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Intensive care unit: mortality score in early prediction of mortality in critical COVID-19 patients

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ABSTRACT

Aims: The mortality data available in the literature with regard to patients with SARS-COV-2, thus requiring hospitalization in the intensive care unit (ICU) are not sufficient. This research aims to compare the correlation between COVID-19 mortality ratios (CMR), AST/ALT and neutrophil/lymphocyte (N/L) ratios of non-smoker COVID-19 patients hospitalized in the ICU and their mortality rates.

Methods: This cross-sectional study was conducted on 77 patients hospitalized in the ICU. Female participants constituted 64.9% (n=50) of the study group while male made up 35.1% (n=27); the mean age was 61.3±14.3 and 66.2% (n=51) of the patients died. To exclude the adverse effect of smoking on mortality, patients were confirmed to be non-smokers by analyzing the cotinine levels in urine samples. For this purpose, patients' age, gender, comorbidities, fever, pulse, blood pressure, saturation values, APACHE scores and biochemical parameters were evaluated.

Results: In the study, 66.2% (n=51) of the patients died during follow-up. Age, urea, creatinine, AST/ALT, N/L ratio and CMR values of the nonsurvivors were significantly higher than those of the survivors. The systolic blood pressure and lymphocyte values of non-survivors were lower than survivors.

Conclusions: The conclusion of the study revealed that CMR scores, AST/ALT levels and the N/L ratio can effectively be utilized in early period to project the mortality rates of non (active) smoking patients with critical COVID-19 infection hospitalized in the ICU.

Keywords: SARS-COV-2; intensive care unit; COVID-19 mortality ratio; cotinine; smokers and non-smokers

INTRODUCTION

Patients in intensive care unit (ICU) due to infectious diseases such as COVID-19 have high mortality rates. It is vital to predict the mortality of patients in the earliest term, prevent mortality, and initiate early aggressive treatment. Smoking is one of the leading factors of increased mortality rates and is the subject of many studies; however, the correlation between smoking, COVID-19, and mortality has not yet been fully elucidated, although different mechanisms have been suggested.[1]

The manifestation of COVID-19 cases ranges from asymptomatic cases having a significant part in the spread of the virus to the severe cases requiring ventilation support, depending on the spectrum of severity.[2,3] Although estimation methods related to COVID-19 have been incorporated into literature, a limited number of studies report on risk factor estimation and mortality analysis of the COVID-19 patients.

The estimation methods include models to estimate high-risk groups[4] diagnostic models to detect COVID-19,[5] and models to estimate mortality rates and severe disease development.[6] However, studies are not sufficiently reliable for various reasons, such as the low number of cases or the variability of results depending on ethnicity. COVID-19 mortality ratio (CMR), through a personalized death risk score, enables to improve triage process, even in systems lacking main resources. CMR is the first risk score verified in a cohort of COVID-19 patients from Europe and the USA.[7]

The CMR model synthesizes multiple clinical data items, such as demographics, laboratory test statistics, symptoms, and comorbidities. A machine learning

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system, the XGBoost algorithm,[8] is used to estimate mortality rates. The score can pick up non-linear features in risk factors and provides an advanced estimation under the "out-of-sample area" under the ROC Curves (AUCs) of 0.90 (95% CI, 0.87-0.94). It discerns new insights confirming acknowledged risk factors including age and oxygen saturation.[7]

The death rate for COVID-19 was observed as 2.8% in men and 1.7% in women in a report from China with 44,672 cases.[9] The smoking rate in China is 52.1% for men and 2.7% for women; therefore, it is suggested that habitual smoking might be associated with a higher prevalence of comorbidity in male.[10]

The role of tobacco use in the etiology of lung cancer and chronic obstructive pulmonary disease (COPD) has been proven. These relationships have been revealed by reporting decades of multi-centre and diverse epidemiologic data.[11] A meta-analysis investigating the severe COVID-19 risk in COPD patients with a history of pre-existing and ongoing smoking reported that habitual smoking exacerbates the progression of COVID-19 causing worse outcomes.[12] Concerning relation between COVID-19 and smoking, analyses in the existing studies revealed that the likelihood of patients with a smoking history developing severe symptoms of COVID-19 is higher than non-smokers. Considering smoking affects the mortality rate in COVID-19 patients, it is suggested that the CMR score can enable to project the probability of mortality of non-smoking patients with critical COVID-19.

We aimed to estimate the risk of mortality in hospitalized COVID-19 patients using a new machine learning (ML) model: the COVID-19 Risk of Mortality (CMR) calculation. Hence, the effect on mortality of CMR, aspartate transaminase/alanine transaminase (AST/ALT) levels, and neutrophil/lymphocyte (N/L) ratios (NLR) of non (active) smokers with COVID-19 in the ICU was investigated.

Our hypothesis in this study; it is to show that the CMR model is a good tool for monitoring surveillance in non-smoking COVID-19 patients in ICU.

METHODS

This cross-sectional study was carried out with the permission of University of Healthy Science, Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.05.2020, Decision No: 2020.05.2.02.058). Written informed consent was provided from all participants. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

Seventy seven non-active smokers with COVID-19 were selected. The primary author personally invited the participants, and the data were collected via face-to-face interviews. 183 patients were treated for three weeks (10-30 May 2021) in the ICU, 137 of whom had COVID-19. While 109 of the patients agreed to participate, 32 participants having smoked in the last two weeks were excluded (**Figure 1**). Written informed consent was provided from all participants.

To prevent selection bias, all COVID-19 patients were included in the research. Additionally, the same investigator collected the data, and the data analysis was done independently.

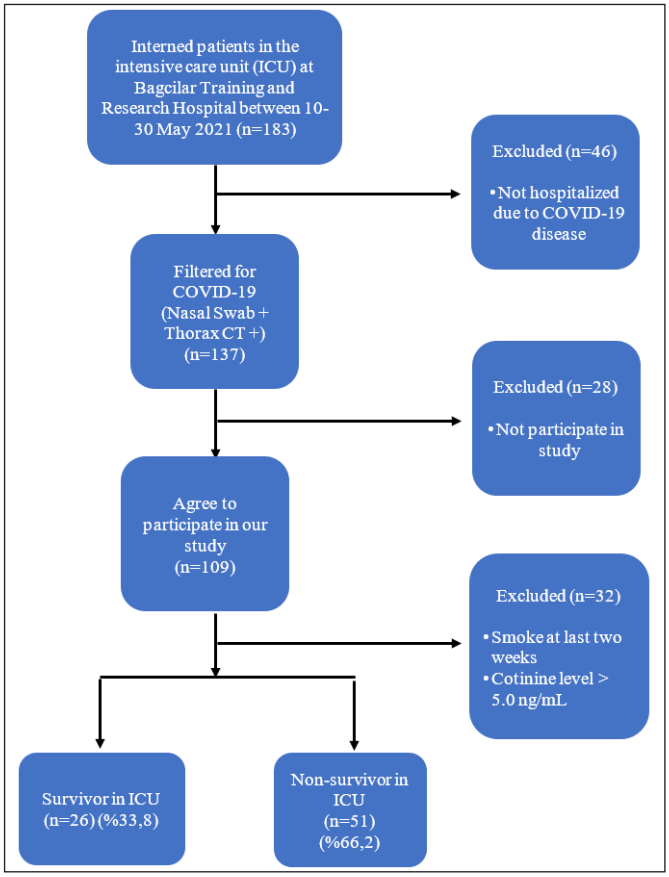

Figure 1. The figure shows the patients selection

Biochemical Analysis

The primary outcome of the study was the mortality ratio from COVID-19. Additionally, demographic features were recorded and urine cotinine levels were tested. With a 2-hour elimination half-life, nicotine is quickly metabolized in the liver into cotinine. Having a 15-hour half-life, cotinine accumulates in urine in proportion to dosage and hepatic metabolism; tobacco users usually excrete cotinine ranging from 1,000 to 8,000 ng/ml. Heavy tobacco users avoiding tobacco for a fortnight exhibit urine cotinine <50 ng/ml. Cotinine concentrations, at 1,000 to 8,000 ng/ml when using a tobacco product, <50

ng/ml after 2 weeks of complete abstinence for a tobacco user, <20 ng/ml for a passively exposed non-tobacco user and measured at <5.0 ng/ml for the non-user.

Since the impact of smoking on COVID-19 prognosis and mortality is not conclusive, the research patients proved not to have been exposed to active or passive smoking in the last two weeks. Thus, impact of smoking was excluded from the study.

Eighteen features -disease severity, age, temperature, gender, oxygen saturation, ALT, AST, urea, creatinine, sodium, potassium, blood glucose, hemoglobin, leukocytes, CRP, mean corpuscular volume, platelets, prothrombin time and comorbidities parameters- were selected for CMR calculation in COVID-19 mortality.[13]

Our secondary outcome in this study is to evaluate the surveillance of COVID-19 disease in non-smoking COVID-19 patients.

Statistical Methods

The NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) was utilized for statistical analysis. Research data were analyzed using descriptive statistical methods and the distribution of data was evaluated with the Shapiro-Wilk Test. The Mann-Whitney test was preferred to compare the quantitative data between two groups without a normal distribution. The Student's t-test was utilized for comparing quantitative data between two groups with a normal distribution. The chi-square test was used to compare the qualitative data between the two groups. The significance was evaluated at $p<0.05$.

Power analysis was performed using the G*Power program to determine the number of samples. The power of the study is expressed as 1-β (β=probability of type II error) and in general studies should have 80% power. According to Cohen's effect size coefficients; it was decided to take 77 people totally, considering that at the level of $\alpha=0.05$.

RESULTS

In the study, 64.9% of the participants (n=50) were female while 35.1% (n=27) were male; the mean age was 61.3±14.3 and 66.2% (n=51) of the patients died. The study showed that, 11 non-survivors died as a result of complications related to underlying chronic diseases (3 patients with coronary artery disease, 3 patients with COPD, 2 patients with CHF, 2 patients with CVA and 1 patient with malignancy) and the other 40 patients died as a result of reasons related to COVID-19 and its complications. The mean number of days the participants were hospitalized in the ICU was 12.5±8.06.

Non-survivors were significantly older with a lower systolic blood pressure values than survivors (p=0.002) (Table 1). No statistically significant difference of mortality risk was found when evaluated based on gender, total hospitalization days, diastolic blood pressure, heart rate, fever, and saturation value (p=0.485, p=0.398, p=0.804, p=0.583, p=0.336 and p=0.815; respectively) (Table 1).

Compared to survivors, non-survivors had higher urea, creatinine, direct bilirubin, and pro-BNP values and lower total protein and lymphocyte values (p=0.035, p=0.023, p=0.018, p=0.012, p=0.031 and p=0.002; respectively).

The difference between survivors and non-survivors with regard to mean glucose, uric acid, AST, ALT, alkaline phosphatase (ALP), GGT, total bilirubin, albumin, LDH, TSH, FT4, FT3, CRP, sedimentation, procalsitonine, IL-6, D-dimer, ferritin, Na, K, Cl, Ca, PT, INR, APTT and hemogram parameters like leukocyte, RBC, hemoglobin, platelet, MCV, MCH, MCHC, RDW, PCT, MPV, PDW, neutrophil, monocyte, eosinophil, and basophil values on mortality rates were not significantly different. Non-survivor group had higher AST/ALT and neutrophil/lymphocyte (NLR) ratios than the other group (p=0.008 and p=0.001; respectively). No statistically significant difference of mortality risk was identified when evaluated based on MPV/PLT and neutrophil/albumin ratios (p=0.836 and p=0.119; respectively) (Table 2).

Table 1. Comparison of mortality risk with regard to scales

Variables		n	Mean±SD	Min-Max (Median)	p
Age (year)	Survivor Nonsurvivor	26 51	53.5±11.2 65.2±14.2	32-81 (52.5) 37-102 (64)	**0.001**[a]
Total hospitalization days	Survivor Nonsurvivor	26 51	11.4±9.7 13.0±7.1	2-38 (8.5) 1-35 (12)	0.398[a]
Systolic blood pressure (mmHg)	Survivor Nonsurvivor	26 51	134.5±18.1 120.4±17.7	100-180 (132.5) 80-160 (120)	**0.002**[a]
Diastolic blood pressure (mmHg)	Survivor Nonsurvivor	26 51	71.4±19.5 68.0±11.7	43-150 (70) 36-90 (70)	0.804[b]
Pulse per minute	Survivor Nonsurvivor	26 51	87.2±13.6 89.2±15.7	65-120 (85.5) 59-129 (88)	0.583[b]
Temperature (°C)	Survivor Nonsurvivor	26 51	36.8±0.5 36.7±0.5	36-38.8 (36.95) 36-38.2 (36.8)	0.336[a]
Saturation (%)	Survivor Nonsurvivor	26 51	92.73±4.25 93±4.98	85-100 (92.5) 78-100 (93)	0.815[a]

a Student t-test (Mean±SD), b Mann Whitney Test (Min-Max/Median). All the p values that were considered statistically significant (<0.05) are identified in bold.

Table 2. Comparison of mortality risk with regard to biochemical parameters

Variables		n	Mean±SD	Min-Max (Median)	p
AST/ALT ratio	Survivor	26	1.54±0.87	0.44-5.13 (1.46)	**0.008**[b]
	Nonsurvivor	51	1.97±0.82	0-4.1 (1.98)	
MPV/PLT ratio	Survivor	26	0.04±0.02	0.01-0.09 (0.04)	0.836[b]
	Nonsurvivor	51	0.04±0.02	0.02-0.12 (0.04)	
Neutrophil/Lymphocyte ratio	Survivor	26	9.51±7.05	2.70-32.67 (8.04)	**0.001**[b]
	Nonsurvivor	51	17.21±13.26	3.73-64.73 (13.7)	
Neutrophil/Albumin ratio	Survivor	26	2.6±1.25	0-5.18 (2.51)	0.119[b]
	Nonsurvivor	51	3.67±2.39	1.15-12.98 (2.91)	

a Student t-test (Mean±SD), b Mann Whitney Test (Min-Max/Median). All the p values that were considered statistically significant (<0.05) are identified in bold. AST:Aspartate Aminotransferase, ALT:Alanine Aminotransferase, MPV:Mean platelet volume, PLT:Platelet count ratio.

No statistically significant relationship could be established between mortality rates and the presence of comorbidities such as diabetes mellitus, hypertension, asthma, COPD, malignancy, chronic renal failure (CRF), congestive heart failure (CHF), cerebrovascular accident (CVA), rheumatism, Alzheimer's, coronary artery disease and complaints of admission to hospital such as cough, shortness of breath, fever, myalgia, loss of appetite, syncope, diarrhea, and abdominal pain (p=0.568, p=0.999, p=0.073, p=0.568, p=0. 623, p=0.099, p=0.594, p=0.069, p=0. 472, p=0.472, p=0.703, p=0.847, p =0.594, p=0.371, p=0.356, p=0.219, p=0.472, p=0.472 and p=0.159; respectively).

As expected non-survivors had higher CMR values (p=0.001). No statistically significant correlation was relieved between mortality rates and APACHE scores (p=0.453) (**Table 3**).

Table 3. Comparison of mortality risk with regard to CMR and APACHE scores

Variables		n	Min-Max (Median)	p
CMR score	Survivor	26	2-61 (13)	**0.001**
	Nonsurvivor	51	5-82 (28)	
APACHE score	Survivor	26	16-41 (28)	0.453
	Nonsurvivor	51	18-40 (28)	

Mann Whitney Test. All the p values that were considered statistically significant (<0.05) are identified in bold. CMR:COVID-19 Mortality Ratios

DISCUSSION

The results of the research indicated that the CMR score, AST/ALT values and N/L ratios of non (active) smoking (ex-smoker) critical COVID-19 patients in ICU provided beneficial data in early prediction of mortality rates.

Contrary to the common belief that smoking deteriorates the consequences associated with COVID-19, studies conducted before 2020 praised the positive impact of smoking on the course of the disease.[14-16] Within this context, to exclude the effect of smoking and to reveal the other factors affecting the mortality rates of non-smoking COVID-19 patients, we focused on the non-smoking patients only.

Factors affecting mortality risk in the ICU patients were reviewed to examine the risk factors related to COVID-19 contributing to the purpose of the study. There is a wealth of complex information evaluating the clinical pattern and mortality risks of COVID-19 patients, but regardless of their smoking habits. Likewise, data from previous researches confirm the presence of a complicated correlation between habitual smoking and disease severity. Some studies conducted during the pandemic suggested a low prevalence of active smoking COVID-19 patients in the general population. Another study with a sample size of 8.28 million in the UK concluded that smoking was associated with milder risks of COVID-19.[14] Although prior tobacco use was related to a higher risk of serious consequences of COVID-19, another study covering 645 cases examining the relationship between the smoking habits of hospitalized patients and the severity of the disease demonstrated that active smoking may have a protective but insignificant effect. Prior smoking habits proved to be related to the exacerbation of severe consequences of COVID-19 in hospitalized patients.[15]

A UK-based study investigating the correlation between smoking habits and COVID-19-related outcomes on 53.002 adults correlated current habitual smoking with COVID-19.[16] A meta-analysis examining 11.590 COVID-19 patients, in which 2.133 (18.4%) had severe COVID-19 and 731 (6.3%) had a history of smoking, revealed that the pattern of the disease was exacerbated in 218 patients (29.8%) with a smoking history whereas the rate was as low as 17.6% in the non-smokers. Thus, the meta-analysis indicated a statistically significant relationship between habitual smoking and the development of COVID-19.[17] Generally, the concordance of the observational analyses demonstrating the relationship between recent smoking behavior and COVID-19 together with the Mendelian Randomisation (MR) analyses demonstrating the correlation with lifetime smoking predisposition and the frequency of smoking support the causal impact of smoking on the severe course of the disease.[18] The results of this research, like those of the prior studies, suggested that habitual smoking is a risk factor affecting the development of COVID-19 and that smokers have a greater risk of exacerbation of COVID-19 compared to

patients who have never smoked. At the same time, a recent cohort study examining the relationship between smoking status and death from COVID-19 found that non-smokers are more likely to survive COVID-19 disease.[19]

A meta-analysis covering 109 articles examining a total of 517.020 COVID-19 patients suggested a statistically significant correlation between habitual smoking and the severity of COVID-19. Accordingly, habitual smoking and the presence of comorbidities (diabetes, hypertension and COPD) have proved to be correlated with the possibility of hospitalization in the ICU, increasing mortality rates.[20] 2023 data also supports that these comorbidities are likely to mediate the effect of smoking on mortality from COVID-19.[21]

In a research on 473.550 patients utilizing the UK Biobank cohort investigating risk factors causing death in COVID-19 cases, the main contributing factors were found to be age, male gender, and black ethnicity. Specifically, black ethnicity, oral steroid use, and hypertension proved to be closely associated with COVID-19.[22] Age was also found to be a notable cause of mortality risk, however, no significant relationship was determined between gender and mortality. Considering comorbidities, although no significant difference was found between hypertension and mortality in accordance with the information obtained herein, low systolic blood pressure proved to be significantly correlated with mortality. Sun et al.'s study, just like ours, supports that low blood pressure may be associated with COVID-19 mortality and may worsen the condition of critical COVID-19 patients.[23]

A cohort study of 521 patients demonstrated that the prevalence of COPD was not high in smoking COVID-19 patients, thus suggested that COPD patients are not under a higher risk of the disease. However, when the SARS-CoV-2 infection first appeared, COPD patients and former smokers were reported to be under the highest risk of mortality. Accordingly, the study suggested that the risk of morbidity was not directly related to COPD and smoking habits, but rather to the presence of comorbidities.[24]

A single-center study investigating whether there is an independent correlation between elevated liver enzyme values and risk of mortality as well as hospitalization of COVID-19 patients in the ICU argued that the three are significantly correlated.[25] Likewise, a multi-center retrospective cohort research examining 5,771 adults with COVID-19 demonstrated that initially AST values and then ALT values of severe COVID-19 patients tend to elevate throughout the course of the disease. Additionally, the abnormality in AST levels was related to the highest risk of mortality compared with other indicators of liver failure experienced during hospitalization.[26] As can be seen in literature, the AST/ALT ratio used in the evaluation of liver enzymes during the course of COVID-19 was correlated with mortality, although the reason for the elevation in liver enzymes is probably multi-factorial.

A study suggested that a dynamic change in neutrophil/lymphocyte ratio (NLR) and D-dimer level can distinguish severe cases of COVID-19 from mild/moderate cases. The NLR ratio was found to be 6.29±3.72 and 2.33±1.22 in the groups with severe and mild/moderate COVID-19 respectively.[27,28] In the current research, the N/L ratio was found as a minimum of 3.73 and a maximum of 64.73 in the hemogram findings of non-surviving patients. In this respect, NLR is suggested for consideration as a significant indicator of mortality and disease severity.

A research on high-risk patients in the ICU diagnosed with COVID-19 may provide further information about disease control strategies. A retrospective study involving 114 adult inpatients with COVID-19 pneumonia, comprising of 19 active smokers (15.9%), 23 ex-smokers (20.1%), and 72 non-smokers (63.1%), concluded that habitual smoking did not have a statistically significant effect on the course of the disease, the duration of hospitalization, the need for non-invasive mechanical ventilation (NIMV), the need for follow-ups in the ICU, and mortality. The study argued that the active smoking rate of hospitalized COVID-19 patients is lower than the population average. Accordingly, it was observed that habitual smoking is not correlated with disease progression, or with prognostic indicators and mortality.[29]

In a meta-analysis of COVID-19 patients, while age, pre-existing comorbidities, severity of the disease based on validated scoring systems and patients' response to disease were correlated with mortality, male gender and increased BMI were not. Therein, related factors were found to have prognostic significance for ICU patients with COVID-19 diagnosis.[30]

As the term "habitual smoking" alone does not specify the number of cigarettes smoked or the duration of smoking, it may be considered as an 'imperfect' measure for evaluating the correlation with severe COVID-19 outcomes. Based on a retrospective cross-sectional study involving 4.611 patients that evaluated whether smoking status, smoking intensity, duration of smoking, and pack/year smoking were related to serious consequences among adult COVID-19 patients, it was concluded that the smoking status, pack/year smoking and smoking intensity of COVID-19 patients correlated with

hospitalization, and smoking intensity also correlated with admission to the ICU.[31] A meta-analysis including 47 researches examining 32.849 hospitalized COVID-19 cases, 8.417 (25.6%) of which had a smoking history, 1.501 current smokers, 5.676 ex-smokers and 1.240 smokers with an unspecified frequency, concluded that smoking history is related to severe COVID-19, mortality, need for mechanical ventilation, and disease progression.[32]

Within this context, our research examined the correlation between mortality and the CMR scoring system, AST/ALT and the N/L ratio in non-smoking COVID-19 patients in the ICU. Cotinine levels were tested from participants' urine samples and the sample structure was specified by excluding individuals who had smoked in the previous two weeks, including passive smokers. Including only the smoking-free patients allowed us to exclude the effect of active and passive smoking on the outcomes of COVID-19. Another strength of our study is that the data were gathered simultaneously at the peak of the pandemic. The data was collected retrospectively and the study was carried out prospectively, thus minimizing the risk of using incomplete data.

Study Limitations

One limitation is that the study provides information from a specific hospital in Turkey. The overall outcome of COVID-19 may differ from the morbidity and mortality figures outside the ICU or in different institutions. During this study, there were higher or lower rates of COVID-19 cases in several countries. The CMR was examined, including the distribution of products with negative cotinine concentration. CMR correlation could be examined in people with high urine cotinine levels. Another limitation of the study is that COVID-19 patients who do not smoke or have low cotinine levels may have further racial and social differences. Additionally, the characteristics of the sample may vary according to different demographic profiles and population characteristics. Final limitation is that data collected throughout a three-week period will not be sufficient for statistical generalizations of the entire year.

CONCLUSION

Consequently, significant findings were identified between COVID-19 and the mortality rates in patients proven to be non-smokers by testing cotinine levels in urine samples. This study is significant as it provides the first data investigating COVID-19-related mortality in non-smoking patients with critical COVID-19 in the ICU. We hereby suggest the extension of our findings in the context of correlation with mortality due to COVID-19 and the submission of further studies in conjunction with future COVID-19 mortality data as they will aid early diagnosis in detecting the long-term sequelae and mortality of COVID-19.

Our research provides data by examining mortality rates of actively non-smoking patients with critical COVID-19. Further research with larger sample size is required to better demonstrate the correlation between smoking and COVID-19, the effects of smoking on COVID-19, and to understand the mechanisms thereof.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Healthy Science, Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 29.05.2020, Decision No: 2020.05.2.02.058).

Informed Consent: All patients signed and free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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