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Original Article

Can Thorax Computed Tomography Severity Score in Coronavirus Disease 2019 Patients Differentiate Smokers from Non-smokers?

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Abstract

OBJECTIVE: The aim of this study was to explore the impact of smoking history on the severity of coronavirus disease 2019 radiologic findings. Therefore, we compared the computed tomography severity scores of smoking coronavirus disease 2019 patients with those of non-smoking coronavirus disease 2019 patients.

MATERIAL AND METHODS: A total of 121 patients were included in our study group. We retrospectively reviewed 121 patients who underwent reverse transcription-polymerase chain reaction sampling and computed tomography examination in our hospital between April 1, 2020, and July 30, 2020. All computed tomography images were independently reviewed by 2 radiologists.

RESULTS: There were 15 (12.4%) active smokers, 38 (31.4%) former smokers, and 68 (56.2%) never-smokers in this study. Among the 85 patients with evidence of pneumonia in thorax computed tomography, mean computed tomography severity scores were 8.02 and standard deviation 5.812. Computed tomography severity scores for patients with pathological computed tomography scans (n = 85) were performed for evaluating smoking status (never-smokers and smokers). We found a statistically significant relationship between computed tomography severity scores of never-smokers (n = 39) and smokers (n = 46) ($Z = 2.243$, $P = .025$). The computed tomography severity scores threshold for differentiating smokers in our study group was 8, with a sensitivity of 52.2% and a specificity of 79.5%. Among the 121 patients, 34 (28.1%) were in the asymptomatic group, 36 (29.75%) were in the mild group, 28 (23.14%) were in the common group, and 23 (19.0%) were in the severe group with severe pneumonia and respiratory distress. Five (1.47%), 16 (44.44%), 14 (50%), and 18 (78.26%) of the patients in these groups were smoking, respectively.

CONCLUSION: Among coronavirus disease 2019 patients, smoking is associated with the progression of the disease and increased adverse effects. In our study, smoking status was significantly correlated with thorax computed tomography findings on admission. Computed tomography severity scores assessment helps to evaluate the disease extent in coronavirus disease 2019 patients.

KEYWORDS: Computed tomography, COVID-19, CT severity score, smoker, smoking
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INTRODUCTION

A new epidemic of unknown disease occurred in Wuhan City, China, at the end of December 2019.[1] The novel coronavirus was established as the source of deep sequencing analysis of samples of the respiratory tract on January 7, 2020. The novel coronavirus is now called severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1,2]

Severe acute respiratory syndrome coronavirus-2 is a part of the coronavirus family, whose name derives from the crown-like appearance of the virion. This feature is due to a glycosylated cell surface spike (S) protein containing 2 main domains, S1 and S2. The SARS-CoV-2 host cell input site is angiotensin-converting enzyme-2 (ACE2). The viral spiked envelope's S2 domain has a high affinity to the ACE2 receptor, which is present in several human organs, particularly the lung epithelium.[3,4] The expression of ACE2 among smokers has been high.[4] Smokers also experience increased ACE2 gene expression in type-2 pneumocytes and alveolar macrophages, especially at the terminal portion of the small airway epithelium, a finding that is not observed in those who never smoked. Smoking increases the risk of coronavirus disease 2019 (COVID-19) and the severity of the disease by causing lung damage.[4,5]

Smoking is linked to progression to serious illness, as substantial research has shown the detrimental effect of smoking habits on lung health and its causal connection with a variety of respiratory diseases.[6] Smoking affects the junctions between cells, leading to increased epithelial permeability, and reduces resistance to infections by impairing mucociliary clearance, causing peribronchiolar inflammation and damaging the immune system.[7,8] Previous studies report that smokers are twice as likely to catch the flu as non-smokers and experience more severe effects. Smokers had higher mortality rates in the previous epidemic of Middle East respiratory syndrome.[9,10] Middle East respiratory syndrome coronavirus belongs

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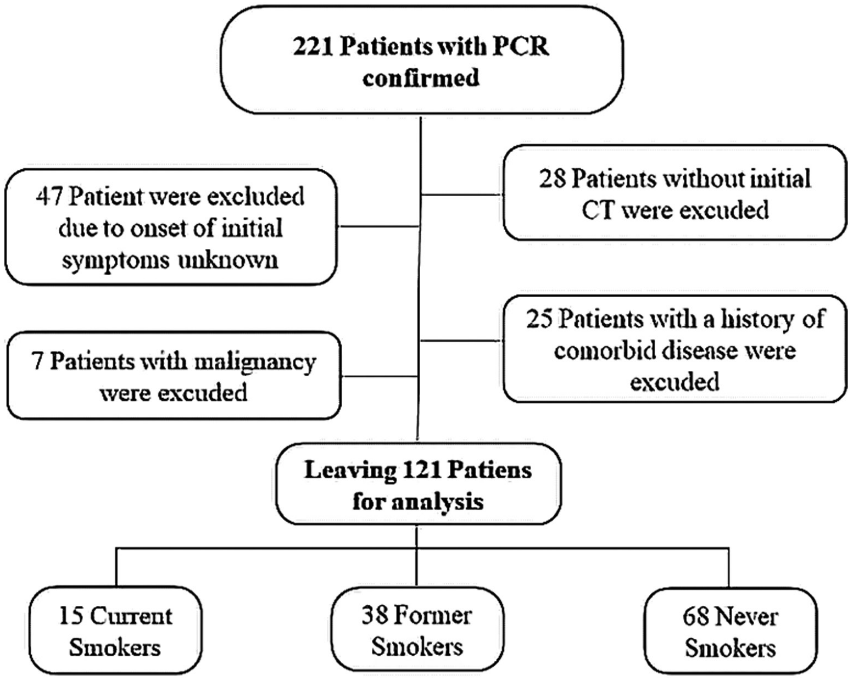

Figure 1. Recruitment flow chart.

to the coronavirus family, like SARS-CoV and SARS-CoV-2. Their structures and mechanisms of infection are similar.[9,11]

To date, several studies have documented the correlation between smoking and the incidence of COVID-19.[12-15] In some trials, smokers were more likely (1.4-fold) to show extreme effects of COVID-19 and their mortality risk was around 2.4 times that of non-smokers.[12,14]

The precise duration of smoking is not recorded in most reports. However, we are yet to find a report determining the magnitude of COVID-19 pneumonia in thorax computed tomography (CT) among smokers.

Imaging plays a significant role in COVID-19 pneumonia diagnosis and management. In highly suspected cases, CT is considered the first-line imaging modality and helps detect improvements during treatment.[16,17] It can detect lung lesions quickly at an early stage with high sensitivity.[18] The severity of the lung involvement in CT images can represent the severity of the disease.

The purpose of this research is to investigate the effect of the history of smoking on the severity of COVID-19 radiological findings. We compared the CT severity scores (CTSS) of smoking COVID-19 patients with those of non-smoking COVID-19 patients.

MAIN POINTS

- Significant damage to the lungs from smoking increases the risk of coronavirus disease 2019 (COVID-19) and the development of serious illness.
- Pneumonia among smokers is more severe than never-smokers, according to computed tomography severity scores (CTSS).
- Semi-quantitative CTSS assessment helps assess the extent of the disease in COVID-19 patients and indicates severity.

MATERIAL AND METHODS

Patients and Groups

This study protocol was approved by Haydarpaşa Numune Training and Research Hospital's Medical Ethics Committee and by the Turkish Ministry of Health, COVID-19 Scientific Research Committee (approval number: 62977267-E.75).

We retrospectively evaluated 121 patients with positive reverse transcription-polymerase chain reaction (RT-PCR) results for COVID-19 whose thorax CTs were obtained in our tertiary hospital between May 10, 2020, and November 30, 2020. The inclusion criteria were as follows: (1) initial RT-PCR test performed on admission day, (2) thorax CT imaging performed within 48 hours after RT-PCR testing, and (3) initial CT examination performed within 14 days (early and progressive phase of the disease) after the onset of initial symptoms.[19] Being under the age of 18 years was the exclusion criterion. Patients with comorbid diseases and malignancies were not included in the evaluation. The time between the onset of the patient's symptoms, the date of the first positive RT-PCR test, and the date of the first thorax CT scan were recorded. Forty-seven cases were excluded because the date of clinical onset was uncertain, and 121 remaining patients (15 current smokers, 38 former smokers, and 68 never-smokers) who met the above criteria were included in our study group (Figure 1).

Image Interpretation

Computed tomography was performed using one of the CT scanners of our hospital (General Electric Healthcare Optima CT 520, USA) allocated for patients with suspected COVID-19. The same device was used in all the patients for the initial images, and the images were acquired using the following parameters: 100 kV, 120 mA, detector coverage: 40.0 mm, helical thickness: 5.0 mm, pitch and speed (mm/rot): 1.531 : 1 and 61.25, respectively, and rotation time: 0.5 seconds. In all patients, CT examinations were conducted without a contrast medium in the supine position. The images were reconstructed using the lung window (width: 1000-1400 HU; level: 750 HU) and the mediastinal window (width: 350 HU; level: 35-40 HU).

Chest Computed Tomography Severity Score Assessment
All CT images were separately checked for the semi-quantitative CT (SCT) study by a board-certified radiologist (BY) with 5 years of experience and a radiologist (AOB) with 17 years of experience at the workstation. Observers were not informed of the experimental results and clinical findings of the patient.

We used CTSS for the assessment of the COVID-19 load on the initial scan received at admission, as defined by Yang et al.[20] This score uses lung opacification as a measure to show the extent of lung involvement. All thin-section CT scans were examined in the lung parenchyma window. The number of lung segments, which was 18, was accepted as 20 in order to facilitate the evaluation and ensure equality. While the posterior-apical segment of the left upper lobe was divided into apical and posterior regions, the anteromedial basal segment of the lower left lobe was divided into anterior and medial basal regions. Dividing the lung into 20 regions allowed us to evaluate both sides symmetrically and equally. No lung opacities or those involving less than 50% or more than 50% of each region were assigned scores of 0, 1, and 2, respectively. The CTSS was defined as the total score given to 20 lung regions, varying from 0 to 40 points.[20] The SCTSS analyses were performed independently and final decisions were made by consensus.

Evaluation of Chest Computed Tomography Features
Two radiologists analyzed all images on a consensus basis for the features mentioned subsequently. The distribution of lesions was classified as central (lesion >3 cm from the pleura), peripheral (closer to the pleura), or both on each CT scan in the involved segments. The lesions were also categorized as unifocal or multifocal and according to attenuation of opacities [the presence of ground-glass opacities (GGO), consolidation, or mix]. Additional findings were also documented, such as the crazy-paving pattern (the thickening of interlobular septum and intralobular lines superimposed with GGO), curvilinear bands, tree-in-bud appearance, air bronchogram sign, air-bubble sign, reversed halo sign (a round GGO focal region surrounded by complete consolidation ring), and bronchiectasis. Coronavirus disease 2019- related other exceedingly rare findings were also investigated, such as cavitation, lymphadenopathy (interpreted as a lymph node with a short axis of at least 1 cm), and pleural effusion. All subjective assessments were carried out in accordance with the thoracic imaging guide.[18,20]

Clinical Classifications
All COVID-19 cases were clinically divided into 4 categories at the time of initial presentation and CT imaging based on clinical, radiological, and laboratory findings as defined by the World Health Organization as follows: the asymptomatic group had no pneumonia findings on CT, the mild group had mild symptoms (weakness, anosmia, etc.) and mild pneumonia in imaging, the common-severe group showed severe symptoms requiring hospitalization, and the severe-critical group had serious respiratory distress, septic shock, respiratory, or other organ failure needing intensive care unit (ICU) admission.[19]

Lymphopenia (<800 µL), the elevation of liver and kidney function tests, high-precision cardiac troponin I, D-dimer (>1000 ng/mL), high lactate, prolonged prothrombin time, decreased fibrinogen, high lactate dehydrogenase, creatine kinase elevation in the presence of inflammatory indicators [C-reactive protein (CRP) (>40 mg/L), ferritin (>500 ng/mL), interleukin-6, etc.] may be considered poor prognostic signs.[19,21]

Statistical Analysis
Statistical analysis was conducted with Statistical Package for the Social Sciences software for Windows, version 25.0. (IBM Corp, Armonk, NY, USA). Descriptive statistical methods (standard deviation, average, rate, percentage, minimum, and maximum) were used to analyze the results. Kolmogorov–Smirnov, Shapiro–Wilk, and graphical tests were utilized to check the suitability of quantitative data to normal distribution. The Student's *t*-test was used for 2-group comparisons of normally distributed quantitative data, while Mann–Whitney *U* test was used for 2-group comparisons of non-normally distributed data. One-way analysis of variance test was utilized for comparison of 3 or more normally distributed groups and Bonferroni test for paired comparisons. Kruskal–Wallis, Bonferroni, and Dunn's tests were used for paired comparisons of 3 or more non-normally distributed groups. Multivariate analysis of covariance (MANCOVA) was used to correct for gender and age differences between groups, where significant effects were observed. The Pearson's chi-square test was used to compare qualitative results. Spearman's correlation analysis was used to assess the relationship among variables. Diagnostic screening assessments (sensitivity, specificity, positive predictive value, and negative predictive value) and receiver operating characteristics curve analysis were used to evaluate the cut-off for CTSS. Significance was assessed at $P < .05$.

The evaluation of the correlation coefficient (r) is made according to the following criterion: The r-value of 0-0.25 was considered poor, 0.26-0.49 as weak, 0.50-0.69 as moderate, 0.70-0.89 as strong, and 0.90-1.00 as very strong.

RESULTS

This study included 121 patients [76 (62.8%) males and 45 (37.2%) females] with positive PCR test results for SARS-CoV-2. Their ages ranged from 21 to 80 years, with a mean age of 44.17 ± 12.65 years. Fifteen (12.4%) active smokers, 38 (31.4%) former smokers, and 68 (56.2%) never-smokers were included in this study.

We observed a significant difference between the ages of patients who did and did not smoke ($P = .003$ and $P < .001$). Paired comparisons revealed that the mean age of those who formerly smoked was higher than those who actively smoked and those who had never smoked ($P = .021$, $P = .008$, and $P < .05$, respectively) (Table 1).

Table 1. Evaluation of Descriptive Features According to Smoking

	Never-Smokers (n = 68)	Current Smokers (n = 15)	Former Smokers (n = 38)	P	Post Hoc
Age (years)					
Median	**42.5**	**39**	**52**	**.003**[**a]	3 > 1.2
Mean ± SD	42.13 ± 11.07	39.47 ± 9.18	49.66 ± 14.76		
Gender (%)					
Female	**54.4%**	**20.0%**	**13.2%**	**.001**[**b]	3.2 > 1
Male	**45.6%**	**80.0%**	**86.8%**		
CT (%)					
Pathological	**57.4%**	**66.7%**	**94.7%**	**.001**[**b]	3 > 1.2
Normal	**42.6%**	**33.3%**	**5.3%**		

[a]One-way ANOVA test; [b]Pearson's chi-square test; **$P < .01$.
CT, computed tomography; SD, standard deviation; ANOVA, analysis of variance.

The mean of the initial CT score measurements of males was 6.84 ± 6.50 and that of the females was 3.67 ± 4.73. Males had a higher mean initial CT score measurement than females. The smoking rate was higher among males compared to females ($P = .001$ and $P < .01$). A significant difference was observed between the initial CTSS measurements by gender ($P = .005$ and $P < .01$).

Eighty-five patients (70.2%) had evidence of pneumonia on admission CT and 36 (29.8%) showed no sign of pneumonia. Among 85 patients with pneumonia, 94.7% were former smokers, 66.7% were active smokers, and 57.4% had never smoked. A statistically significant difference was found between the CT results of the cases according to smoking ($P = .001$ and $P < .01$).

Among the 85 patients with evidence of pneumonia in thorax CT, the mean CTSS and standard deviation were 8.02 and 5.812, respectively. Pair-wise comparisons of CTSS in patients with pathological CT scans (n = 85) were performed for smoking status [never-smokers and smokers (current or former)] using Mann–Whitney *U* test, which revealed a significant relationship between CTSS of never-smokers (n = 39) and smokers (n = 46) ($Z = 2.243$, $P = .025$). A statistically significant relationship was found between CT scores of never-smokers (n = 39) and former (n = 36) smokers ($Z = 2.702$, $P = .007$). No statistically significant relationship was found between active smokers (n = 10) with either never-smokers or former smokers ($P > .05$).

As age showed a significant correlation with initial CTSS and there were significant age differences between smoking groups, a MANCOVA analysis was performed to correct for age differences (Table 2). We found age to be a significant covariate for CT score ($P < .01$). The same process was also applied to gender, which was not found to be a significant covariant ($P = .901$, partial ETA squared = 0). Therefore, gender correction was not performed for the final analysis. Age-corrected mean CTSS were calculated for 85 patients with abnormal CT scans (CTSS higher than 0). Pair-wise comparison between age-corrected CTSS of smokers (current and former) versus never-smokers showed a significant mean CTSS difference of 3.03 (95% CI: 0.79-5.26; $P = .008$).

Receiver operating characteristics curve analysis revealed 64% area under the curve ($P = .023$). A CTSS >8 differentiated smokers in our study group with a sensitivity of 52.2% and a specificity of 79.5% (Figure 2).

We observed a significant difference between the D-dimer measurements in terms of smoking status ($P = .011$ and $P < .05$). Paired comparisons revealed that D-dimer measurements of current and former smokers were higher than those of non-smokers ($P = .008$ and $P < .01$). C-reactive protein values of the cases also significantly differed by smoking status ($P = .001$ and $P < .01$): CRP values of the subjects who were former smokers were higher than that of never-smokers ($P = .001$ and $P < .01$), and current and former smokers' CRP values were higher than that of non-smokers ($P = .001$ and $P < .01$). *White Blood Cell*, Neutrophile, and *Lymphocyte* measurements of the patients were similar between the smoker groups ($P > .05$).

Among 121 patients, 34 (28.1%) were asymptomatic, 36 (29.75%) had mild disease, 28 (23.14%) had common-severe

Table 2. Age-Corrected Mean CTSS According to Smoking Groups

	Mean CTSS	Age-Corrected Mean CTSS (Mean age: 47.65)	Standard Error
Never-smokers	6.15	6.38 (95% CI: 4.73-8.02)	0.83
Current smokers	7.80	8.91 (95% CI: 5.61-12.2)	1.66
Former smokers	10.11	9.56 (95% CI: 7.82-11.3)	0.873
Smokers (current and former)	9.61	9.42 (95% CI: 7.91-10.9)	0.759

95% CI; age-corrected means were calculated using MANCOVA for a mean age of 47.65 years.
CTSS, computed tomography severity score; MANCOVA, multivariate analysis of covariance.

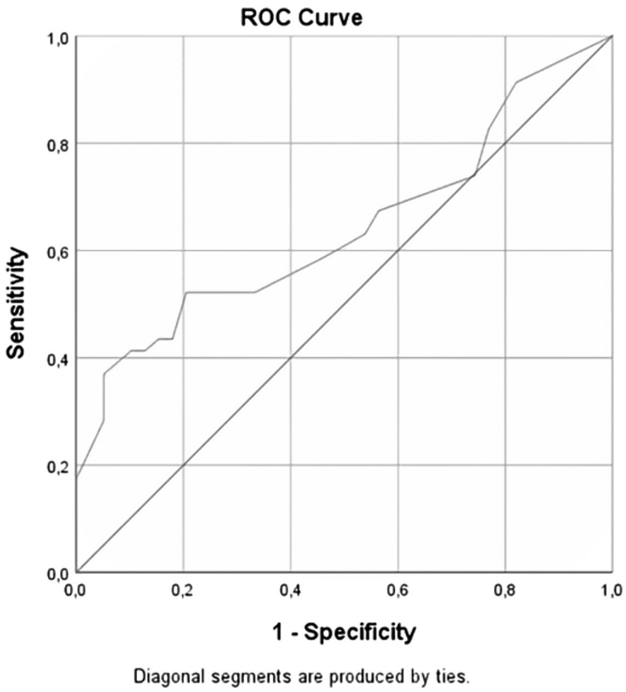

Figure 2. ROC curve for initial CTSS levels according to smoking status. ROC, receiver operating characteristic curve; CTSS, computed tomography severity score.

disease, and 23 (19.0%) had severe-critical disease with severe pneumonia and respiratory distress. Five (14.7%), 16 (44.44%), 14 (50%), and 18 (78.26%) of the patients in these groups were smokers (current and former smokers), respectively.

The CT images of a 52-year-old non-smoker male patient with a mild clinic diagnosis of COVID-19 were demonstrated to be low (Figure 3).

The CT images of a 45-year-old male patient with a common clinic diagnosis of COVID-19 are shown in Figure 4. He had a fever, respiratory symptoms without respiratory distress, and pneumonia in imaging.

Coronal CT images of a 59-year-old former smoker male patient with a severe clinic diagnosis of COVID-19 are also shown in Figure 5. He had a fever, respiratory symptoms with respiratory distress, need for oxygen, and severe pneumonia.

The clinical pictures of patients differed according to smoking status (P = .001 and P < .01). In the asymptomatic group, the rate of non-smokers was higher than that of former smokers. There were no substantial differences in the mild and common-severe groups. In the severe disease group, the rate of patients who were former smokers was higher than that of never-smokers and current smokers (Table 3). All 4 cases in need of ICU were current or former smokers, and 1 former smoker died.

DISCUSSION

Smoking causes serious lung damage, which raises the risk of COVID-19 and the development of serious illnesses. In our study, smoking status was significantly correlated with thorax CT findings on admission. Semi-quantitative CTSS assessment helps in determining the amount of disease and severity in COVID-19 patients. In age-corrected MANCOVA analysis, smokers had higher age-corrected CTSS compared to never-smokers. Although the means calculated with MANCOVA may be affected by outliers because of the small sample size and slight left skew of the data, it was noted that significant outliers (above third quartile + 1.5 interquartile range) with high CTSS (2 outliers with score = 16) were only present in the never-smokers' group and their removal would not affect the statistical significance of the results. We also performed a rank-based Mann–Whitney U test to confirm the significant difference between these groups. The CTSS threshold for differentiating smokers in our study group was 8, with a sensitivity of 52.2% and a specificity of 79.5%.

Of the 121 patients, smokers (current and former) had a higher number of serious cases of COVID-19 than never-smokers in our study. All 4 cases in need of ICU were current or former smokers, and 1 death occurred in the former group. To avoid the confounding effects of comorbidities such as diabetes mellitus and hypertension on COVID-19 pneumonia, we excluded cases with comorbid diseases from our study, which may explain the low mortality rate.

There have been several studies on the effectiveness and usability of CTSS. Yang et al[20] used thorax CTSS to determine the load of COVID-19 at admission. Significant differences were observed between mild and serious cases in terms of lung opacity scored in each lung area (P < .05). They

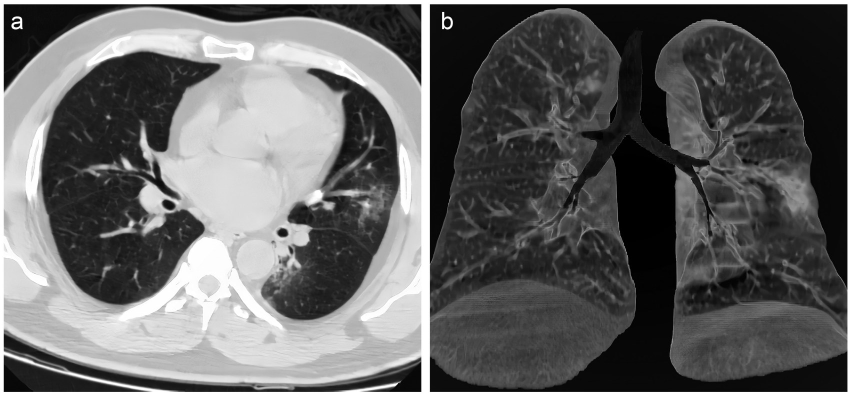

Figure 3. (A) Axial chest CT image shows GGO in the inferior lingular segment of left upper lobe and posterior segment of left lower lobe, CTSS is 4. (B) Volumetric CT image of the same patient shows bilateral and peripheral GGO. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

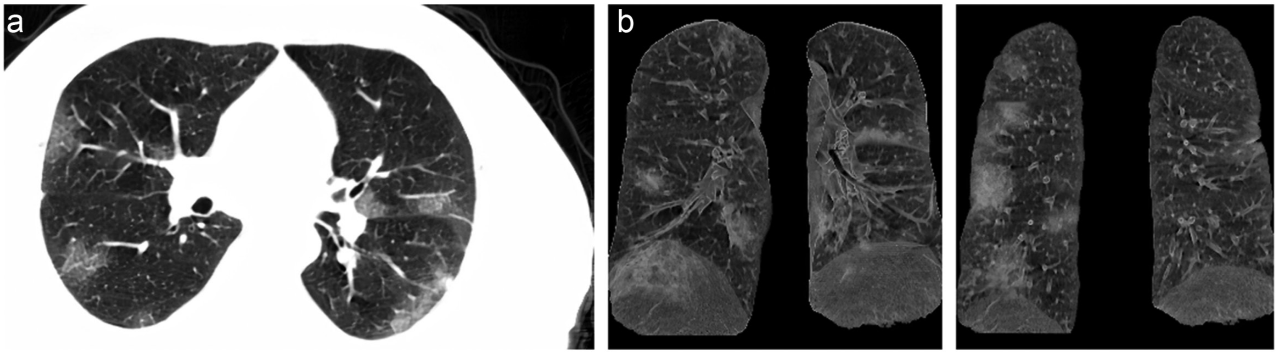

Figure 4. (a) Axial chest CT image shows bilateral, peripheral GGO with less than 50% involvement in all lobes, CTSS is 15. (b) Volumetric CT images of the same patient show bilateral and peripheral GGO. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

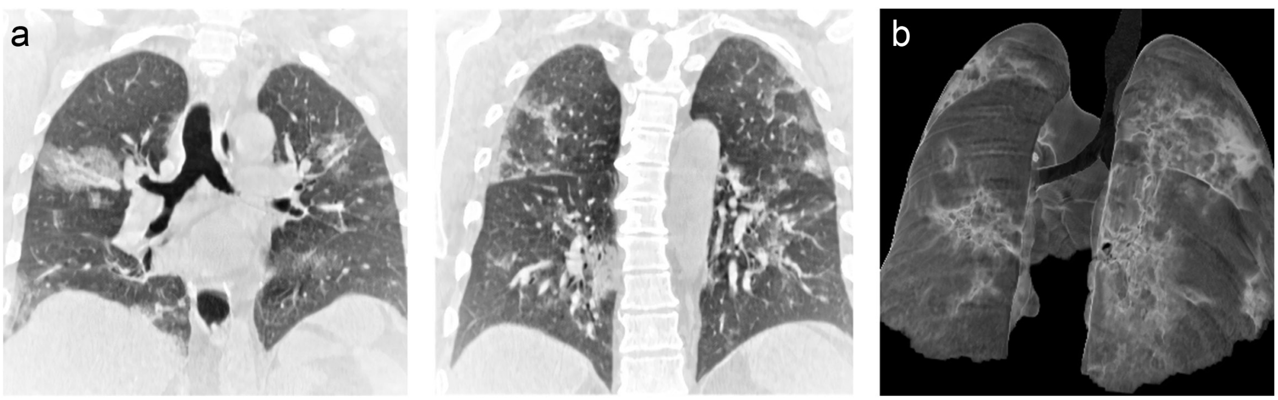

Figure 5. (a) Coronal chest CT images show bilateral, central, and peripheral distribution GGO and consolidation with more than 50% involvement in all lobes, CTSS is 21. (b) Volumetric CT image of the same patient shows bilateral, widespread GGO, and consolidation. GGO, ground-glass opacities; CT, computed tomography; CTSS, computed tomography severity score.

observed that CTSS was higher in serious cases compared to mild cases. They also established that a CTSS threshold of 19.5 could classify serious COVID-19, with a sensitivity of 83.3% and a specificity of 94%, resulting in an Negative Predictive Value of 96.3%.

Several studies on the impact of smoking on COVID-19 and COVID-19 pneumonia have been published.[14] However, we have not seen any research showing the impact of smoking on COVID-19 in terms of thorax CTSS.

Guan et al identified clinical characteristics of patients with COVID-19. There were 1099 smoking patients, 173 with serious symptoms and 926 with mild symptoms. Among severe patients, 16.9% were current smokers and 5.2% were former smokers, while among non-severe patients, 11.8% were current smokers and 1.3% were former smokers. In addition, 25.5% were active smokers and 7.6% were former smokers in the group of patients either in need of mechanical ventilation, ICU admission, or those who died. Among the rest, 11.8% were active smokers and 1.6% were former smokers. No statistical analysis was conducted to assess the relationship between disease severity and smoking status.

Similarly, the clinical characteristics of 140 patients with COVID-19 were presented by Zhang et al.[13] The findings showed that 3.4% of severe patients (n = 58) were active smokers and 6.9% were former smokers; compared with non-severe patients (n = 82), 0% of them were active smokers and 3.7% of them were former smokers, resulting in an OR of 2.233 (95% CI: 0.65-7.63; *P* .2). Smokers had more severe

Table 3. Evaluation of Clinical Status According to Smoking

COVID-19 Severity	Never-Smokers (n = 68)	Current Smokers (n = 15)	Former Smokers (n = 38)	*P*
Asymptomatic	29 (42.6)	3 (20.0)	2 (5.3)	**.001**[**b]
Mild	20 (29.4)	6 (40.0)	10 (26.3)	
Common	14 (20.6)	4 (26.7)	10 (26.3)	
Severe	5 (7.4)	2 (13.3)	16 (42.1)	

[b]Pearson Chi-square test; [**]$P < .01$.
COVID-19, coronavirus disease 2019.

cases of COVID-19 compared to non-smokers, similar to our study. They had also substantially higher ICU admission and subsequent mechanical ventilation requirement.

In our study, the rates of being symptomatic and hospitalization were higher in COVID-19 cases with a history of smoking. A fatal outcome is more likely to occur among smokers (current and former). In addition, pneumonia in smokers is more severe than never-smokers according to initial CTSS.

There were several limitations to this retrospective study. First, some data were missing because we only had access to clinical and laboratory data from patient files. The sum of pulmonary opacification with CTSS is a visual semi-quantitative assessment. The CTSS suggests that the amount of pulmonary opacification is a substitute for the COVID-19 severity. Furthermore, the findings have not been histologically confirmed.

CONCLUSION

Among COVID-19 patients, smoking is associated with the progression of the disease and increased adverse effects. Semi-quantitative CTSS assessment helps evaluate the disease extent in COVID-19 patients. Also, it is useful for observers and allows consensus.

Ethics Committee Approval: This study protocol was approved by Haydarpaşa Numune Training and Research Hospital's Medical Ethics Committee and by the Turkish Ministry of Health, COVID-19 Scientific Research Committee (Approval number: 62977267-E.75).

Informed Consent: This study was carried out retrospectively using the recorded data of the patients in the health information systems. This submission does not include images that may identify the person.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – B.Y.; Design – B.Y.; Supervision – B.Y.; Resources – B.Y., A.Ö.B., U.Y.Y.; Materials – B.Y., A.Ö.B., U.Y.Y.; Data Collection and/or Processing – R.B., U.Y.U.; Analysis and/or Interpretation – B.Y., R.B., U.Y.U.; Writing Manuscript – B.Y., A.Ö.B., R.B., U.Y.U.; Critical Review – B.Y., A.Ö.B., R.B., U.Y.U.

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