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RESEARCH ARTICLE

Cross-sectional analysis of tobacco addiction in hospitalized COVID-19 patients

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ABSTRACT

Cross-sectional analysis of tobacco addiction in hospitalized COVID-19 patients

Introduction: *The COVID-19 pandemic has become an important health issue with consequences for special populations since 2019. Tobacco use is an important public health issue and tobacco users are a risk group for lung infections.*

Materials and Methods: *The aim of this study is to obtain information about disease prevalence and severity, laboratory parameters, and changes in radiological findings between smokers and non-smokers who were hospitalized, followed up, and treated for COVID-19, and to find answers to critical questions regarding the response to antiviral and supportive therapy. Two hundred eighty-six patients who were hospitalized and treated between March 2020-February 2021 in the COVID-19 Isolation Ward of Başkent University Hospital were included in the study. The patients were grouped as current smokers, non-smokers, and ex-smokers. The groups were compared in terms of symptoms, laboratory findings, radiological findings, and treatment response.*

Results: *The median age of the patients included in the study was 59 (IQR= 32). Of the patients, 40.6% were female and 59.4% were male. In our study, we discovered that there were fewer female smokers (p< 0.001). When the current smokers (n= 56), non-smokers (n= 159), and ex-smokers (n= 71) were compared based on their findings, it was found that dyspnea was more common in current smokers (p= 0.009). Lung involvement was found to be more common (p= 0.002) and multifocal in the current smokers group*

(p= 0.038). The levels of oxygen saturation at the times of admission and discharge were lower in current smokers (p= 0.002 and p= 0.038). The need for nasal oxygen and noninvasive mechanical ventilation was also found to be higher in current smokers (p= 0.008 and p= 0.039). Systemic steroid requirement was higher in current smokers (p= 0.013). There was no statistically significant difference in terms of mortality between current smokers, ex-smokers, and non-smokers (p= 0.662).

Conclusion: *The analysis of the findings of the patients hospitalized in the COVID-19 isolation ward indicated that COVID-19 leads to a more serious course in patients with a history of smoking.*

Key words: *COVID-19; smoking; SARS-CoV-2; COVID-19 pneumonia*

ÖZ

Hastanede yatan COVID-19 hastalarında tütün bağımlılığının kesitsel analizi

Giriş: *COVID-19 pandemisi 2019 yılından itibaren özel gruplar için sonuçları önemli bir sağlık sorunu haline gelmiştir. Tütün tüketimi önemli bir halk sağlığı sorunudur ve tütün kullanıcıları akciğer enfeksiyonları için risk grubudur. Bu çalışmanın amacı yatarak tedavi gören, sigara içen ve içmeyen COVID-19 hastalarında hastalığın prevalansı ve şiddeti, laboratuvar parametreleri ve radyolojik bulgulardaki değişiklikler hakkında bilgi sahibi olmaktır.*

Materyal ve Metod: *Çalışmaya Başkent Üniversitesi Hastanesi COVID-19 İzolasyon Servisinde Mart 2020-Şubat 2021 tarihleri arasında yatarak tedavi gören iki yüz seksen altı hasta dahil edildi. Hastalar halen sigara içen, içmeyen ve sigarayı bırakmış olarak gruplandırıldı. Gruplar semptomlar, laboratuvar bulguları, radyolojik bulgular ve tedaviye yanıt açısından karşılaştırıldı.*

Bulgular: *Çalışmaya alınan hastaların ortanca yaşı 59 (IQR= 32) idi. Hastaların %40,6'sı kadın, %59,4'ü erkekti. Çalışmamızda kadın hastaların daha az sigara içtiği görüldü (p< 0,001). Sigara içenler (n= 56), içmeyenler (n= 159) ve sigarayı bırakanlar (n= 71) bulguları açısından karşılaştırıldığında, sigara içenlerde nefes darlığının (p= 0,009), akciğer tutulumunun (p= 0,002) daha sık olduğu ve akciğer tutulumunun multifokal (p= 0,038) olduğu görüldü. Halen sigara içenlerde hastaneye başvuru ve taburculuk anındaki oksijen satürasyon düzeyi daha düşüktü (p= 0,002 ve p= 0,038), nazal oksijen ve noninvaziv mekanik ventilasyon ihtiyacı daha yüksek bulundu (p= 0,008 ve p= 0,039), daha fazla sistemik steroid gerekli oldu (p= 0,013). Sigara içenler, sigarayı bırakanlar ve içmeyenler arasında mortalite açısından istatistiksel olarak anlamlı bir fark yoktu (p= 0,662).*

Sonuç: *COVID-19 servisinde yatan hastaların bulgularının analizi, sigara öyküsü olan hastalarda COVID-19'un daha ciddi bir klinik seyir izlediğini gösterdi.*

Anahtar kelimeler: *COVID-19; sigara; SARS-CoV-2; COVID-19 pnömonisi*

INTRODUCTION

Coronavirus disease (COVID-19), caused by SARS-CoV-2, spread around the world in 2019, causing a pandemic (1). The relationship between tobacco use and disease severity can be listed among the unknowns and concerns about COVID-19 disease. Conditions most commonly reported to lead to severe illness in COVID-19 are being over 65 years of age, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), hypertension (HT), coronary artery disease (CAD), cerebrovascular disease (CVH), chronic kidney disease (CKD), neurological disorders, pregnancy, and smoking, which was added later to this list (2). It is known from previous experience that smoking increases the risk of respiratory tract infections. Smoking causes structural changes in the respiratory tract and a decrease in the immune response and is an important risk factor for bacterial and viral infections (3,4).

Previous studies showed that smokers are twice as likely to get influenza and have more severe symptoms than non-smokers, and smokers were reported to have higher mortality in the previous MERS-CoV outbreak (1).

Cigarette smoke has been associated with an increase in the expression of angiotensin-converting enzyme-2 (ACE-2) surface receptors, through which SARS-CoV-2 enters host cells and type 2 pneumocytes in particular. Binding of SARS-CoV-2 virus to ACE-2 cell surface proteins shields it from the immune surveillance systems, keeps it attached to the host cell longer, the host becomes an effective carrier, and has the potential to spread further infection. In addition, smoking increases the severity of the inflammatory response associated with COVID-19, creating a predisposition to cytokine storms (5).

In our study, we aimed to investigate the prevalence, severity, and clinical characteristics of COVID-19 disease in smokers and non-smokers.

MATERIALS and METHODS

Study Design and Population

A total of 286 patients who were hospitalized and treated in the COVID-19 Isolation Ward of Başkent University Hospital between March 2020-February 2021 were included in the study. The patients were grouped as current smokers, non-smokers, and ex-smokers. The groups were compared in terms of symptoms, laboratory findings, radiological findings, and treatment response.

Patient Management

Nasopharyngeal swab samples were used to diagnose COVID-19, and the diagnostic test Bioeksen reverse transcriptase-polymerase chain reaction (PCR) was used to detect SARS-CoV-2. At the time of initial diagnosis, radiological imaging was performed on the majority of hospitalized patients using low-dose computed tomography of the thorax. Antero-posterior chest X-ray was used in the follow-ups. Patients were categorized as mildly ill (outpatient treatment only), moderately ill (admission to the general inpatient room), or severely infected (mechanical ventilation, intensive care unit admission, or death) based on the national guidelines (6). All patients with SARS-CoV-2 infection were followed in single rooms in accordance with droplet and contact precautions, and visits were not allowed in patient rooms. The staff wore personal protective equipment in accordance with institutional protocols.

Antiviral, Anticytokine, Anticoagulant, and Immunomodulator Therapy Protocols

Based on the national guidelines (6) on the treatment of COVID-19, patients without any complications received antiviral favipiravir treatment for 5-10 days in mild and moderate pneumonia, and for 10 days in severe pneumonia. Remdesivir treatment was administered for five days to selected patients. Anticoagulant therapy was provided to all hospitalized COVID-19 patients unless active bleeding or thrombocytopenia was present. In cases with persistent signs of inflammation that did not respond to glucocorticoid treatment or in cases of severe macrophage activation syndrome (MAS) with rapid progression, anti-cytokine drugs tocilizumab (intravenous) and anakinra (subcutaneous) therapy were used under the guidance of rheumatology and immunology specialists. Steroid treatment was increased from a low dose (5 mg/day) of methylprednisolone to a higher dose (methylprednisolone 1 mg/kg/day, dexamethasone 6 mg/day) according to the patient's clinical condition. In patients who did not respond to this therapy or who developed MAS, methylprednisolone at a 250 mg/day dose was used for three days. Plasma therapy was also applied concurrently in eligible patients.

Statistical Analysis

The suitability of numerical variables to normal distribution was examined with the Kolmogorov-Smirnov test of normality and mean ± standard deviation for normally distributed variables and median (minimum-maximum) values for non-normally distributed variables were given as descriptive statistics. Categorical variables are shown as frequency (n) and percentage (%). Kruskal-Wallis analysis of variance was used to analyze the differences of the measurement variables according to the groups. Post-hoc Tukey test was performed to define which group or groups are significant from each of them. The Pearson chi-square test was used to test the significance of categorical variables between groups when assumptions were met, and the Fisher exact chi-square test was used when they were not. Univariate logistic regression analysis was applied to the variables that resulted in a significant difference between groups, and variables with $p< 0.25$ were included in the multiple logistic regression analysis. Type I error probability was determined as $\alpha= 0.05$ in all hypothesis tests and statistical evaluations were made using the SPSS v25.0 software package.

RESULTS

The median age of all patients was 59 years (IQR= 32), the median age of non-smokers was 54 years (IQR= 35), ex-smokers was 51 years (IQR= 22.3), and current smokers was 70 years (IQR= 17) (Table 1). The difference between the groups in terms of median age was significant ($p< 0.001$). Of all patients, 40.6% (n= 116) were female (non-smokers 56%, ex-smokers 26.8%, current smokers 16.9%) and 59.4% (n= 170) were male (non-smokers 44.0%, ex-smokers 73.2%, current smokers 83.1%) (Table 1). There was a significant difference between the two sexes in terms of their smoking behavior ($p< 0.001$). The most common comorbidities were HT (48.3%), CAD (29.1%), and COPD (13%), respectively. In addition, HT (69.0%), CAD (50.7%), and COPD (26.8%) were more prevalent among current smokers than ex-smokers and non-smokers ($p< 0.001$, $p< 0.001$, $p< 0.001$, respectively) (Table 1).

Table 1. Socio-demographic characteristics and comorbidities of the patients

Demographic variables	Non-smokers n= 159 (%)	Ex-smokers n= 56 (%)	Current smokers n= 71(%)	Total n= 286 (%)	P
Age	54 (IQR= 35)	51 (IQR= 22.3)	70 (IQR= 17)	59 (IQR= 32)	0.001
Female	89 (56.0)	15 (26.8)	12 (16.9)	116 (40.6)	0.001
Male	70 (44.0)	41 (73.2)	59 (83.1)	170 (59.4)	
Comorbidities					
COPD	12 (7.5)	6 (10.9)	19 (26.8)	37 (13.0)	0.001
Asthma	7 (4.4)	-	4 (5.6)	11 (3.8)	0.216
HT	73 (45.9)	16 (28.6)	49 (69.0)	138 (48.3)	0.001
CAD	35 (22.2)	12 (21.4)	36 (50.7)	83 (29.1)	0.001
Cancer	12 (7.6)	3 (5.4)	8 (11.3)	23 (8.1)	0.487
CRF-CKD	17 (11.39)	3 (5.6)	15 (22.4)	35 (12.9)	0.015
Liver disease	7 (4.4)	3 (5.4	5 (7.0)	15 (5.2)	0.728

COPD: Chronic obstructive pulmonary disease, HT: Hypertension, CAD: Coronary artery disease, CRF-CKD: Chronic renal failure-chronic kidney disease.
Values are expressed as n (%), median (IQR), p< 0.05; significant.

Table 2. Distribution of symptoms

Symptoms	Non-smokers n= 159 (%)	Ex-smokers n= 56 (%)	Current smokers n= 71(%)	Total n= 286 (%)	P
Fever	76 (47.8)	33 (58.9)	35 (49.3)	144 (50.3)	0.355
Dyspnea	38 (24.1)	22 (39.3)	30 (42.3)	90 (31.6)	0.009
Cough	68 (43.01)	27 (48.2)	27 (38.0)	122 (42.8)	0.531
Fatigue	105 (66.5)	31 (55.4)	34 (48.6)	170 (59.9)	0.028
Loss of taste and smell	15 (9.5)	2 (3.6)	3 (4.3)	20 (7.1)	0.204
Sore throat	39 (24.7)	14 (25.5)	2 (2.9)	55 (19.4)	0.001
Headache	17 (10.8)	13 (23.6)	4 (5.7)	34 (12.0)	0.007
Nasal discharge	3 (1.9)	-	-	3 (1.1)	0.422
Nausea- vomiting	8 (5.0)	3 (5.4)	7 (9.9)	18 (6.3)	0.427
Diarrhea	15 (9.4)	3 (5.4)	5 (7.0)	23 (8.0)	0.585

Values are expressed as n (%), median (IQR), p< 0.05; significant.

The most common symptoms were fatigue (59.9%), fever (50.3%), cough (42.8%), and dyspnea (31.6%). Dyspnea was significantly common in current smokers (p= 0.009). According to the regression analysis, dyspnea symptoms were 6.32 times higher in patients with severe clinical status compared to patients with mild clinical status (p< 0.001). Fatigue and sore throat were more common in non-smokers (p= 0.028 and p< 0.001) (Table 2).

The comparison of the laboratory findings of the patients is presented in Table 3. Hematocrit (Hct), neutrophil/lymphocyte ratio (N/LR), creatine, potassium, D-dimer, troponin, creatine phosphokinase-MB (Ck-MB) and blood urea nitrogen (BUN) values were higher in active smokers (p= 0.014, p= 0.039, p= 0.002, p= 0.007, p< 0.001, p< 0.001, p= 0.040, p< 0.001 respectively).

The comparison of the radiological data of the patients is presented in Table 4. Radiological involvement was observed in 92.5% of active smokers (p= 0.002). Involvement in the form of multiple foci was observed in 65.7% (n= 46) of active smokers (p= 0.038). It was observed that lung involvement was more prevalent and multifocal in active smokers

Table 3. Comparison of the patients' laboratory findings

Laboratory findings	Non-smokers n= 159	Ex-smokers n= 56	Current smokers n= 71	Total n= 286	p
Hb (g/dL)	13.7 (3.0)	14.5 (2.4)	13.6 (3.0)	13.8 (3.0)	0.093
Hct (%)	40.7 (8.9)	43.9 (7.0)	40.0 (9.27)	40.9 (9.0)	0.014
WBC (mcL)	6.8 (3.7)	7.4 (5.6)	7.1 (4.0)	7.0 (4.0)	0.052
PLT (10^3/µ)	206.0 (9.6)	204.0 (8.9)	212.0 (112.0)	207.0 (95.5)	0.715
NLR	3.1 (3.2)	3.7 (4.2)	3.9 (5.2)	3.6 (3.9)	0.039
Lymphocyte (mcL)	1.4 (0.9)	1.4 (0.9)	1.2 (1.0)	1.4 (0.9)	0.106
ALT (unit/L)	18.0 (18.0)	22.0 (20.0)	20.0 (14.0)	19 (18.0)	0.381
AST (unit/L)	20.0 (14.8)	20.0 (20.5)	23.0 (16.0)	21.0 (16.0)	0.864
BUN (mg/dL)	14.5 (13.7)	13.0 (8.0)	20.0 (23.0)	16.0 (16.0)	0.001
Creatine (mg/dL)	0.9 (0.5)	0.9 (0.4)	1.2 (1.0)	0.9 (0.5)	0.002
Procalcitonin (µg/L)	0.2 (0.3)	0.2 (0.8)	0.2 (0.4)	0.2 (0.3)	0.418
CRP (mg/dL)	25.9 (74.9)	26.6 (82.7)	40.3 (84.4)	29.4 (77.3)	0.499
Sodium (mEq/L)	138.0 (6.0)	138.0 (6.0)	138.0 (7.0)	138.0 (6.0)	0.748
Potassium (mEq/L)	4.2 (0.5)	4.2 (0.5)	4.4 (0.7)	4.2 (0.7)	0.007
D-dimer (µg/mL)	0.6 (1.0)	0.6 (1.9)	1.3 (2.6)	0.7 (1.6)	0.001
PTT (sn)	27.5 (6.4)	26.2 (6.0)	27.6 (55.0)	27.2 (5.8)	0.646
PT (sn)	12.5 (2.3)	12.7 (3.3)	12.6 (2.3)	12.6 (2.4)	0.645
LDH (U/L)	213.0 (121)	209.0 (117.0)	234.0 (86.3)	221.5 (111.3)	0.250
Troponin (ng/mL)	4.0 (14.0)	2.0 (11.8)	10.0 (36.8)	4.0 (15.8)	0.001
Ck-MB (ng/mL)	0.9 (0.9)	1.0 (1.9)	1.7 (1.5)	1.1 (1.5)	0.040
Ferritin (ng/mL)	155.5 (240)	145.0 (422.5)	180.5 (571)	164.2 (262.8)	0.407
IL-6 (pg/mL)	249 (39)	-	97.2 (77.0)	24.9 (65.1	0.505

Values are expressed as median (IQR), p< 0.05; significant.
Hb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell, Plt: Platelet, NLR: Neutrophil/lymphocyte ratio, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, CRP: C-reactive protein, PTT: Partial thromboplastin time, PT: Prothrombin time, LDH: Lactate dehydrogenase, Ck-MB: Creatine kinase myocardial band, IL-6: Interleukin-6.

(p= 0.002). Cavity and pleural effusion were also observed more frequently in active smokers (p= 0.005 and p= 0.032).

Current smokers had lower oxygen saturation levels at the time of hospital admission (93) and discharge (95), and this was significant compared with the other groups (p= 0.002, p= 0.038). and a higher need for nasal oxygen and noninvasive mechanical ventilation (p= 0.008, p= 0.039) and it was observed that more systemic corticosteroids were needed (p= 0.013) (Table 5). Corticosteroid was a significant treatment modality in patients with severe clinical conditions (p= 0.046). The need for corticosteroids was 13.45 times higher in patients with severe disease compared to patients with a mild clinical condition. It was observed that the duration of hospitalization was longer in current smokers (p= 0.003). When analyzed by logistic regression analysis, it was seen that smoking affected clinical severity 2.55 times when compared to non-smokers between mild to moderate clinical severity (p= 0.004) (Table 6). Mortality was not different between current smokers, ex-smokers, and non-smokers (p= 0.662). Treatment methods affecting mortality are presented in Table 7.

DISCUSSION

Tobacco consumption is a major public health problem, associated with more than 8 million deaths worldwide each year (7). The COVID-19 pandemic has also become a major health concern since 2019 with long-term consequences for the health of the global population.

Table 4. Comparison of the patients' radiological findings

Radiological findings	Non-smokers n= 159 (%)	Ex- smokers n= 56 (%)	Current smokers n= 71 (%)	Total n= 286 (%)	p
Radiological involvement	170 (73.0)	65 (87.8)	37 (92.5)	272 (78.4)	0.002
Right-lung involvement	108 (69.2)	34 (60.7)	47 (67.1)	189 (67.0)	0.511
Left-lung involvement	94 (60.3)	31 (55.4)	47 (67.1)	172 (61.0)	0.395
Bilateral-lung involvement	82 (52.6)	22 (38.2)	40 (49.3)	144 (43.2)	0.118
Upper-lobe involvement	66 (42.3)	21 (50.0)	34 (62.5)	121 (42.1)	0.450
Middle-lobe involvement	46 (29.5)	13 (23.6)	23 (32.9)	82 (29.2)	0.516
Lower-lobe involvement	95 (60.9)	31 (56.4)	48 (69.6)	174 (62.1)	0.288
Multiple foci	88 (56.4)	24 (42.9)	46 (65.7)	158 (56.0)	0.038
Single foci	34 (21.8)	20 (35.7)	11 (15.7)	65 (23.0)	0.024
Ground-glass	109 (69.9)	38 (67.9)	50 (71.4)	197 (69.9)	0.908
Consolidation	39 (23.1)	9 (16.1)	15 (21.4)	60 (21.3)	0.569
Nodule	32 (20.5)	12 (21.4)	15 (21.4)	59 (20.9)	0.982
Cavity	-	-	4 (5.7)	4 (1.4)	0.005
Pleural effusion	20 (12.8)	4 (7.1)	16 (22.9)	40 (14.2)	0.032
Central	41 (27.5)	9 (18.0)	22 (31.4)	72 (26.8)	0.254
Peripheral	105 (70.5)	36 (72.0)	50 (72.5)	191 (71.3)	0.949

Values are expressed as n (%), p< 0.05; significant.

Table 5. Comparison of patients' respiratory support treatments, medical treatments, and mortality rates

	Non-smokers n= 159 (%)	Ex-smokers n= 56 (%)	Current smokers n= 71 (%)	Total n= 286 (%)	P
SpO_2 at the time of hospitalization	95 (IQR= 4)	96 (IQR= 3.5)	93 (IQR= 4)	95 (IQR= 4.8)	0.002
SpO_2 at the time of discharge	96 (IQR= 4)	96 (IQR= 2.5)	95 (IQR= 2)	96 (2.8)	0.038
High-flow oxygen therapy	9 (5.5)	3 (5.1)	6 (8.6)	18 (6.1)	0.679
Nasal-O_2 requirement	33 (20.5)	15 (25.4)	28 (40.0)	76 (26.2)	0.008
Noninvasive mechanical ventilation	3 (1.8)	2 (3.4)	6 (8.6)	11 (3.8)	0.039
Invasive mechanical ventilation	10 (6.1)	3 (5.1)	4 (5.8)	17 85.8)	0.960
Extracorporeal membrane oxygenation	1 (0.6)	-	-	1 (0.3)	0.676
Hemodialysis	11 (1.3)	2 (3.4)	5 (7.4)	18 (6.2)	0.640
Favipiravir	99 (62.7)	31 (55.4)	40 (57.1)	170 (59.9)	0.570
Hydroxychloroquine	44 (27.8)	23 (41.1)	18 (25.4)	85 (29.8)	0.113
Plasma therapy	9 (5.7)	2 (3.6)	6 (8.6)	17 (6.0)	0.523
Tocilizumab	2 (1.3)	1 (1.8)	1 (1.4)	4 (1.4)	0.960
Steroid	29 (18.6)	11 (20.0)	25 (36.2)	65 (23.2)	0.013
Exitus	14 (8.9)	5 (8.9)	9 (12.7)	28 (9.8)	0.662

Values are expressed as n (%), median (IQR), p< 0.05; significant.

Among the patients included in our study, the majority of the current smokers were male. It has been shown in various studies that COVID-19 infection is more severe in the male sex (8). This result also explains the greater number of male patients admitted to the pandemic ward due to their clinical sever-

Table 6. Effect of smoking status on clinical status

Clinical Status		n	Odds ratio	95% Confidence Interval for the coefficients		p
				Lower	Top	
Middle	**Regression Constant**					<0.001
	Current smokers	26	2.55	1.34	4.85	0.004
	Ex-smokers	11	0.94	043	2.05	0.88
	Non-smokers	32	a	a	a	a
Severe	**Regression Constant**					<0.001
	Current smokers	10	1.84	0.77	4.40	0.166
	Ex-smokers	5	0.80	0.28	2.33	0.69
	Non-smokers	17	a	a	a	a
Mortality	**Regression Constant**					0.00
	Current smokers	71	1.49	0.46	4.69	0.377
	Ex-smokers	56	1.09	0.61	3.63	0.988
	Non-smokers	159	a			0.651

[a]: Reference Category, p< 0.05; significant.

ity. In addition, a second reason could be the higher rate of smoking among males in our country (9).

In our study, dyspnea was most common in the current smoker group. According to the results of the regression analysis, the symptom that affected the clinical status the most was dyspnea. When this group was analyzed more thoroughly, it was seen that radiological involvement was higher, COPD and coronary artery disease were more prevalent as comorbidities, and respiratory failure was more prevalent in this group than in the others. Based on all these findings, we hypothesized that the prevalence of dyspnea was higher in current smokers due to the high prevalence of ventilation and perfusion disorders in this patient group.

BUN, creatine, and potassium levels were significantly different between groups, higher in current smokers. This result can be explained by the fact that chronic renal failure was a more prevalent comorbidity in the current smoker group.

Current epidemiological findings suggest that active smoking is associated with increased disease severity and mortality in hospitalized COVID-19 patients. Smoking is believed to upregulate the ACE-2 receptor and induce a "cytokine storm," which may lead to poorer outcomes in COVID-19 patients (5). Zhao et al. concluded that the risk of severe COVID-19 increased approximately two-fold in smokers [Odds Ratio (OR)= 1.98, 95% CI= 1.29-3.05] (10). Zheng et al. discovered that smokers had an accelerated disease progression in COVID-19 in their meta-analysis, which included data from thirteen studies involving 3027 patients (OR= 2.51, 95% CI= 1.39-3.32, p= 0.0006) (11). In their multivariate logistic regression analysis, Liu et al. stated that smoking history is a risk factor for disease progression (OR= 14.28, 95% CI= 1.58-25.00; p= 0.018) (12). In a meta-analysis of 11.590 COVID-19 patients, 2133 (18.4%) had disease progression and 731 (6.3%) had a history of smoking, patients with a smoking history had more disease progression than non-smokers. This meta-analysis demonstrated that there is an association between smoking and COVID-19 progression (OR= 1.91, 95% CI= 1.42-2.59, p= 0.001) (13). In our study, radiological lung involvement was higher in current smokers. CRP, D-dimer, troponin, ferritin, and IL-6 levels, which are markers of inflammation, were higher in current smokers. Moreover, hypoxia, steroid use, and continued oxygen demand at discharge were higher in these patients compared to other groups. Therefore, the results of our study corroborate the view that COVID infection has a more severe course in current smokers.

Among patients requiring intensive care unit and mechanical ventilation, or who died, there was a higher percentage of active and ex-smokers; smokers were 1.4 times more likely to have severe COVID-19

Table 7. Treatment methods affecting mortality

	Exitus Yes-No				
			95% Confidence Interval for the coefficients		
	n	Odds ratio	Lower	Top	p
Corticosteroids					
No	65				
Yes	215	11.50	4.77	27.75	<0.001
RC		7.63			0.003
High flow oxygen therapy					
No	16				
Yes	267	9.11	3.08	26.93	<0.001
RC		3.88			0.00
Nasal O_2					
No	74				
Yes	206	9.17	3.83	21.95	<0.001
RC		8.17			0.00
Noninvasive mechanical ventilation					
No	11				
Yes	272	9.02	2.56	31.85	<0.001
RC		3.60			0.00
Invasive mechanical ventilation					
No	16				
Yes	266	na	35.76	2382.89	<0.001
RC		1.13			0.81
Hemodialysis					
No	18				
Yes	262	8.14	2.83	23.41	<0.001
RC		4.48			0.00
Hydroxychloroquine					
No	85				
Yes	200	0.26	0.07	0.87	0.029
RC		13.83			0.00
Anticytokine therapy					
No	4				
Yes	280	9.77	1.32	72.26	0.026*
RC		3.12			0.03
Favipiravir					
No	169				
Yes	114	1.24	0.55	2.79	0.604
RC		9.34			0.00
Convalescent plasma					
No	17				
Yes	265	3.09	0.93	10.22	0.065
RC		5.71			0

RC: Regression constant, na: Not available. p< 0.05; significant.

symptoms (RR= 1.4, 95% CI= 0.98-2.00), and were approximately 2.4 times more likely to be admitted to the intensive care unit, and required more mechanical ventilation or had a higher mortality rate than non-smokers (RR= 2.4, 95% CI= 1.43-4.04) (14). In a meta-analysis of 47 peer-reviewed articles with a total of 31.871 COVID-19 patients, 5.759 (18.1%) had disease progression and 5.734 (18.0%) had a history of smoking, and an association between smoking and progression of COVID-19 was confirmed (OR= 1.56, 95% CI= 1.32-1.83, p= 0.001). Smoking was associated with an increased risk of death from COVID-19 (OR= 1.19, 95% CI= 1.05-1.34, p= 0.007). This effect was found to be most pronounced in people under the age of 45. Smoking has been identified as an independent risk factor for severe progression of COVID-19, including death (15).

In a meta-analysis of 15 studies involving 2.473 COVID-19 patients, Alqahtani et al. reported more severe complications and higher mortality rates in active smokers with COVID-19 (16). One of the largest cohort studies ever conducted in the UK found active smoking to be associated with a higher risk of COVID-19 mortality when adjusted for age and sex (HR= 1.25, 95% GA= 1.12-1.40). In the same study, a higher risk of COVID-19 mortality was detected in ex-smokers compared to non-smokers (HR= 1.8, 95% CI= 1.7-1.9). This association was found to be significant even after the adjustments for additional risk factors such as body mass index, chronic respiratory diseases, diabetes, hypertension, and chronic heart disease (fully adjusted HR= 1.25, 95% CI= 1.18-1.33) (17). A meta-analysis of 1399 patients found no significant association between smoking and COVID-19 disease severity, despite a trend for higher risk (OR= 169, 95% CI= 0.41-6.92) (18). Some researchers question the validity of these studies, highlighting the flaws in the statistical analyses and potential bias regarding selected smoker populations in the analyses. In addition, some studies argue that such a conclusion was reached because statistical adjustments were not made for confounding factors such as age, gender, and comorbidities (19,20).

In our study, although pneumonia and respiratory failure were more common in current smokers, there was no significant difference in mortality between ex-smokers, non-smokers, and current smokers. This can be attributed to the fact that systemic steroids were used at a higher rate and for a longer period in current smokers in accordance with Ministry of Health guidelines (21) due to the severity of the clinical status being greater than in other groups in our study. Hence, studies conducted to date have shown that systemic steroids reduce mortality and morbidity in severe COVID-19 patients (22,23). The regression analysis performed in our study also showed that steroid use is one of the treatment methods that affect mortality.

It is noteworthy that some of the studies analyzed by Farsalinos et al., one of the studies advocating that pharmaceutical nicotine should be considered as a potential treatment option in COVID-19 due to its deep-rooted immunomodulatory effects, were supported by companies that promote the use of smokeless tobacco products (24).

CONCLUSION

Given that smoking has adverse effects on lung function and immunity, the finding that it is associated with COVID-19 progression is not surprising (13). Our analysis corroborates that smoking is a risk factor for COVID-19 severity and that smokers suffer from COVID-19 more severely than non-smokers. To reduce COVID-19 mortality rates, which is a global health issue, it is critical to identify patients in high-risk groups and, in particular, to get them to quit smoking.

Limitations

Our study has some limitations. Since our study was conducted during the COVID-19 pandemic, there was a lack of detailed history-taking, so the use of smokeless tobacco products and hookah could not be evaluated. The relationship between smoking and COVID-19 should also be corroborated by studies that will be conducted in larger patient groups, particularly outpatient groups.

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CONFLICT of INTEREST

There is no conflict of interest in our study.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: GDY

Analysis/Interpretation: MYÇ

Data acqusition: DT, HOÇ, BRS, MB, ASÖ, MEN, ŞT, KH

Writing: GDY

Clinical Revision: GU, MŞA

Final Approval: All of authors

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