reaction (RT-PCR) tests who received inpatient treatment in COVID-19 clinics between November 2020-April 2021 were reviewed retrospectively. Patients were divided into two groups smokers and non-smokers. We compared two groups' age, gender, laboratory parameters, mortality status, and disease severity. We included PCR proven 165 smokers and 351 non-smokers who needed hospitalization. The number of female patients was significantly lower in the smoker group (F/M: 33/132)($p < 0.001$). The clinically severe patient rate was higher in the smoker group ($p = 0.005$). Although the rate of mortality and patients who need ventilatory support were higher in the smoker group, the differences could not reach statistical significance. This study showed smokers had a more severe COVID-19 course than non-smokers, but the clinical outcome of severe/critical patients was not affected by the smoking status. Therefore, smokers should quit smoking urgently to be affected by the pandemic at a minimum level.

Keywords: COVID-19, smoking, disease severity, mortality, mechanical ventilator

Corresponding Author:
Yusuf Taha Güllü,
E-mail:
tahagullu@gmail.com;
yusuftaha.gullu@omu.edu.tr

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Introduction

Coronavirus disease 2019 (COVID-19) is a newly defined pandemic agent. It may cause variable clinical conditions ranging from mild acute respiratory infection to acute respiratory failure and even death. The main route of entry of the virus is the nose, mouth, and upper respiratory tract and, less frequently, the conjunctival mucosa (Huang et al., 2020). Smoking is a well-recognized cause of cancer, cardiovascular disease, and chronic obstructive pulmonary disease (COPD)-related

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premature deaths and an essential risk factor that increases a predisposition to respiratory system infections and other systemic infections. The causes generating a predisposition to infections in smokers are divided into structural changes and reduced immune response (Arcavi & Benowitz, 2004). Structural changes are characterized by peribronchial and alveolar inflammation, fibrosis, increased mucosal permeability, mucociliary activity insufficiency, and respiratory epithelium deterioration (Dye & Adler, 1994). Humoral and cellular immunity are negatively affected in smokers (Sopori et al., 1998). Smoking increases the predisposition to viral infections. Publications on COVID-19 disease widely discussed the viral infection and the factors that lead to the variability in the clinical conditions. It is reported that gender and smoking are associated with increased disease severity (Guan et al., 2020). Changes in the lungs due to smoking can directly affect the process and outcome of the disease.

In this study, we have aimed to reveal the relationship between smoking and the clinical severity of COVID-19.

Methods

The charts of the patients aged 18 and older with positive real-time polymerase chain reaction (RT-PCR) tests hospitalized in our tertiary health center between November 2020 and April 2021 were scanned retrospectively after the local ethics committee approval (June 25, 2021, and B.30.2.ODM.0.20.08/433). Written informed consent was obtained from all participants who participated in this study. A total of 601 patients were treated in this period, and vaccinated 85 patients were excluded. Patients' demographical data, clinical severity [non-severe, severe (SpO_2 <90%, respiratory rate >30/min, signs of severe distress), and critical (requires life-sustaining treatment, acute respiratory distress syndrome, sepsis, septic shock)] (World Health Organization, 2021), laboratory parameters (leukocyte, neutrophil, monocyte, platelet counts, hemoglobin levels, C-reactive protein (CRP), D-dimer, ferritin, aspartate aminotransferase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), and procalcitonin levels), thorax computed tomography involvement, and mortalities were obtained from patient files. The patients were divided into two groups according to their current smoking status as smokers and non-smokers. We compared the acquired data between the groups.

Statistical Analysis

The collected data were analyzed using the Statistical Package for the Social Sciences software version 26 package program (IBM SPSS Corp., Armonk, NY, USA). Pearson's Chi-square analysis was used in the hypothesis testing of the categorical data. Parametric or non-parametric independent unpaired test methods were used in hypothesis testing of the metric data. All hypotheses were tested at a .05 significance level. Multivariate logistic regression analysis was performed to determine the smoking-related significant risk factors.

Results

A total of 516 (165 smokers and 351 non-smokers) PCR-proved patients who needed hospitalization during COVID-19 infection were included. Female patients were significantly lower in the smoker group (female/male: 33/132, $p < .001$). Hospitalized smoker patients were older than non-smokers (65.13 ± 12.95 vs. 61.58 ± 15.70, $p = .016$). Past medical history evaluation reveals that smoker patients have higher incidence of COPD (42 (25.4%) vs. 2 (.5%), $p < .001$), coronary artery disease (CAD) (56 (33.9%) vs. 63 (17.9%), $p < .001$), and malignancy (28 (16.9%) vs. 32 (9.1%), $p = .009$)) as predicted. In the smoker group, the clinically severe patient rate was higher (188 (53.5% vs. 110 (66.6%), $p = .005$). Although the rate of patients that needed ventilatory support was higher in the smoker group, the difference could not reach statistical significance. Hospitalized patients' discharge status was insignificant ($p = .838$, Table 1).

The evaluation of the laboratory values reveals that neutrophil count and the neutrophil – lymphocyte ratio (NLR) were significantly higher, and lymphocyte count was lower in the smoker group. C-reactive protein, D-dimer, and ferritin levels were significantly higher in smoker participants, while procalcitonin levels were lower in the smoker group (Table 2).

Table 1.
Demographics, Past Medical History, and Hospitalization Process Comparison

	Non-smoker (*n* = 351)	**Smoker (*n* = 165)**	***p***
Sex (female), *n* (%)	189 (53.8)	33 (20)	<.001
Sex (male), *n* (%)	162 (46.2)	132 (80)	<.001
Age	61.58 ± 15.70	65.13 ± 12.95	.016
Past medical history			
Asthma, *n* (%)	28 (7.9)	9 (13.8)	.300
COPD, *n* (%)	2 (.5)	42 (25.4)	<.001
CAD, *n* (%)	63 (17.9)	56 (33.9)	<.001
HT, *n* (%)	162 (46.1)	86 (52.1)	.206
DM, *n* (%)	96 (27.3)	57 (34.5)	.095
Malignancy, *n* (%)	32 (9.1)	28 (16.9)	.009
Clinical severity (severe), *n* (%)	188 (53.5)	110 (66.6)	.005
Ventilatory support during hospitalization			.130
No MV, *n* (%)	212 (60.3)	84 (50.9)	
HFNO, *n* (%)	100 (28.4)	58 (35.1)	
NIMV, *n* (%)	16 (4.5)	6 (3.6)	
Intubation, *n* (%)	23 (6.5)	17 (10.3)	
Discharge status			.838
Excitus, *n* (%)	134 (38.1)	67 (40.6)	.598
Home ventilation, *n* (%)	20 (5.6)	10 (6.0)	
Good condition, *n* (%)	197 (56.1)	88 (53.3)	

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HT = hypertension; DM = diabetes mellitus; MV = mechanical ventilation; HFNO = high-flow nasal oxygen; NIMV = non-invasive mechanical ventilation; p = probability $p < 0.05$ statistically significant.

Table 2.
Comparison of Laboratory Values Between the Groups

	Non-smoker (n = 351)	Smoker (n = 165)	p
WBC (/μL)	7.959.83 ± 4.763.75	8.677.25 ± 5.209.75	.138
Neutrophils (/μL)	6.197.81 ± 4.437.49	7.115.87± 4.951.17	.039
Lymphocyte (/μL)	1.140.06 ± 824.19	1.002.24± 846.26	.003
NLR	8.25 ± 10.35	11.29 ± 14.12	.001
Hemoglobin (g/dL)	12.39 ± 2.11	12.55 ± 2.37	.325
Monocyte (/μL)	541.28 ± 1,121.99	502.07 ± 338.53	.222
Platelet (10^3/μL)	207.52 ± 96.05	206.55 ± 92.61	.735
CRP (mg/L)	96.2 ± 94.36	119.21 ± 91.51	.001
D-dimer (ng/mL)	1.963.46 ± 2.655.6	2.755.74± 3.207.7	.002
Ferritin (ng/mL)	803.94 ± 1.226.05	964.2 ± 1548.13	.035
AST (U/L)	44.6 ± 46.17	50.42± 59.78	.349
ALT (U/L)	32.59 ± 31.58	42.04 ± 57.27	.276
GGT (U/L)	58.62 ± 105.32	63.09 ± 77.36	.168
LDH (U/L)	455.04 ± 325.96	456.79 ± 271.73	.685
Procalcitonin (ng/mL)	1.9 ± 9.3	1.58 ± 6.19	.004

WBC = white blood cells; NLR = neutrophil/lymphocyte ratio; CRP = C-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; p = probability $p < 0.05$ statistically significant.

Multivariate logistic regression analysis was performed to determine the smoking-related risk factors. Patient's age, gender, comorbid diseases (diabetes mellitus, hypertension, CAD, COPD, asthma, and malignancy), clinical severity of the disease, need for mechanical ventilation, white blood cell, neutrophil, lymphocyte, monocyte, hemoglobin, thrombocyte, CRP, D-dimer, ferritin, AST, ALT, GGT, LDH, and procalcitonin levels were primarily analyzed by univariate logistic regression analysis. Gender, comorbid diseases (COPD, CAD, and malignancy existence), clinical severity of the disease, neutrophil, lymphocyte, neutr ophils/lymphocyte ratio, CRP, D-dimer, ferritin, and procalcitonin levels were included in the multivariate logistic regression analysis (Table 3 and Table 4). In the multivariate logistic regression analysis, the variable selection was performed using the enter addition method. The variables found to be significant in the model were gender, COPD, and CAD existence (Table 5). In the final step in the model, it was determined that smoking patients have a 49.71- and 1.96-times increased risk for COPD and CAD, respectively. The male gender has a 3.79-fold increased risk for smoking (Table 3).

The effect of smoking on the risk factors among the clinically severe/critical patients was compared. A total of 298 patients (female/male: 114/184) were identified in the study group. The number of smoking female patients was significantly lower (female/male: 18/92, $p < .001$). Smoker-critical patients were older (66.68 ± 12.04 vs. 62.10 ± 15.13, $p = .007$). The rate of COPD [26 (23.6%) vs. 1 (.5%), $p < .001$], CAD [39 (35.5%) vs. 38 (20.2%), $p = .004$], and malignancy [19 (17.3%) vs. 16 (8.5%), $p = .02$)] was higher in smoking patients. The discharge status was insignificant among the groups (Table 4). The laboratory values in severe/critical patients show that non-smoker patients' lymphocyte count was higher (1083.83 ± 959.97 /mL vs. 825.73 ± 853.96 /mL, $p = .02$) and

Table 3.
Multivariate Logistic Regression Analysis of Smoking-Related Risk Factors

				95% CI for EXP(B)	
	Wald	p	OR	Lower	Upper
Gender	29.307	.000	3.799	2.343	6.159
COPD	27.231	.000	49.712	11.463	215.597
CAD	7.088	.008	1.968	1.196	3.239

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease.
Model χ^2= 496.254; $p < .001$, Hosmer and Lemeshow Test: $p = .926$.

Table 4.
Demographics, Past Medical History, and Hospitalization Process Comparison of Critical Patients Aaccording to Smoking Status

	Non-smoker (n = 188)	Smoker (n = 110)	p
Sex (female), n (%)	96 (51.1)	18 (16.4)	<.001
Sex (male), n (%)	92 (48.9)	92 (83.6)	<.001
Age	62.1 ± 15.13	66.68 ± 12.04	.007
Past medical history			
Asthma, n (%)	16 (8.5)	6 (5.5)	.330
COPD, n (%)	1 (0.5)	26 (23.6)	<.001
CAD, n (%)	38 (20.2)	39 (35.5)	.004
HT, n (%)	96 (51.1)	61 (55.5)	.464
DM, n (%)	64 (34)	39 (35.5)	.805
Malignancy, n (%)	16 (8.5)	19 (17.3)	.023
Ventilatory support during hospitalization			.701
No MV, n (%)	49 (26.1)	29 (26.4)	.955
HFNO, n (%)	100 (53.2)	58 (52.7)	.938
NIMV, n (%)	16 (8.5)	6 (5.5)	.330
Intubation, n (%)	23 (12.2)	17 (15.5)	.431
Discharge status			.267
Excitus, n (%)	116 (61.2)	60 (54.5)	.262
Home ventilation, n (%)	18 (9.6)	8 (7.3)	
Good condition, n (%)	55 (29.3)	42 (38.2)	

COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease; HT = hypertension; DM = diabetes mellitus; MV = mechanical ventilation; HFNO = high-flow nasal oxygen; NIMV = non-invasive mechanical ventilation; p = probability $p < 0.05$ statistically significant.

Table 5.
Comparison of Laboratory Values in Critical Patients According to Smoking Status

	Non-smoker (n = 351)	Smoker (n = 165)	p
WBC (/μL)	9055.8 ± 5408.88	9028.25 ± 5620.62	.967
Neutrophils (/μL)	7428.51 ± 5106.08	7724.8 ± 5274.25	.633
Lymphocyte (/μL)	1083.83 ± 959.97	825.73 ± 853.96	**.020**
NLR	10.99 ± 12.97	13.83 ± 16.04	.097
Hemoglobin (g/dL)	12.35 ± 2.01	12.46 ± 2.46	.671
Monocyte (/μL)	440.74 ± 322.6	445.91 ± 299.54	.891
Platelet (10^3/μL)	213.28 ± 89.95	196.51 ± 88.87	.120
CRP (mg/L)	126.25 ± 104.6	135.7 ± 89.88	.429
D-dimer (ng/mL)	2465.81 ± 3028.39	3184.24 ± 3420.38	.061
Ferritin (ng/mL)	1031.6 ±1503.11	1173.77 ± 1814.38	.467
AST (U/L)	51.23 ± 52.87	57.53 ± 70.36	.382
ALT (U/L)	35.45 ± 34.58	47.98 ± 67.79	**.036**
GGT (U/L)	61.43 ± 127.56	63.67 ± 80.66	.868
LDH (U/L)	544.94 ± 347.92	518.16 ± 286.71	.495
Procalcitonin (ng/mL)	2.76 ± 11.26	1.91 ± 6.67	.469

WBC = white blood cells; NLR = neutrophil/lymphocyte ratio; CRP = C-reactive protein; AST = aspartate transaminase; ALT = alanine transaminase; GGT = gamma glutamyl transferase; LDH = lactate dehydrogenase; p = probability $p < 0.05$ statistically significant.

ALT levels were lower (35.45 ± 34.58 U/L vs. 47.98 ± 67.79 U/L, p = .036) compared to smokers (Table 5).

Discussion

Our study reveals that smoker patients had more severe COVID-19 disease course than non-smokers. Hospitalized smoker COVID-19 patients were older and had a higher rate of comorbid conditions such as COPD, CAD, and malignancy. In smoking patients, the neutrophil count and neutrophil – lymphocyte ratio were higher, while the lymphocyte count was lower. In smokers, inflammatory markers such as CRP, D-dimer, and ferritin except procalcitonin levels were significantly higher. The evaluation of clinically severe patients' data revealed no significant difference in ventilation support and discharge status as well as laboratory data except lymphocyte count and ALT levels between smokers and non-smokers.

Smoking is a well-recognized risk factor for many respiratory diseases. Since both cellular and humoral immunity are negatively affected in smokers, a predisposition to respiratory infections increases (Arcavi & Benowitz, 2004; Sopori et al., 1998). There are conflicting articles in the literature about COVID-19 and the smoking relationship. While there are meta-analysis results that show smoking is associated with COVID-19 progression, on the other hand, there are also articles defending there is no relationship between smoking and disease severity (Lippi & Henry, 2020; Patanavanich & Glantz, 2020; Ugur Chousein et al., 2020). Research conducted in Iran found that COVID-19 had a more severe course and caused mortality in smokers (Heydari & Arfaeinia, 2021). In the study of Caliskan et al. a significant relationship was found between smoking, disease severity, and mortality in hospitalized patients diagnosed with COVID-19 (Caliskan & Saylan, 2020). In our study, the rate of clinically severe patients was significantly higher in the smoker group (53.5% vs. 66.6%, p = .005). Considering the discharge status data, although rates were higher in the smoker group, the difference was insignificant (p = .838). The available evidence suggests that smoking is associated with increased disease severity and mortality in hospitalized COVID-19 patients (World Health Organization, 2020)

In our study, 68.02% of COVID-19 patients were non-smokers, while 31.98% were smokers. This rate is similar to the smoking rate of people over the age of 15 in Turkey (28%), announced in the Turkey Health Survey, conducted by the Turkish Statistical Institute in 2019. Although the risk of contracting the disease in smokers was similar to that of the society in the current study, the disease had a more severe course in smokers. These people need respiratory support devices more, and the disease progresses more deadly (TUİK, 2020) (Table 1).

In the current study, evaluation of the laboratory values reveals that neutrophil count and NLR were significantly higher while lymphocyte count was lower in the smoker group. The research conducted by Kargın et al reported that the neutrophil count, NLR, and ferritin levels were higher in smokers (Cetin Kargin, 2021). A meta-analysis of 5350 COVID-19 patients from 25 studies revealed elevated serum CRP, D-dimer, and ferritin levels were also associated with poor prognosis (Huang et al., 2020). Those values were also associated with disease severity and significantly higher in smokers in our study.

Subgroup analysis of clinically severe patients shows no significant effect of smoking status on clinical outcomes in our study. Once patients are admitted to the intensive care unit, the inflammatory process has dominance and individual-related factors such as past medical history, comorbidities, and genetic conditions, which affect the immunological balance, primarily determine the clinical outcome. No specific therapeutic agents have been proven for COVID-19-related critical illness. Supportive care (antibiotics, immunoglobulins, corticosteroids, and mechanical ventilation) has still had a key role in the management of these patients, which requires close follow-ups (L. Chen et al., 2020).

In conclusion, compared to non-smokers, smoker COVID-19 patients more frequently need hospitalization and respiratory support. It has also been shown that smoker patients' inflammatory markers level was higher and clinical course were more severe than non-smokers. The clinical outcome of severe patients was not affected by the smoking status. This may suggest that once the inflammatory process gets the dominance, smoking status does not directly affect the disease outcome. Although

smoking does not contribute to the outcome of patients with severe clinical conditions, it is recommended that they stop smoking immediately since the proportion of patients who progress to a serious clinical condition is higher in smokers.

Limitations and Suggestions for Future Research

Our study has limitations, such as retrospective and single-center hospitalized patient design. At the same time, the lack of information about the patients' amount and duration of smoking is also one of our important limitations.

The current study revealed that COVID-19 smoker patients had a more severe disease course; therefore, smoking cessation should be encouraged by mobile-text messaging cessation programs, nicotine replacement therapies, and other approved medications. Further multicenter studies need to be conducted to prove this.

Ethics Committee Approval: Ethical committee approval was received from the Ethics Committee of Ondokuz Mayıs University (approval no: B.30.2.ODM.0.20.08/433).

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Genişletilmiş Özet

Sigaranın Hastanede Yatan COVID-19 Hastalarında Hastalık Şiddeti ve Mortalitesi Üzerindeki Etkisi

Amaç

COVID-19, yeni tanımlanmış bir pandemic etkenidir. Sigara dumanına maruz kalma, aşırı mukus üretimi ile birlikte artmış mukozal inflamasyona, inflamatuar sitokinlerin ekspresyonuna ve bozulmuş mukosiliyer klirense neden olur. Sigaraya bağlı olarak akciğerlerde meydana gelen değişiklikler, hastalığın seyrini doğrudan etkileyebilir. Bu çalışmada sigara ile COVID-19'un klinik şiddeti arasındaki ilişkiyi değerlendirdik.

Yöntemler

Kasım 2020-Nisan 2021 tarihleri arasında COVID-19 kliniklerinde yatarak tedavi gören real-time polimeraz zincir reaksiyonu (RT-PCR) testi pozitif olan hastaların dosyaları retrospektif olarak incelendi. Aşılı olan hastalar çalışmaya dahil edilmedi. Hastalar sigara içenler ve içmeyenler olarak iki gruba ayrıldı. Yaş, cinsiyet, laboratuvar parametreleri, ölüm durumu ve hastalık klinik şiddeti (şiddetli SpO_2 <% 90 olan, solunum sayısı >30/dakika olan ve ciddi solunum yetmezliği bulguları olanlar ile şiddetli olmayan grup bu bulgulara sahip olmayanlar) iki grup arasında karşılaştırıldı.

Bulgular

Çalışmaya hastaneye yatırılan PCR testi pozitif 165 sigara içen ve 351 sigara içmeyen olmak üzere toplamda 516 hasta dahil edildi. Sigara içen grupta kadın hasta sayısı anlamlı olarak daha düşüktü (K/E: 33/132) ($p <$,001). Sigara içen hastaların içmeyenlere göre daha yaşlı olduğu gözlendi (65,13 ± 12,95 vs 61,58 ± 15,70, $p =$,016). Sigara içen grupta klinik olarak ağır hasta oranı daha yüksekti ($p =$,005). Sigara içen grupta mortalite ve solunum desteğine ihtiyaç duyan hasta oranı daha yüksek olmasına rağmen aradaki fark istatistiksel olarak anlamlı bulunmadı. Klinik olarak şiddetli olan hastalara bakıldığında hastalığın klinik gidişatı sigara içme durumundan etkilenmedi.

Sonuç

Bu çalışma, sigara içenlerin sigara içmeyenlere göre COVID-19 hastalığını daha ağır geçirdiğini, solunum desteği cihazlarına daha fazla ihtiyaç duyduklarını ve ölüm oranlarının daha fazla olduğunu gösterdi. Bu nedenle pandemiden minimum düzeyde etkilenmek için sigara içenlerin acilen sigarayı bırakmaları gerekmektedir.