Smoking and COVID-19

Sigara İçmek ve COVID-19

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RESPIRATORY CASE REPORTS

Abstract

It is known that SARS-CoV-2 affects the respiratory tract and causes pneumonia and respiratory failure in patients. Smoking increases susceptibility to many respiratory diseases, including infections, and affects the prognosis and mortality of these diseases. The increased levels of angiotensin converting enzyme-2, which is a binding receptor for SARS-CoV-2 in the lungs, suggest that smoking has negative effects on patients with COVID-19. In this review, the relationship between smoking and COVID-19 is examined with a review of current literature.

Key words: Smoking, COVID-19, pandemic, pneumonia.

Özet

SARS-CoV-2'nin solunum yollarını etkilediği ve hastalarda pnömoni ve solunum yetmezliğine neden olduğu bilinmektedir. Sigara içmek enfeksiyonlar dahil birçok solunum yolu hastalığına yatkınlığı artırmakta ve bu hastalıkların prognozunu ve ölüm oranını etkilemektedir. Akciğerlerde SARS-CoV-2 için bağlanma yeri olduğu bildirilen anjiyotensin dönüştürücü enzim-2'nin artan seviyeleri, sigaranın COVID-19 hastalığı üzerinde olumsuz etkileri olduğunu düşündürmektedir. Bu derlemede, sigara ve COVID-19 arasındaki ilişki, mevcut literatürle birlikte incelenmiştir.

Anahtar Sözcükler: Sigara içme, COVID-19, pandemi, pnömoni.

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More than 1.4 million people have died due to COVID-19 worldwide since December 2019, when the first case was reported (1). In just 8 months, many scientific articles related to the disease have been published, and the epidemiological, clinical, laboratory and radiological findings of the disease have been described. The disease is known to be transmitted through the respiratory tract, and pneumonia is detected in approximately 5–10% of patients with COVID-19. Those with advanced forms of the disease require intensive care, and patients develop acute respiratory distress syndrome. Mortality is generally related to respiratory failure and the development of sepsis in intensive care (2,3).

Smoking increases the frequency of many malignant and benign lung diseases, and is the most known proven cause of lung cancer (4). In addition, interstitial lung diseases such as idiopathic pulmonary fibrosis, histiocytosis X, desquamative interstitial pneumonia, respiratory bronchiolitis associated interstitial lung disease, and acute eosinophilic pneumonia are more common in smokers (5,6). Epidemiological studies have stated that the risk of upper and lower respiratory tract infections is high in smokers. The proinflammatory properties of smoking are well known, including the increased production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and granulocyte-macrophage colony-stimulating factor (GM-CSF), and an increased the accumulation of immune cells in the airway. Due to the complex nature of the immune system, however, it is difficult to predict the nature of the total immune response to microbial agents, given that non-affected defense mechanisms may compensate for the affected areas (7-9). Smoking also increases the development of tuberculosis.

Altet et al. (10) found that passive smoking, which is correlated also with urine cotinine levels, increased the risk of active tuberculosis by approximately 5 times in a prospective study (11). Since COVID-19 affects primarily the respiratory system, studies tend to focus on chronic respiratory diseases, such as chronic obstructive pulmonary disease (COPD) and smoking in patients with COVID-19. That said, studies comparing smoking rates in patients with COVID-19 have reported different results in terms of those in need of intensive care, and those succumbing to the disease, among others.

In this review, we investigate the different smoking rates of patients treated for COVID-19, and ascertain whether or not the disease is more severe in smokers.

Pathogenesis

Angiotensin converting enzyme 2 (ACE-2) is a type I transmembrane metallocarboxypeptidase that was first identified two decades ago, and breaks down angiotensin II to and angiotensin- (1-7). ACE-2 is present in the respiratory system, heart and gastrointestinal system (12,13). Leung MJ et al. (14) obtained cytological brushing samples from smoking patients, and made COPD diagnoses via a bronchoscopy approach, and also examined the ACE-2 expression in the resected lung tissue. The study included 10 smoking patients with COPD, nine non-smoking controls and eight healthy smokers. The ACE-2 gene was expressed significantly higher in smokers than in non-smokers.

Higher ACE-2 levels in active smokers and in patients with COPD may partially explain the severe COVID-19 increase in this population. Smoking cessation and the close follow-up of these groups are very important in COVID-19 prevention, and early diagnoses are emphasized in this patient group.

SARS-CoV-2 has type-1 transmembrane spike (S) glycoproteins that contains two different functional proteins (S1 and S2) regulating entry into the host cell by the virus. The S1 subunit binds to the ACE-2 receptor (15), and the airway epithelium is the main entry point for COVID-19 into the body. ACE-2 is the experimentally validated SARS-CoV-2 receptor (16). The S protein of SARS-CoV-2 has a significantly higher affinity for ACE-2 and its binding rate is higher than for SARS-CoV (17,18). Type-2 pneumocytes express the ACE-2 protein (19). Since ACE-2 is a binding site for COVID-19, it may be considered a target for therapies to be developed for its treatment.

Cai G et al. (20) reported a 25% increase in pulmonary ACE-2 expression in smokers, which may indicate that smokers are at higher risk of COVID-19 infection than non-smokers. That said, there are also studies making conflicting claims. Changeux JP et al. (21) argued that active smoking may protect against COVID-19, suggesting that the nicotinic acetylcholine receptor (nAChR) plays an important role in the development of COVID-19 infection. According to this hypothesis, the virus enters the body through the olfactory system neurons and/or lungs rather than the ACE-2 receptors in the lungs. nAChR is present in the lung epithelium, and may be the binding receptor in the lungs when the virus enters the body.

Table 1: The studies about Smoking and COVID-19

Study	Study	Study design	Comparison	Smoking Rate	Outcomes
Zhou F, et al. (22)	n: 191 adult inpatients (aged ≥18 years) with laboratory confirmed COVID-19	A retrospective cohort study	Yes	Current smokers: n=11 (6%), • Non-survivors (n: 54): n=5 (9%) • Survivors (n: 137): n=6 (4%) (p=0.21)	54 patients died during hospitalization and 137 were discharged. No statistically significant difference between the smoking rates of survivors and non-survivors (p=0.21) with regard to mortality from COVID-19.
Zhang JJ, et al. (23)	n: 140 hospitalized patients with SARS-CoV-2	A retrospective study	Yes	Non-severe patients: (n=82) • Former smokers: n=3 (3.7%) • Current smokers: n=0 Severe patients: (n=58) • Former smokers: n=4 (6.9%) • Current smokers: n=2 (3.4%) (p= 0.448 and 0,170)	Low prevalence of smokers and no allergic diseases despite of drug hypersensitivity and urticaria was self-reported by any patients, indicating that allergic diseases and smoking history may not be the susceptible factors for COVID-19
Huang C, et al. (24)	n: 41 Laboratory confirmed 2019-nCoV patients, n:13 needed to be admitted to the ICU	A prospective study	Yes	Current smokers: n=3 • ICU care (n:13): n=0 • Non-ICU care (n: 28): n=3 (11%) Current smokers in ICU care vs non-ICU care patients (p=0.31)	28 (68%) of 41 patients were discharged and 6 (15%) patients died.
Guan WJ, et al. (25)	n:1099 Patients with Laboratory confirmed COVID-19	A retrospective study	No	Severe cases (n:173) • 16.9% current smokers • 5.2% former smokers • 77.9% never smokers Non-severe cases (N:926) • 11.8% current smokers • 1.3% former smokers • 86.9% never smokers Needed mechanical ventilation, ICU or died • 25.8% current smokers • 7.6% former smokers • 66.7% non-smokers No mechanical ventilation, ICU or death • 11.8% current smokers • 1.6% former smokers • 86.7% never smokers	No statistical analysis for evaluating the association between the severity of the disease outcome and smoking status was conducted.
Liu W, et al. (26)	n: 78 Patients tested positive for COVID-19	A retrospective multicenter cohort study	Yes	Progression Group (n:11) • n:3 (27.3%) smokers Improvement/stabilization group (N:67) • n:2 (3 %) smokers	Progression group • n: 11 (14.1%) Improvement/stabilization group • n: 67 (85.9%)

				Multivariate logistic regression analysis indicated that the history of smoking was a risk factor of disease progression (OR=14.285; 95% CI: 1.577–25.000; p= 0.018)	Several factors that led to the progression of COVID-19 pneumonia were identified, including age, history of smoking, maximum body temperature at admission, respiratory failure, albumin, C-reactive protein.
Yang X, et al. (27)	n: 52 critically ill adult patients with SARS-CoV-2 pneumonia who were admitted to ICU	A single centered, retrospective, observational study	No	Smoking: • Survivors (n: 20): N: 2 (10%) • Non-survivors (n: 32): n: 0 • All patients: n: 2 (4%)	Compared with survivors, non-survivors were older (64·6 years vs 51·9 years), more likely to develop ARDS (26 [81%] patients vs 9 [45%] patients), and more likely to receive mechanical ventilation (30 [94%] patients vs 7 [35%] patients), either invasively or non-invasively. Most patients had organ function damage, including 35 (67%) with ARDS, 15 (29%) with acute kidney injury, 12 (23%) with cardiac injury, 15 (29%) with liver dysfunction, and one (2%) with pneumothorax. 37 (71%) patients required mechanical ventilation. Hospital-acquired infection occurred in seven (13·5%) patients
Guan WJ, et al. (28)	n: 1590 laboratory confirmed hospitalized patients with COVID-19	A retrospective case study	No	Former/current smokers: • Total: n: 111 (7%) • No comorbidity: n: 64 (5.4%) • Having comorbidity: n: 47 (11.8%)	After adjusting for age and smoking status, patients with COPD (HR 2.68, 95%CI 1.42-5.05), diabetes (HR 1.59, 95%CI 1.03-2.45), hypertension (HR 1.58, 95%CI 1.07-2.32) and malignancy (HR 3.50, 95%CI 1.60-7.64) were more likely to reach to the composite endpoints than those without.
Wang R, et al. (29)	n: 125 hospitalized patients with COVID-19	A retrospective descriptive study	Yes	n: 16 (12.8%) of them have a history of smoking. • Critical patients (n: 25): 7 (28%) • Non-critical patients (n: 100): 9 (9%) P value: 0.027	Old age, chronic underlying diseases and smoking history may be risk factors to worse condition.
Miyara M, et al. (30)	n: 482 COVID-19 patients (n: 139 outpatients and n: 343 inpatients)	A cross-sectional survey	Yes	Inpatient group: • Rate of daily smoking: 4.4% (5.4% of men and 2.9% of women) Outpatient group: • Rate of daily smoking: 5.3% (5.1% of men and 5.5% of women) The daily smokers rate in French population: 25.4% The rate of current daily smokers was significantly lower in COVID-19 outpatients and inpatients (80.3% and 75.4%, respectively), as compared to that in the French general population with standardized incidence ratios according to sex and age of 0.197 [0.094- 0.41] and 0.246 [0.148-0.408]. These ratios did not significantly differ between the two groups (P=0.63).	The study highlights for the first time a dramatic decreased prevalence of daily current smokers both in COVID-19 outpatients and inpatients as compared to the general population.

ICU; Intensive care unit

Scientific Articles

Most scientific articles investigating the associations between smoking and COVID-19 are of Chinese origin, with fewer studies from other countries. The clinical course and risk factors related to mortality in hospitalized adult patients with COVID-19 were examined in a retrospective multicenter cohort study by Zhou F et al. (22) (Table 1). Of the 191 patients included in the study, 137 recovered and 54 died while hospitalized, with smoking rates of 4% (n = 6) and 9% (n = 5), respectively, but the difference was not statistically significant (p = 0.21). Smoking was not found to be statistically associated with mortality in a univariate analysis (Odds ratio (OR) = 2.23, 95% Confidence interval (CI): 0.65-7.63, p = 0.20), although only a small number of patients were enrolled in the study.

Zhang JJ et al. (23) made a retrospective analysis of the clinical features of 140 patients hospitalized with COVID-19. Severe COVID-19 was defined based on the presence of such criteria as respiratory rate ≥30/min, resting SpO_2 ≤93% or oxygenation index (PaO_2/FiO_2) ≤300 mmHg in room air.

Only nine of the 140 patients were smokers, including both active and former smokers, of which seven quit smoking and two were current smokers. While four (6.9%) of the seven patients who quit smoking were diagnosed with severe COVID-19, severe COVID-19 was diagnosed in only two patients (3.4%) who were current smokers. The study found that smoking was not related with COVID-19 severity (p = 0.448 and p = 0.170). In addition, when patients with a smoking index (daily number of cigarettes smoked × year) of <400 and those with ≥ 400 were compared, no significant difference was noted between the cumulative effect of smoking and the severity of the disease (p> 0.999). In the present study, it was found that although it seemed that smokers were less susceptible to COVID-19, the values did not reach a statistically significant level, and COVID-19 may be more severe in smokers (23).

The clinical features of 41 patients who were hospitalized with COVID-19 were prospectively investigated by Huang C et al. (24) in two groups, being those treated in the intensive care unit (ICU) (n = 13) and those who were not treated in the ICU (n = 28), and the clinical parameters of the two groups were compared. Active smoking was identified in 0% of those treated in the ICU and in 11% (n = 3) in those treated in the clinic, with no statistically significant difference (p = 0.31). In total, 68 percent (28/41) of the patients recovered and 15 percent (6/41)

died. Due to the limited number of smoking patients, no conclusion was made suggesting a link between smoking and the need for ICU admission.

Guan WJ et al. (25) made a retrospective analysis of the clinical characteristics of 1,099 patients, including both inpatients and outpatients, being treated for COVID-19. The primary endpoints of the study were ICU need, invasive mechanical ventilation use or death. At the time of hospital admission, 926 of the patients were determined as non-severe and 173 as severe COVID-19. The rate of patients with primary endpoints was 6.1% (n = 67). Under the never smoker, former smoker and current smoker classifications, smoking rates were 86.9% (793/913), 1.3% (12/913) and 11.8% (108/913) respectively in non-severe COVID-19 patients; 77.9% (134/172), 5.2% (9/172) and 16.9% (29/172) in patients with severe forms of the disease; and 66.7% (44/66), 7.6% (5/66) and 25.8% (17/66) in those with primary endpoints and 86.7% (883/1019), 1.6% (16/1019) and 11.8% (120/1019) in those without primary endpoints, respectively. No statistical comparison was made of the groups in the study, although the rate of smoking (previous or active) was noted to be higher in those with severe COVID-19. In addition, the rate of smoking (previous or active) was also higher in patients with a primary endpoint, including the need intensive care, mechanical ventilation or death. This study suggests that smoking patients may be more susceptible to severe COVID-19.

The factors associated with the course of COVID-19 in 78 patients treated in hospital were examined in the multicenter retrospective cohort study conducted by Liu W et al. (26). Possible factors causing the worsening of COVID-19 pneumonia were investigated in the progression (n = 11) and recovery/stabilization (n = 67) groups in the study. A history of smoking was identified in 27.3% (n = 3) of the progression group and in 3% (n = 2) of the recovery/stabilization group, with similar results in the two groups (p = 0.018). Smoking was found to be a risk factor for COVID-19 progression in a multivariate logistic regression analysis (OR = 14.285; 95% CI: 1.577–25.000; p = 0.018), and it was further concluded that older age, higher body temperature, presence of respiratory failure at presentation, lower serum albumin and higher C-reactive protein levels were risk factors for COVID-19 pneumonia progression.

Yang et al. (27) investigated the clinical course and outcomes of 52 critically ill patients with COVID-19 pneumonia in a single-center, retrospective observational study, in which critically ill patients were defined as those

who were mechanically ventilated in the ICU or who needed oxygen supplementation of $FiO_2 \geqslant 60$ %. The primary outcomes of the study were the 28-day mortality rates after admission to the ICU, and the secondary outcomes were the incidence of patients with COVID-19 and acute respiratory distress syndrome (ARDS), and the ratio of patients requiring mechanical ventilation. Analysis included two groups, being survivors (n = 20) and non-survivors (n = 32). Smoking was identified in 10% (n = 2) of the survivors and in 0% of those who died. No statistical comparison was made related to smoking, as the authors believed a meaningful interpretation may would not be possible due to the low number of cases and the low number of smoking patients.

Comorbidities and their effects on the disease were retrospectively analyzed by Guan et al. (28) in a study of 1,590 patients with COVID-19. The primary composite endpoints were admission to ICU and the need for invasive mechanical ventilation or mortality, with the risk of each compared in terms of the number or presence of comorbidities. The total smoking rate (former/current) in the study was 7% (111/1,590), and the smoking rate (previous/active) was 5.4% (n = 64/1,191) in those without comorbidities (previous/active) and 11.8% (n = 47/399) in those with comorbidities. It is known that age and smoking are risk factors for comorbidities even in the general population, and so it was suggested in this study that the presence of COPD, diabetes mellitus, hypertension and malignancy may cause a poor prognosis after adjusting for age and smoking in a hazard regression model. In this study, it did not seem possible to establish a relationship between smoking and the course of COVID-19.

Wang et al. (29) made a retrospective analysis of the clinical and epidemiological characteristics of 125 patients hospitalized with COVID-19. Among the 25 critically ill patients, the rate of active smoking was 28% (n = 7), and the rate of active smoking in non-critical patients was 9% (n = 9), and the difference was statistically significant (p = 0.027). The authors concluded that older age, the presence of an underlying disease and smoking may be risk factors for a worsening course of COVID-19.

Miyara et al. (30) made a cross-sectional investigation of the relationship between smoking and susceptibility to COVID-19 in symptomatic patients treated for COVID-19 either as inpatients (n = 343) or outpatients (n = 139). The smoking rate was 4.4% among the inpatients (5.4% in males; 2.9% in females) and 5.3% among the outpatients (5.1% in males; 5.5% in females). While the mean smoking rate was 25.4% (28.2% for males; 22.9% for females) in the French population, the smoking rates were similar between the outpatients and inpatients. It was concluded in the study that the contribution of daily smoking to the risk of development of symptomatic COVID-19 was very low when compared to the general population, although such a stated finding may be inappropriate due to the small sample size. Furthermore, the criteria for hospitalization/outpatient treatment were not clearly stated in the study, with groups established based on such subjective criteria as severe/non-severe symptoms, and so it would not really be appropriate to speak of a link between smoking and disease severity of the disease based on the available data.

There have been three systematic reviews and/or meta-analyses related to smoking and COVID-19. Zhao et al. (31) examined the effect of smoking and COPD on the severity of COVID-19, involving 11 case series in their review, and reported a pooled odds ratio of 4.38 (95% CI: 2.34-8.20) for COPD and 1.98 (95% CI: 1.29–3.05) for smoking for severe COVID-19 development. One study in particular affected the results, and it was reported that smoking history was not associated with COVID-19 severity in a subgroup analysis after this study was excluded. The reasons for this were interpreted as the exclusion of the study, which involved a large number of patients, and the lack of discrimination made between active and former smokers in other studies. It has been stated that a history of COPD and smoking contributes to the progression and worsening of COVID-19 (31).

Vardavas et al. (32) carried out a systematic review of smoking and COVID-19 in their analysis of five studies, and found the symptoms of severe COVID-19 to be 1.4-times greater (Relative risk (RR) = 1.4, 95% CI: 0.98–2.00) and the need for ICU and mechanical ventilation or mortality to be 2.4-times greater (RR = 2.4, 95% CI: 1.43–4.04) in smokers than in non-smokers. The authors concluded that smoking may be associated with COVID-19 severity and adverse outcomes.

Comorbidities in inpatients with COVID-19 were investigated by Emami et al. (33) in a meta-analysis of 10 previous studies. The prevalence of smoking was calculated as 7.63% of patients, while hypertension, cardiovascular diseases, diabetes mellitus, COPD, malignancy and chronic kidney disease were identified the most common comorbid diseases. The authors made no comment on the relationship between COVID-19 severity and smoking, but said that patients with underlying diseases were common among those with COVID-19, and such people

should avoid close contact with other members of the community.

CONCLUSION

Smoking may affect the risk of contracting COVID-19, and may also influence the severity and mortality associated with the disease. Different results have been reported in studies examining smoking and COVID-19 that may be attributable to the relatively low number of COVID-19 cases and smokers in the studies. Furthermore, the workload of health systems during the COVID-19 pandemic, deficiencies in the registration system and the retrospective nature of the studies may also influence the findings. In conclusion, smoking increases the severity and mortality of COVID-19, especially in hospitalized patients, and so during the ongoing COVID-19 pandemic in particular, more attention should be paid to smoking cessation approaches, and patients should advised accordingly.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - K.C., T.C., Z.K.; Planning and Design - K.C., T.C., Z.K.; Supervision - K.C., T.C., Z.K.; Funding - K.C., T.C., Z.K.; Materials - T.C., K.C.; Data Collection and/or Processing - T.C., K.C.; Analysis and/or Interpretation - K.C., T.C., Z.K.; Literature Review - K.C., T.C., Z.K.; Writing - K.C., T.C., Z.K.; Critical Review - T.C., Z.K.

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