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Chest Image Staging and Prevalence of Current Smoking Among Hospitalized COVID-19 Patients in Turkey

ABSTRACT

Objective: Novel coronavirus disease is a new infectious agent of the respiratory tract characterized by severe acute respiratory syndrome. For this disease, there are limited data with regard to the clinical characteristics of the patients and prognostic factors.

Methods: We collected data from 213 patients who were hospitalized into COVID-19 isolation with positive PCR test results. We recorded various patient values, including blood test results. We also noted age, gender, additional diseases, duration of discharge, whether they live or die, whether they smoke, and their radiological staging.

Results: In CT imaging with a staging of maximum 4 points and minimum 0 points, the mean value resulted in 1.95. The average radiological stage of the dead patients' group was reported as 2.56. There was a correlation between the radiological predictor and the outcome status ($P = .002$). The number of smokers was 14 (6.5%). Of the 26 patients who died, 3 were smokers and 23 were non-smokers.

Conclusion: Fourteen patients in the study were smokers. While in COVID-19 isolation service, only a small rate of smoking was observed. That supports the theory that smoking has no negative impact on COVID-19 development. There was also a correlation between the radiological predictor and the outcome status. It seems that an elevated radiological stage is a predictor of death.

Keywords: COVID-19, SARS-CoV-2, smoking, computed tomography, predictor factors

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INTRODUCTION

Novel coronavirus disease (COVID-19) is a new infectious agent of the respiratory tract characterized by severe acute respiratory syndrome (SARS). SARS-CoV-2 started in Wuhan, China, in December 2019 and quickly evolved into a rapidly spreading pandemic.[1] Because of its high infectivity and mortality, it is considered a serious public health threat.[2]

Although most patients are asymptomatic or have mild symptoms and a good prognosis, COVID-19 can progress to more severe illnesses, including pneumonia, acute respiratory distress syndrome, multiple organ failure, or even death.[3,4] The aim of successful treatment is the reduction of complications and mortality. Basic disease treatment is also needed to prevent secondary infection.

For this disease, there are limited data with regard to the clinical characteristics of the patients and prognostic factors.[5] Chronic diseases and old age have been assumed to be associated with adverse disease prognosis. Little attention has been given to the role of smoking in the transmission of SARS-CoV2. Smokers contract more respiratory infections including cold (commonly rhinoviruses), than non-smokers. Smokers also develop influenza twice as often and show increased rates of bacterial pneumonia and tuberculosis. The damage caused to the lungs by smoking makes these patients more susceptible to pulmonary infections, both bacterial and viral.[6]

There are two opposing opinions about the effect of smoking on COVID-19's severity. It has recently been reported that ACE2 gene expression, which is known to be a cellular entry

gateway for SARS-CoV-2, is higher in smokers. This expression is also the upregulation associated with smoking and suggests that smoking contributes to a higher number of viral receptors and may support the findings of the recent case series research.[7,8] However, the second opinion is that smoking prevents the downregulation of angiotensin-converting enzyme 2 (ACE2) and that this downregulation is harmful due to uncontrolled ACE2 and angiotensin II activity (9). It has been observed that decreased ACE2 availability contributes to lung injury and increases the chance of development of acute respiratory distress syndrome (ARDS).[9]

Therefore, it is very important to find the related factors of disease severity in clinical practice. In this study, we compared the clinical and laboratory findings and computed tomography (CT) features of 223 ordinary COVID-19 cases.

METHODS

This study was done based on the data of the patients hospitalized in the COVID-19 isolation department in Istanbul Bahcelievler State Hospital. We got our ethics committee approval from Istanbul Bakırkoy Sadi Konuk Research Hospital with 2020/242 protocol code and 2020-12 decision number.

It was performed on 223 patients who were evaluated in the emergency department and then hospitalized between April 11 and May 17, 2020, and whose COVID-19 polymerase chain reaction (PCR) test result was positive. Within the scope of the COVID-19 protocol we conducted in our hospital, patients with cough, sore throat, and respiratory distress are transferred from the emergency triage to the isolation area. Depending on the patient's history, which is taken while a PCR test is administered, hemogram, biochemistry blood tests, and pulmonary computed tomography may be requested. The patient's history includes questions regarding additional illness and smoking. If the patient has respiratory distress, high fever, bad general condition, accompanying chronic disease, old age, and high computed tomography staging, we prepare by referring to other studies,[4,10] interned to the isolated service for COVID-19. According to the directive from the Turkish Ministry of Health, we started our treatment with 200 mg hydroxychloroquine sulfate (Plaquenil; Sanofi, Paris, France), 500 mg azyhtromycin (Azitro; Deva Ilaç, Istanbul, Turkey), 30 mg oseltamavir (Enfluvir; Atabay Pharmaceutical, Istanbul, Turkey), 6000 U Enoxapirin sc. (Clexane; Sanofi, Paris, France) and a 1 g vitamin C iv (Redox-C; Bayer, Istanbul, Turkey). If oxygen saturations are below 90, favipiravir (Zhejiang Hisun pharmaceutical, China) treatment is initiated. On the first day of the patient's hospitalization, we sent routine blood tests for hemogram, full biochemistry, serology, coagulation markers, troponin, ferrritin, and D-dimer levels. If patients have normalized laboratory tests, no fever and no respiratory distress for at least 3 days, and a good general condition, they are discharged with an explanation of isolation rules.

We collected data from 213 patients who were admitted into COVID-19 isolation with positive PCR test results. We recorded various patients' values, including white blood cell (Wbc), neutrophil, lymphocyte, platelet, mean platelet volume (MPV), ferritin, D-dimer, troponin-I, c-reactive protein (CRP), magnesium, calcium, creatinine, and lactate dehydrogenase (LDH). We also noted age, gender, additional diseases, duration of discharge, whether they live or die, whether they smoke, and their radiological staging. Written informed consent was obtained from all participants who participated in this study.

While inquiring about additional diseases, we used the E-Nabız System that was organized by the Turkish Ministry of Health. This system incorporates a large amount of information, such as what diagnoses patients have had before, the operations they have undergone, and the medications they have been prescribed. For patients who are referred with a pre-diagnosis of COVID-19, smoking-related information is gathered and recorded before the PCR test and confirmed during hospitalization.

In the case of our hospital, chest images were examined by the same radiologist who conducted the earlier tests. A semi-quantitative scoring obtained from CT images was used to determine the severity of COVID-19's pulmonary involvement. Each lung lobe was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), and 4 (76–100%) according to the COVID-19 involvement percentage. The total involvement score (0–20) of all five lobes was obtained, and CT evaluation was performed in the lung parenchyma window. A Toshiba Alexion device with 16 detectors, extant in our own hospital, was used. Scoring was performed according to the ground glass opacity appearance of COVID-19, which is the typical lung involvement, and the percentage of consolidations. Of the original 223 patients, those with atypical COVID-19 findings (n = 4), lung malignancy (n = 2), and atelectasis (n = 4) were excluded from the study, leaving 213 participants.

Statistical Analysis

Mean, standard deviation, lowest and highest median, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov–Smirnov test. The Mann-Whitney *U*-test was used in the analysis of quantitative independent data. Chi-square test was used in the analysis of qualitative independent data, and Fischer's test was used when the chi-square test conditions were not met. The effect level was investigated with univariate and multivariate logistic regression. Statistical Package for the Social Sciences (SPSS) version 27.0 (IBM SPSS Corp.; Armonk, NY, USA) was used in the analysis.

MAIN POINTS

- The radiological stage seems statistically significant in predicting death.
- We did not see any significant effect of smoking on mortality. There was also no significant effect on discharge time.
- Gender and age did not have a significant effect on death.
- We saw smaller-than-expected smoking rates in hospitalized patients who tested positive for COVID-19.

RESULTS

There were 223 patients in our research and 118 of them were male (55.4%). The average age was 56 years (Table 1). The number of

Table 1. Biostatistics Results

	Min-Max	Median	Mean± SD/n (%)
Age	15.0-89.0	56.0	56.0±16.4
Gender			
Female			95 (44.6)
Male			118 (55.4)
Radiological stage	0.0-20.0	7.0	7.8±4.3
I			70 (35.2)
II			75 (37.7)
III			46 (23.1)
IV			8 (4.0)
Aditional diseases			
(–)			87 (40.8)
(+)			126 (59.2)
Smoking			
(–)			199 (93.4)
(+)			14 (6.6)
WBC	1.7-26.9	5.5	6.2±2.9
Neutrophil	0.8-22.8	3.6	43±2.6
Lenfocytes	0.4-5.5	1.2	1.3±0.6
Platelet	55.0-657.0	220.0	240.4±97.2
MPV	7.6-12.1	10.1	10.1±0.8
Ferritin	9.3-1500.0	229.0	349.6±368.0
D-dimer	0.0-8.0	0.4	0.9±1.4
Troponin	0.6-127.6	5.0	10.1±16.6
CRP	0.5-487.1	55.0	77.2±73.5
Magnesium	1.3-2.9	2.0	2.0±0.3
Calsium	7.0-10.6	8.6	8.6±0.6
Creatinine	0.4-2.5	0.8	0.9±0.3
LDH	56.0-2569.0	281.0	331.9±219.0
Discharge time	2.0-68.0	10.0	13.8±10.0

patients who died was 26 (12.2%). The average age of the 26 patients who died was 60.9 years and the majority were men (17 males, 9 females). The mortality rate of men was 14.4%, and the mortality rate of women was 9.4% but the mortality is not statistically significant with age and gender ($P > .05$) (Table 2).

In CT imaging with a staging of maximum 4 points and minimum 0 points, the mean value resulted in 1.95. The average radiological stage of the dead patients group was reported as 2.56. There was a correlation between the radiological predictor and the outcome status ($P < .05$). In other words, the radiological stage seems statistically significant in predicting death.

One hundred twenty-seven patients (59.6%) had chronic disease (hypertension, diabetes mellitus, congestive heart disease, asthma, chronic obstructive pulmonary disease, or other cardiovascular diseases). Of the 26 deceased patients, 13 had a chronic disease, 9 had multiple chronic diseases, and 4 patients did not have any chronic diseases. As expected, the effect of additional chronic disease on death was significant ($P < .05$).

The number of smokers was 14 in 127 patients (6.5%). Of the 26 patients who died, 3 were smokers and 23 were non-smokers. Male patients were more likely to be smokers ($P < .05$) (Table 4).

However, there was no significant distribution of smoking regarding age ($P > .05$). The effect of smoking on radiological staging could not be demonstrated ($P > .05$). We did not see any significant effect of smoking on mortality ($P > .05$). There was also no significant effect on discharge time ($P > .05$)

The average discharge time was 13.8 days. Before starting the study, we expected those with high radiological staging to have a longer discharge time. We strengthened this statistically. Stages 3-4 have a longer discharge time compared to stages 1-2 ($P < .05$). Also, patients with additional disease have longer discharge time ($P < .05$) (Table 5).

In our study, gender and age did not have a significant effect on death ($P > .05$). WBC, neutrophil, platelet, MPV, ferritin, magnesium values did not differ significantly ($P > .05$) in the group with and without mortality. In the mortality group, the lymphocyte and calcium levels were significantly lower ($P < .05$) than the non-mortality group. D-Dimer, troponin, CRP, creatine, and LDH values were significantly higher ($P < .05$) in the mortality group than in the non-mortality group.

In predicting mortality in the univariate model; radiological stage, additional disease, lymphocyte, D-dimer, troponin, CRP, calcium, creatine, and LDH values showed significant ($P < .05$) efficacy. (Table 3)

Additional diseases, D-dimer, and calcium value showed significant independent ($P < .05$) efficacy in predicting mortality in a multivariate model (Table 3).

DISCUSSION

SARS-CoV-2 infection continues to be an urgent public health challenge in China and throughout the world. Most infected patients have mild illness and completely recover after 2 weeks. However, once infected patients progress to severe illness with acute respiratory distress syndrome, over 10% of them worsen in a short period of time and die.[3] As the pathogenesis of SARS-CoV-2 infection is unknown, there is no standard specific treatment and most patients receive symptomatic treatment. Thus, a further understanding of the pathogenesis and treatment of the disease is urgently needed. In Figure 1, the effects of variable changes on dead and living groups are shown.

Previous studies have found that some routine laboratory biomarkers are out of reference ranges and are higher in more severe disease.[11] In accordance with those studies, we also found that some biomarkers, such as lactate dehydrogenase, troponin, and D-dimer, were higher in cases of severe illness, but these biomarkers were not all specific to SARS-CoV-2. Similar to other viral infections, neutrophils showed no obvious change in mild cases, while inflammatory biomarkers such as CRP were increased.

There is a small amount of research that says that smoking could increase the risk of COVID-19 via upregulation of

Table 2. Biostatistics Results

	Mortality (−)		Mortality (+)		
	Mean±SD/n (%)	Median	Mean±SD/n (%)	Median	*P*
Age	55.3±16.5	55.0	61.0±14.7	62.5	.100[t]
Gender					
Female	86 (46.0)		9 (34.6)		.274[X²]
Male	101 (54.0)		17 (65.4)		
Radiological stage	7.3±4.1	7.0	11.0±4.7	12.0	.000[m]
I	65 (37.4)		5 (20.0)		.000[X²]
II	71 (40.8)		4 (16.0)		
III	33 (19.0)		13 (52.0)		
IV	5 (2.9)		3 (12.0)		
Additional disease					
(−)	83 (44.4)		4 (15.4)		.005[X²]
(+)	104 (55.6)		22 (84.6)		
Smoking					
(−)	176 (94.1)		23 (88.5)		.387[X²]
(+)	11 (5.9)		3 (11.5)		
WBC	6.15±2.86	5.46	6.48±2.95	5.13	.785[m]
Neutrophil	4.14±2.53	3.56	5.10±2.79	4.12	.050[m]
Lenfocyte	1.39±0.64	1.23	0.85±0.31	0.81	.000[m]
Platelet	245.6±100.3	225.0	203.0±60.2	198.0	.058[m]
MPV	10.1±0.8	10.1	10.1±0.9	10.1	.983[t]
Ferritin	334.3±357.0	219.8	459.9±431.0	296.5	.163[m]
D-dimer	0.76±1.12	0.38	1.89±2.38	0.65	.019[m]
Troponin	8.67±14.39	4.30	20.65±25.96	9.15	.000[m]
CRP	72.4±71.6	49.0	111.5±78.7	113.4	.010[m]
Magnesium	2.01±0.27	2.01	1.97±0.36	1.91	.452[t]
Calcium	8.71±0.53	8.70	8.15±0.55	8.05	.000[m]
Creatinine	0.85±0.34	0.78	1.03±0.40	0.89	.008[m]
LDH	318.4±216.3	270.0	428.9±218.2	366.0	.002[m]
Discharge time	12.6±9.0	10.0	22.6±12.1	21.0	.000[m]

[t]Independent sample test; [m]Mann–Whitney *U*-test; [X²]Ki-kare test (Fischer test).

ACE-2 expression, a known cellular entry gateway for SARS-CoV-2.[7,8] However, there are a few inconsistencies with this hypothesis. First of all, the spike protein of the virus is responsible for ACE-2 binding, and it requires its counterpart to be localized on the plasma membrane in order to be subsequently internalized.[12,13] Therefore, the gene expression does not conclusively indicate increased viral infection risk. Second, it is known that ACE-2 expression is downregulated on plasma membranes following SARS-CoV-2 infection because of internalization of ACE-2-virus samples.[14] Third, simple ACE-2 expression on plasma

Table 3. Biostatistics Results

	Univariate Model			Multivariate Model		
	OR	95% GA	*P*	OR	95% GA	*P*
Radiological stage	1225	1103-1360	.000			
Additional diseases	4389	1456-13 236	.009	7145	1740-29 343	**.006**
Lenfocytes	0053	0013-0210	.000			
D-dimer	1469	1174-1839	.001	1376	1063-1782	**.015**
Troponin	1027	1009-1046	.004			
CRP	1006	1001-1011	.016			
Calcium	0017	0045-0304	.000	0089	0030-0266	**.000**
Creatinine	3205	1204-8533	.020			
LDH	1002	1000-1003	.049			

Logistic Regression (Forward LR).

Table 4. Biostatistics Results

	Smokers		Non Smokers		
	Mean ± SD/n (%)	Median	Mean±SD/n (%)	Median	*P*
Age	56.3±16.4	56.0	51.2±15.5	48.0	.258[t]
Gender					
Female	93 (46.7)		2 (14.3)		.018[X²]
Male	106 (53.3)		12 (85.7)		
Radiological stage	7.7±4.4	7.0	9.0±4.3	8.0	.347[m]
I	68 (36.0)		2 (20.0)		.348[X²]
II	71 (37.6)		4 (40.0)		
III	42 (22.2)		4 (40.0)		
IV	8 (4.2)		0 (0.0)		
Additional diseases					
(–)	81 (40.7)		6 (42.9)		.874[X²]
(+)	118 (59.3)		8 (57.1)		
WBC	6.19±2,87	5.46	6.21±2.95	5.34	.875[m]
Neutrophil	4.23±2.58	3.61	4.61±2.58	3.60	.552[m]
Lenfocyte	1.34±0.64	1.21	1.01±0.42	0.87	.021[m]
Platelet	241.1±95.9	222.0	229.9±118.2	191.0	.390[m]
MPV	10.08±0.83	10.10	10.02±1.06	10.05	.788[t]
Ferritin	323.0±340.8	213.7	728.0±523.8	571.9	.002[m]
D-dimer	0.90±1.42	0.38	0.89±0.73	0.65	.136[m]
Troponin	9.75±14.98	4.90	15.55±32.56	5.65	.336[m]
CRP	75.2±73.6	52.6	106.2± 66.9	1152	.047[m]
Magnesium	2.01±0.28	1.99	2.01±0.26	2.01	.990[t]
Calcium	8.66±0.57	8.60	8.44±0.52	8.30	.124[m]
Creatinine	0.87±0.34	0.79	0.96±0.48	0.85	.409[m]
LDH	330.9±222.6	281.0	346.5±164.7	274.0	.742[m]
Mortality					
(–)	176 (88.4)		11 (78.6)		.387[X²]
(+)	23 (11.6)		3 (21.4)		
Discharge time	13.6±10.0	10.0	16.8±9.6	14.5	.112[m]

[t]Independent sample test; [m]Mann–Whitney *U*-test; [X²]Ki-kare test (Fischer test).

membranes may not be an important element in the establishment of a potential risk factor for virus infection. In fact, once the spike protein is bound to ACE-2, the cell is required to trigger a complex series of biochemical activities and molecular signals in order to internalize the virus.[12] The view that overexpression of ACE2 is harmful does not take into account more recent evidence that upregulation of ACE2 may in fact be protective against disease severity.[9] Experimental data suggest that infection with SARS-CoV-2 leads to downregulation of ACE2, and this downregulation is harmful because of uncontrolled ACE and angiotensin II activity.[8,9] It has been observed that decreased ACE2 availability contributes to lung injury and increases the risk of ARDS development.[9,15] Therefore, higher ACE2 expression, while it seems paradoxical, may protect against the acute lung injury caused by COVID-19.[16]

Table 5. Biostatistics Results

	Discharge time			
	Min-Max	Median	Mean±SD	*P*
Additonal diseases				
(–)	2.0-68.0	9.0	11.9±9.8	.004[m]
(+)	4.0-44.0	12.0	15.2±9.9	
Radiological stage				
I-II	2.0-68.0	10.0	12.6±9.1	.019[m]
III-IV	4.0-42.0	12.5	17.3±12.0	

[m]Mann–Whitney *U*-test.

In our study, we observed smaller-than-expected smoking rates in hospitalized patients who tested positive for COVID-19 that statistically catalyzed this study. We performed our study with inpatients because their progress was easy to follow and similar studies were performed in hospitalized patients.

Fourteen of the patients in the study were smokers (6.5%). In the latest studies on the prevalence of smoking in Turkey, the nationwide rate of smoking was 25.7%.[17] One in four people in Turkey is a smoker, while in COVID-19 isolation service, only a 6.5% rate of smoking was observed. This supports the theory that smoking has no negative impact on COVID-19 development. In the review

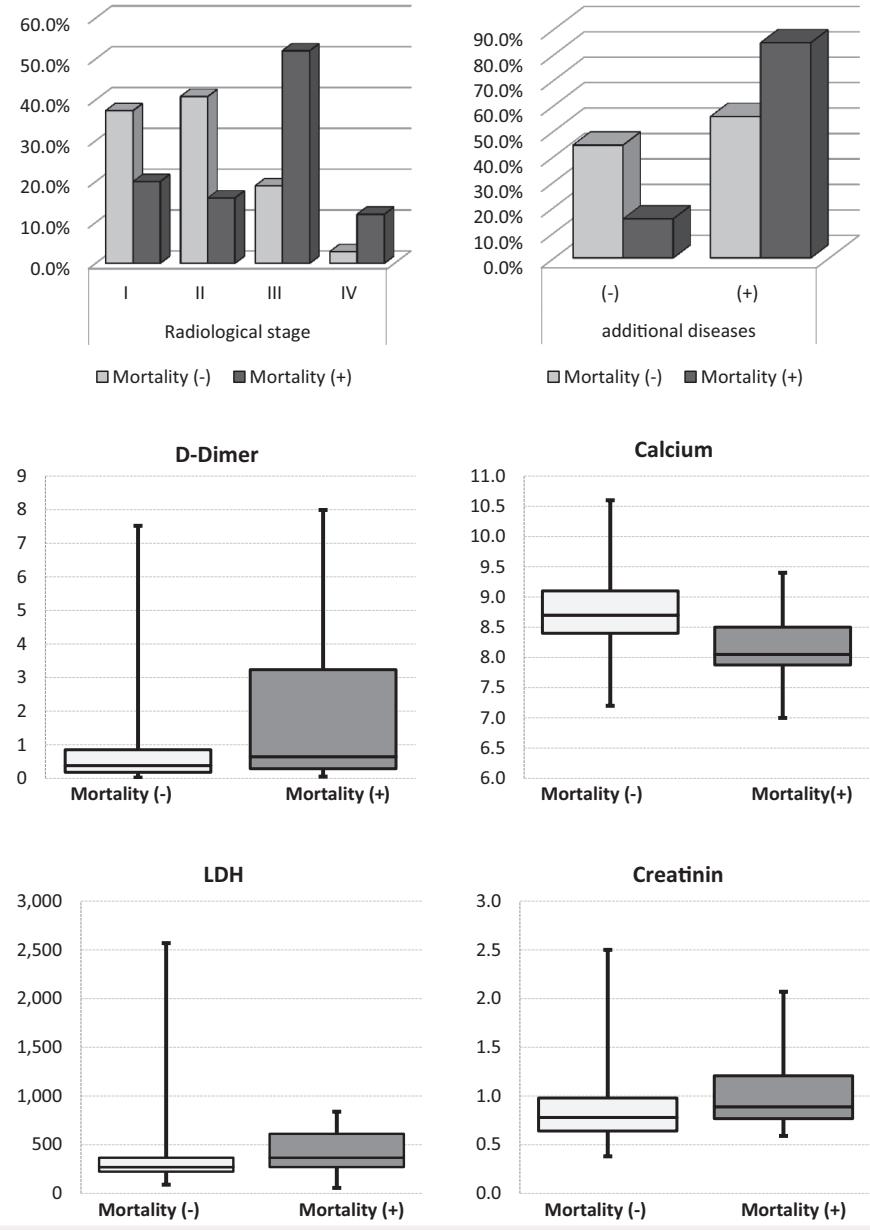

Figure 1. Effects of Creatinin, LDH, D-Dimer, Calcium, radiological stage and chronic diseases on mortality.

showing the relationship between smoking and COVID-19 in China, where the smoking prevalence is 26.6%, 5960 patients' smoking rates have changed between 1.4 and 12.6%. This study, conducted with patients hospitalized in COVID-19 isolation service, claimed that smoking did not meet the hospitalization criteria for COVID-19, and on the contrary, it may reduce risk. The results of our study are similar to and supportive of these results. At the same time, the CT scores we used to stage the severity of the disease were not statistically related to smoking ($P > .05$). We did not see any significant effect of smoking on mortality rate ($P > .05$) or on discharge time ($P > .05$).

A semi-quantitative scoring obtained from CT images was used to determine the severity of COVID-19's pulmonary involvement. A CT scan was performed during the first day of the patient's hospitalization. Each lung lobe was scored as 0 (0%), 1 (1–25%), 2 (26–50%), 3 (51–75%), or 4 (76–100%), according to the COVID-19 involvement percentage. The total involvement score of 5 lobes (0–20) was obtained, and a CT evaluation was performed in the lung parenchyma window. Scoring was performed according to the ground glass opacity appearance of COVID-19, which is the typical lung involvement, and according to the percentage of consolidations. In CT imaging with a staging of maximum 4 and minimum 0 points, the mean value was 1.95.

The average radiological stage was reported as 2.56 in the dead patients' group. There was a correlation between the

radiological predictor and the outcome status ($P < .05$). It seems that an elevated radiological stage is a predictor of death.

We do not have a standard discharge time at our hospital. When the patients show no fever, no respiratory distress, normalized laboratory tests, and good general condition for at least three days, we discharge them. The average discharge time was 13.8 days. According to our data, we can calculate the average discharge time by scoring their CTs. A high point CT stage will likely delay discharge ($P < .05$).

In conclusion, observation of a consistently low prevalence of smoking among hospitalized COVID-19 cases, together with the potential mechanisms through which nicotine interacts with the inflammatory process and the renin–angiotensin–aldosterone system, highlights that the relationship between smoking and COVID-19 should be further investigated. The complex interaction between smoking and the renin-angiotensin-aldosterone/ACE-2 systems presents multiple challenges to the researcher, the clinician, and the COVID-19 patient. However, CT staging appears to be a very important prognostic factor that may be helpful in the future, especially regarding death and discharge times.

The shortcomings of our study are that our most recent information about current cigarette prevalence in Turkey is from 2014, our patient numbers are low, and we do not have any data on electronic cigarette usage versus traditional heat-based cigarette usage.

Ethics Committee Approval: Ethical committee approval from Istanbul Bakırkoy Sadi Konuk Research Hospital with 2020/242 protocole code and 2020-12 decision number.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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