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Association of Smoking Status with Outcomes in Intensive Care Unit with COVID-19

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Abstract

Aim: The effect of smoking on patients hospitalized in the intensive care unit (ICU) due to Coronavirus disease-2019 (COVID-19) infection is unknown. The study determines the relationship between COVID-19 and smoking status on the development of disease and critical illness.

Materials and Methods: The patient files and hospital information system records of COVID-19 patients over the age of eighteen who were hospitalized in the ICU of our hospital between March 2020 and January 2021 and confirmed by polymerase chain reaction method were retrospectively reviewed.

Results: 1.003 of 226 COVID-19 patients included in the study, 58% were male, and the mean age was 65.38 (±14.99). The patients' smoking status was categorized as non-smokers, ex-smokers, and current daily smokers (74.8%; 23%; 2.2%; respectively). The most common comorbid disease of the patients was hypertension (58%). One hundred seventy-nine patients were given respiratory support with invasive mechanical ventilation (IMV), and 37.2% were discharged. The mean duration of IMV application, hospitalization, and hospitalization in the ICU was 7.11 (±5.51); 14.42 (±10.25), respectively; it was 7.58 (±6.29) days. The average APACHE-II score was 23.87±8.86. Mortality was statistically significantly higher in those who received mechanical ventilator support from patients with no smoker stage and without the comorbid disease (p=0.009).

Conclusion: Although the percentage of current smokers in patients hospitalized in the ICU due to COVID-19 is relatively low, we believe that polygenetic and multiple factors can explain it. It should not be recommended that tobacco products be administered for either preventive or therapeutic purposes in the case of COVID-19 infection.

Keywords: COVID-19, critical care, hospitalization, public health, smoking

Introduction

According to the weekly report of the World Health Organization (WHO) dated February 13, 2021, over 174 million confirmed cases and more than 3.7 million deaths had been reported since the start of the Coronavirus disease-2019 (COVID-19) (1). The first documented COVID-19 in Turkey was reported from İstanbul on March 11, 2020. Since this date, a total of over 9.136.565 cases and more than 80 thousand deaths have been observed (2). From the beginning of the pandemic to the present, the "pandemic management guideline" were updated periodically by the scientific board of the Turkish Ministry of Health for health professionals. The severity and course of the disease are affected depending on the characteristics of the patient, such as advanced age, male gender, underlying conditions such as cancer, chronic renal failure, chronic obstructive pulmonary diseases, coronary artery disease, immunodeficiency status (3,4). To avoid smoking-related diseases, it is advised to quit or not to start if one has never used it or stopped and seek behavioral and pharmacological treatment if necessary (5,6). Unfortunately, the rate of smoking in Turkey is quite high compared to many developed countries such as European countries. According to 2019 Turkish Statistical Institute data, when tobacco users were examined by age groups, the highest rate was 42.8% in the 35-44 age group, while the daily smoker rate among aged 15 and over was 18.4% in the European population (7,8). In fact, in countries such as South

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Africa and India, cigarette sales are prohibited during curfews (6). According to WHO's report on the global tobacco epidemic, 2019: with WHO's MPOWER (**M**onitor tobacco use and prevent on policies, **P**rotect people from tobacco use, **O**ffer help to quit tobacco use, **W**arn about the dangers of tobacco, **E**nforce bans on tobacco advertsing, promotion and sponsorship, **R**aise taxes on tobacco) campaign, which started in 2003 for protecting people from tobacco smoke, between 2007 and 2017, smoking rates decreased from a global average of 22.5% to 19.2%, showing a relative reduction of 15% over ten years (9). Although there are studies on the smoking relationship of COVID-19 infection, there is not enough data on this subject. A review study found that smoking does not carry a risk in terms of disease but takes a chance in serious illness, mechanical ventilation, and death (10). In some studies, it has been shown that there is no significant relationship between active smoking and severe disease in COVID-19 patients (11). Therefore, a definite conclusion could not be formed in the literature.

In this study, we tried showing the relationship between COVID-19 and the smoking status of 226 critically hospitalized patients due to COVID-19 infection in the intensive care unit (ICU). The state of being infected with COVID-19 and its effect on developing critical illness contributed to the literature.

Materials and Methods

Study Design and Patient Characteristics

The ethics committee has approved the study by University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital (file number: 2021/22, date: 11.03.2021). The patient files and hospital information system records of COVID-19 patients over the age of 18 who were hospitalized in the ICU of our hospital between March 2020 and January 2021 and confirmed by polymerase chain reaction (PCR) method were retrospectively reviewed.

Infection of COVID-19 is confirmed using PCR testing from nasal or endotracheal aspirate from patients with typical viral pneumonia (ground-glass opacities, air space consolidation, bronchovascular thickening in the lesion, traction bronchiectasis). Additionally, patients with signs of consolidation or infiltration that are not specific to viral pneumonia have been examined.

It is used to express cigarettes, fabricated and rolled tobacco, or tobacco products such as cigars, hookah, pipes. The patients' smoking status was divided into three categories as non-smokers, ex-smokers, and current daily smokers. Patients who have never smoked in their lives are named non-smokers. Current daily smokers are the ones who consume cigarettes daily and whose cigarettes vary depending on the day. Finally, ex-smokers are the ones who smoked in varying amounts regularly or quit smoking intermittently rather than every day.

In addition to smoking status, demographic pieces of information, other diseases, presence of invasive and non-invasive mechanical ventilation (NIMV), length of stay in an ICU, total hospital stay, outcomes, and estimated mortality risks calculated by APACHE II score (Acute Physiology and Chronic Health Evaluation) (10) of the patients were recorded. APACHE II score system includes a 12-point acute physiology score (including temperature, heart rate, respiratory rate, mean arterial pressure, oxygen partial pressure, Ph, K+, Na+, creatinine, hematocrit, white blood cell counts, and Glasgow coma scale), Age, and chronic health evaluation.

Within the scope of the study, 1.003 COVID-19 patients whose clinical or chest computed tomography findings were hospitalized in the ICU were examined. Two hundred-sixty of these patients whose clinical and chest computed tomography findings were thought to be compatible with COVID-19 were included in the study because to the data were complete. Of these patients, 229 had a positive PCR test, and 31 had a negative PCR test. Three of the patients with positive PCR tests were excluded from the study due to a lack of data. And 226 patients were included in the study. Flowchart of patient selection is as follows (Figure 1):

Selection of Participants:

Inclusion criteria of the study;

- >18 years old.

Patient with respiratory failure in ICU needing NIMV or invasive mechanical ventilator (IMV).

- Patient with a COVID-19 PCR test (+).

Exclusion criteria of the study;

- <18 years old.
- Pregnancy.
- The patient was followed up outside the covid ICU.
- Patient with missing or insufficient hospital data.

Statistical Analysis

The conformity of the numerical variables to the normal distribution was tested with the Shapiro-Wilk test. Student's t-test was used to compare normally distributed variables in the two groups. The Mann-Whitney U test was used to compare non-normally distributed variables in the two groups. Relationships between categorical variables were tested with the chi-square test. The ROC curve was used to determine the cut points for

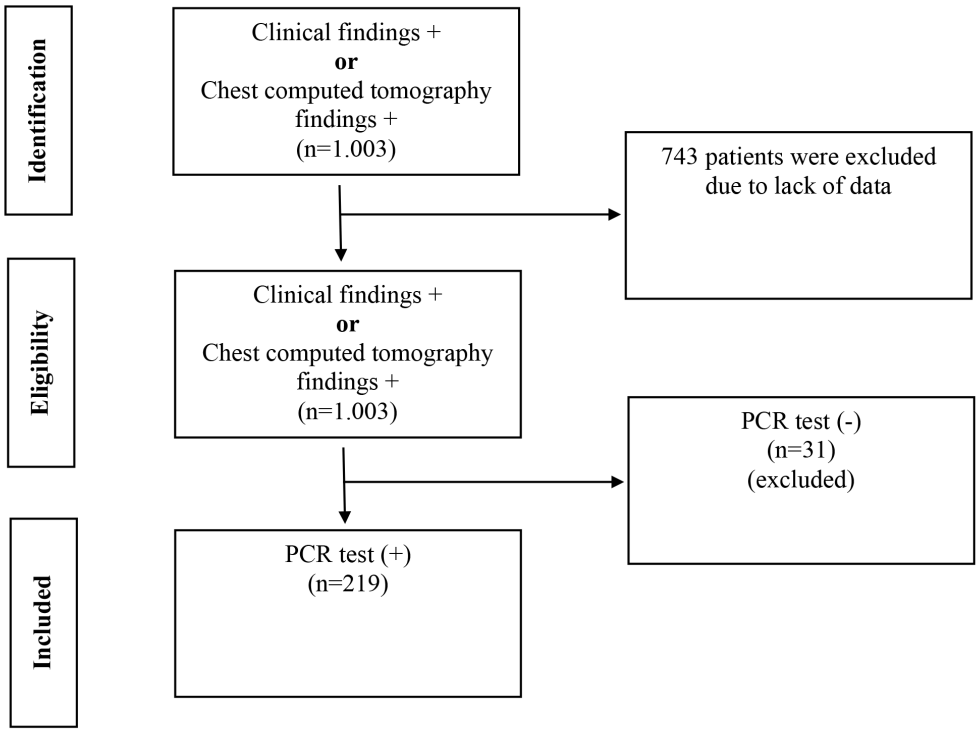

Figure 1. Flow chart of patient selection
PCR: Polymerase chain reaction

the APACHE score. The Statistical Package for the Social Sciences 22.0 Windows version package program was used in the analysis. P<0.05 was considered significant.

Results

Two hundred twenty-six patients were included in the study, 58% of these patients were male, and the mean age was 65.38 (±14.99). 74.8% of them were non-smokers, 23% of them were ex-smokers, and interestingly, at least 2.2% of them were current daily smokers. The most common comorbid disease of the patients was hypertension (58%). One hundred seventy-nine patients were given respiratory support with IMV, and 37.2% were discharged (Table 1).

While the mean duration of IMV application of the patients was 7.11 (±5.51) days, the mean duration of NIMV application was found to be 2.91 (±3.28) days. The mean hospital and ICU length of stay of the patients were 14.42 (±10.25), respectively; it was 7.58 (±6.29). The mean APACHE II score was 23.87±8.86 (Table 2).

The discrimination of the APACHE II score for mortality status was found to be good [AUC=0.870±0.023, (p<0.001)]. If the APACHE II score is above 23, sensitivity is 68.31% [95% confidence

Table 1. Baseline characteristics of patients infected with COVID-19

Baseline characteristics		**n (%)**
Gender	Male	131 (58)
	Female	95 (42)
Smoking status	Daily current smokers	5 (2.2)
	Not-smokers ever	169 (74.8)
	Ex-smokers	52 (23)
Comorbidity		
COPD		34 (15)
HT		131 (58)
DM		78 (34.5)
CHF		59 (26.1)
Malignancy		20 (8.8)
NIMV		79 (35)
IMV		179 (79.2)
Outcome	Survivor	84 (37.2)
	Non-survivor	142 (62.8)

COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CHF: Chronic heart failure, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation, COVID-19: Coronavirus disease-2019

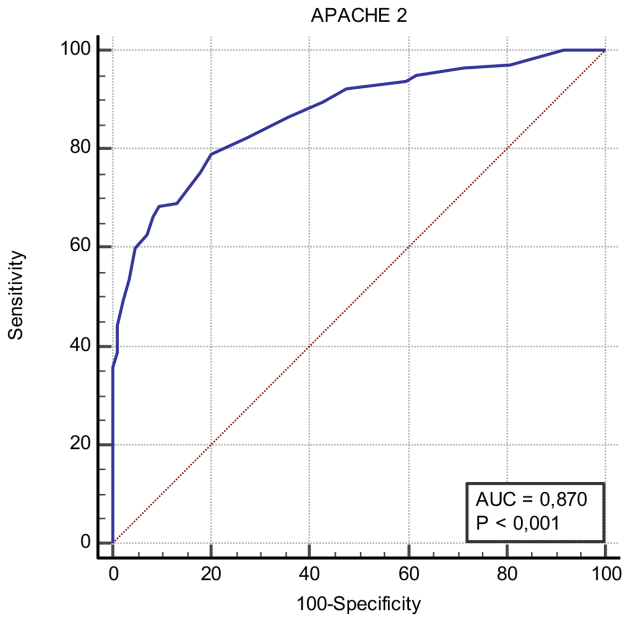

Figure 2. Receiver operating characteristic curves for predicting mortality based on APACHE II score for patients infected with COVID-19

COVID-19: Coronavirus disease-2019

interval (CI)=60.0-75.9], specificity 90.48% (95% CI=82.1-95,8) to distinguish patients with mortality (Figure 2). We found that the mean APACHE II score of the patients who died was significantly higher than the patients who survived.

The mean age of the patients who died (68.86±12.63 years) was significantly higher than those who survived (p=0.001). No significant relationship was found between the gender and smoking status of the patients and mortality (p=0.520, p=0.619; respectively). The mortality rate of patients with chronic disease and hypertension from these diseases was higher than the others, and this rate was statistically significant (p=0.023, p=0.007; respectively).

We observed that patients who underwent IMV were significantly more mortal (p=0.001) (Table 3).

When the relationship between survival and mortality of the patients who underwent mechanical ventilation was evaluated according to comorbidity status, it was determined that all the patients with comorbidities who were not mechanically ventilated survived, and mortality developed in only a patient who had no comorbidity and were not mechanically ventilated (p=0.001; 0.004; respectively) (Table 4).

When the relationship between survival and mortality in mechanically ventilated patients was examined based on smoking and comorbidity status, mortality was significantly higher in those who received mechanical ventilator support from ex-smokers and non-smoker stage patients with comorbidity (p=0.001). While there was no statistically significant difference in mortality between ex-smokers and non-comorbid patients who received mechanical ventilation support versus those who did not (p=0.410), mortality was statistically significantly higher in those who received mechanical ventilation support from patients who were non-smokers and did not have a comorbidity (p=0.009) (Table 5). This table was not subjected to statistical analysis due to the small number of active smokers.

Discussion

In this retrospective study, 226 patients hospitalized in the ICU were examined. Male gender and advanced age (>65) are most frequently associated with mortality and severity of the disease, according to an analysis of a large amount of data obtained at the beginning of the pandemic. The presence of comorbidities (hypertension, diabetes, etc.) in the patient also contributes (5,11,12). In our study, we observed that male gender and advanced age were correlated with the severity of the disease course, following the literature, hypertension was the most common chronic disease among the patients, and this was significantly higher in cases with a mortal approach. Studies suggest that malignancy, a comorbidity, is more susceptible to

Table 2. Descriptive statistics for numeric variables

Descriptive statistics	n	Mean±SD	Median (min-max)
Age	226	65.38±14.99	66 (18-96)
Duration of IMV (days)	164	7.11±5.51	6 (1-30)
Duration of NIMV (days)	79	2.91±3.28	1 (1-18)
Length of stay in the hospital (days)	226	14.42±10.25	12 (1-59)
Length of stay in the ICU (days)	226	7.58±6.29	6 (1-32)
APACHE II score	226	23.87±8.86	22 (5-55)

*A p-value less than 0.05 (typically ≤0.05) is statistically significant, Mann-Whitney U test.
Min-max: Minimum-maximum, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, ICU: Intensive care unit, SD: Standard deviation

Table 3. Relationship between variables and mortality

Variables		Non-survivor	Survivor	
		n (%)	n (%)	p
Gender	Male	80 (56.7)	51 (60.7)	0.520
	Female	62 (43.7)	33 (39.3)	
Smoking status	Not-smokers ever	104 (73.2)	65 (77.4)	0.619
	Ex-smokers	34 (23.9)	18 (21.4)	
	Daily current smokers	4 (2.8)	1 (1.2)	
Comorbidity	No	24 (16.9)	25 (29.8)	0.023*
	Yes	118 (83.1)	59 (70.2)	
COPD	No	118 (83.1)	74 (88.1)	0.310
	Yes	24 (16.9)	10 (11.9)	
HT	No	50 (35.2)	45 (53.6)	0.007*
	Yes	92 (64.8)	39 (46.4)	
DM	No	89 (62.7)	59 (70.2)	0.248
	Yes	53 (37.3)	25 (29.8)	
CHF	No	99 (69.7)	68 (81)	0.063
	Yes	43 (30.3)	16 (19)	
Malignancy	No	132 (93)	74 (88.1)	0.214
	Yes	10 (7)	10 (11.9)	
NIMV	Not receiving	96 (67.6)	51 (60.7)	0.294
	Receiving	46 (32.4)	33 (39.3)	
IMV	Not receiving	1 (0.7)	46 (54.8)	0.001*
	Receiving	141 (99.3)	38 (45.2)	
Mechanical ventilation	Not receiving	1 (0.7)	39 (46.4)	0.001*
	Receiving	141 (99.3)	45 (53.6)	

*A p-value less than 0.05 is statistically significant, chi-square test.
COPD: Chronic obstructive lung disease, HT: Hypertension, DM: Diabetes mellitus, CHF: Chronic heart failure, NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

Table 4. The relationship of mechanical ventilated patients with survival and mortality by comorbidity status

				Non-survivor	Survivor	
				n (%)	n (%)	p
Comorbidity	Yes	NIMV	Yes	35 (29.9)	21 (35.6)	0.445
			No	82 (70.1)	38 (64.4)	
		IMV	Yes	117 (100)	28 (47.5)	0.001*
			No	0 (0)	31 (52.5)	
		Mechanical ventilation	Received	117 (100)	30 (50.8)	0.001*
			Not received	0 (0)	29 (49.2)	
	No	NIMV	Yes	10 (47.6)	11 (45.8)	0.905
			No	11 (52.4)	13 (54.2)	
		IMV	Yes	20 (95.2)	10 (41.7)	0.001*
			No	1 (4.8)	14 (58.3)	
		Mechanical ventilation	Received	20 (95.2)	14 (58.3)	0.004*
			Not received	1 (4.8)	10 (41.7)	

*A p-value less than 0.05 (typically ≤0.05) is statistically significant, chi-square test.
NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

Table 5. The relationship of mechanical ventilated patients with survival and mortality by smoking and comorbidity status

						Non-survivor	Survivor	
						n (%)	n (%)	p
Smoking status	Ex-smokers	Comorbidity	Yes	NIMV	Yes	7 (21.2)	6 (40)	0.293
					No	26 (78.8)	9 (60)	
				IMV	Yes	33 (100)	7 (46.7)	0.001*
					No	0 (0)	8 (53.3)	
				Mechanical ventilation	Received	33 (100)	9 (60)	0.001*
					Not received	0 (0)	6 (40)	
			No	NIMV	Yes	0 (0)	1 (33.3)	0.410
					No	1 (100)	2 (66.7)	
				IMV	Yes	1 (100)	2 (66.7)	0.410
					No	0 (0)	1 (33.3)	
				Mechanical ventilation	Received	1 (100)	2 (66.7)	0.410
					Not received	0 (0)	1 (33.3)	
	Not-smokers ever	Comorbidity	Yes	NIMV	Yes	28 (33.3)	15 (34.1)	0.931
					No	56 (66.7)	29 (65.9)	
				IMV	Yes	84 (100)	21 (47.7)	0.001*
					No	0 (0)	23 (52.3)	
				Mechanical ventilation	Received	84 (100)	21 (47.7)	0.001*
					Not received	0 (0)	23 (52.3)	
			No	NIMV	Yes	10 (50)	10 (47.6)	0.879
					No	10 (50)	11 (52.4)	
				IMV	Yes	19 (95)	8 (38.1)	0.001*
					No	1 (5)	13 (61.9)	
				Mechanical ventilation	Received	19 (95)	12 (57.1)	0.009*
					Not received	1 (5)	9 (42.9)	

*Significant at the $p<0.05$ level. Chi-square test.
NIMV: Non-invasive mechanical ventilation, IMV: Invasive mechanical ventilation

severe acute respiratory syndrome infection and complications such as ICU admission, the need for IMV and mortality. In the study of Moiseev et al. (13), it was stated that a relationship between malignancy and COVID-19 was proven to be insufficient compared to the available data. In our study, we found that the mortality rate of patients with malignancy was 50%. Still, we believe that mortality may be affected not only by the malignancy but also by other diseases, the patient's general condition, lung capacity, and cancer stage. In conclusion, malignancy was not a significant factor in COVID-19 infection-related survival in our study.

Although there were many scientific studies during the pandemic, a clear and single parameter is showing the course of the disease could not be obtained. The APACHE II score is frequently used in studies because of its ability to distinguish clinical severity. It can not only predict mortality but also assist the clinician in airway management decisions. In patients treated in the ICU for COVID-19, Cheng et al. (14) found high-flow oxygen inhalation with an APACHE II score of 9.5, NIMV support with a score of 9.5-12, and invasive ventilator support with a score of >12.5 can be considered. If this score was >11.5, the patient would be at a risk of death. Because of the study, it was stated that it is an effective indicator in the estimation of disease severity and mortality. In some studies, the median mean of the APACHE II score in COVID-19 patients hospitalized in the ICU is 17 and differs between patients who died and lived with serious illness (15). As in other studies, the APACHE II score average of patients who died in our study was significantly higher than that of surviving patients. The APACHE II (median mean 22) value is significant in terms of mortality discrimination.

Patients with severe COVID-19 infection generally need mechanical ventilators, and the mortality rate is high in these

patients who are followed up under ICU conditions (16-19). Our study observed that the mortality of patients who did not undergo mechanical ventilation was significantly lower when both comorbidity and smoking status of the patients were considered, which is consistent with the literature.

Smoking is an essential factor in cardiovascular and lung diseases. It shows its effect through nicotinic receptors overexpressed in heart tissue, blood vessels, and lung cells (20,21). Nicotinic receptors activated by this effect of smoking increase protease activation, apoptosis, and inflammatory response. According to studies, the COVID-19 virus exerts its influence through a similar receptor. Of course, the impact of cigarettes depends on the nicotic receptor and shows the effect of many toxins such as carbon monoxide and polycyclic aromatic hydrocarbons. It is thought that smoking affects the outcome of patients infected with COVID-19 for such reasons (22).

A meta-analysis examining the prevalence of smoking in hospitalized COVID-19 patients in China shows that current smoking is not a predisposing factor for hospitalization for COVID-19 (23). In the report of the US CDC consisting of 7.162 COVID-19 cases from the first months of the pandemic, the current smoker rate of patients was reported as 1.3% and the ex-smoker rate as 2.3% (24). In another study conducted in China in 2019, the characteristics of patients with COVID-19 infection were examined. It was determined that 85.4% of the patients and 77.9% of those who had severe illnesses were never smokers (25). In the study of Petrilli et al. (19), it was not determined that tobacco use was associated with an increased risk of hospitalization or critical illness, and it was even observed that it was protective in terms of hospitalization. Ho et al. (26), on the other hand, found that it is not associated with in-hospital mortality due to COVID-19 pneumonia.

Contrary to these studies, other studies show that the severity of COVID-19, in-hospital mortality rate, and the need for mechanical ventilation increase, especially in patients with a smoking history (27-29). According to the study results, the rate of the current daily smokers was 2.2%, and the rate of ex-smokers was 23%. Notably our ICU patients mainly consist of non-smokers, and ex-smokers. Although there was no significant difference in the mortality rate in our study, the development of mortality in 80% of active smokers (4 of five patients) may lead us to investigate the factors that prevent the patient from becoming infected. Still, we can conclude that it can significantly increase mortality after infection.

However, smokers generally have an increased risk of comorbidities, particularly cardiovascular and chronic respiratory diseases. Therefore, it is an expected result that the risk of hospitalization due to COVID-19 is higher in people with smoking-related comorbidity than in healthy smokers. Apart from these effects, we believe that polygenetic factors have an impact. There is still no conclusive evidence for the effect of smoking on the disease and severity of COVID-19.

Study Limitations

- There is a possibility that some patients who describe themselves as ex-smokers have quit smoking because they have the disease or shortly before the illness. Because of this, the duration of smoking cessation in some patients could not be evaluated objectively.

- Due to the low rate of current smokers included in the study, comparison between ex-smokers and non-smokers could not be made sufficiently.

- Only patients hospitalized in the ICU of a city hospital were included in the study population.

- The study was conducted retrospectively. Patient data were obtained from hospital medical data. Therefore, detailed medical records could not be reached.

Conclusion

It is seen that the percentage of current smokers in patients hospitalized in ICU due to COVID-19 during the pandemic period in societies with high smoking rates, such as Turkey and China is relatively low. Although it is impossible to express this situation with a single factor, we think it is possible to explain it due to polygenetic and multifactorial reasons. Because of our study, although the percentage of current smokers is determined to be low, it should not be defended that tobacco products are given neither for protection nor for treatment against COVID-19 infection.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Kocaeli Derince Training and Research Hospital of Local Ethics Committee (file number: 2021/22, date: 11.03.2021).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: D.H., Concept: M.S., Design: M.S., Data Collection or Processing: D.H., Analysis, or Interpretation: D.H., M.S., Literature Search: M.S., Writing: D.H., M.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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