

Original Article



Artificial Intelligence-guided Total Opacity Scores and Obstructive Sleep Apnea in Adults with COVID-19 Pneumonia

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Abstract

OBJECTIVE: We previously demonstrated that artificial intelligence (AI)-directed chest computed tomography (CT)-based total opacity scores (TOS) are associated with high-risk obstructive sleep apnea (OSA) based on the Berlin Questionnaire. In the current study, we examined the association between TOS severity and OSA severity based on polysomnography (PSG) recordings among participants with a history of Coronavirus disease-2019 (COVID-19) infection.

MATERIAL AND METHODS: This was a post-hoc analysis of 56 patients who underwent CT imaging after being diagnosed with COVID-19 pneumonia as well as overnight PSG for a validation study with a median of 406 days after the initial COVID-19 onset. The AI software quantified the overall opacity scores, which included consolidation and ground-glass opacity regions on CT scans. TOS was defined as the volume of high-opacity regions divided by the volume of the entire lung, and severe TOS was defined as the score ≥ 15 . OSA was defined as an apnea-hypopnea index (AHI) of at least 15 events/h.

RESULTS: In total, 21 participants had OSA and 35 had no OSA. The median TOS was 10.5 [interquartile range (IQR) 1.6-21.2] in the OSA group and 2.8 (IQR 1.4-9.0) in the non-OSA group ($P = 0.047$). In a multivariate logistic regression analysis, OSA, AHI, and oxygen desaturation index were associated with severe TOS ($P < 0.05$ for all, respectively) adjusted for age, sex, body mass index, and hypertension.

CONCLUSION: AI-directed CT-based TOS severity in patients with COVID-19 pneumonia was associated with OSA severity based on PSG recordings. These results support our previous findings suggesting an association between questionnaire-based high-risk OSA and worse outcomes in COVID-19 pneumonia.

KEYWORDS: Obstructive sleep apnea, COVID-19, artificial intelligence, chest CT

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INTRODUCTION

Severe acute respiratory syndrome-Coronavirus-2 has led to a global epidemic, severely affecting the medical, economic, and service sectors since its outbreak in late December 2019.¹ As of September 19, 2024, there were 776.137,815 cases and 7.061,330 deaths worldwide.² Most individuals infected with Coronavirus disease-2019 (COVID-19) experience a range of symptoms, from undetectable to mild to severe, at the beginning of the pandemic. With appropriate medication and social distancing, many infected individuals have recovered at home. However, people with underlying medical conditions are at higher risk of hospitalization or more severe outcomes.

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Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder, affecting almost 1 billion people globally.^{3,4} The condition is described as recurrent upper airway resistance that leads to decreases or interruptions in airflow, accompanied by increased respiratory attempts.⁵ The prevalence of OSA increases with age and body mass index (BMI).⁶ Individuals with diabetes, high blood pressure, smoking, and asthma are also more likely to develop OSA⁷ and have an increased risk of severe COVID-19 outcomes.⁸

In the early stages of the COVID-19 outbreak, it has been reported that patients with OSA are more prone to COVID-19 infection and could be at higher risk of experiencing more severe symptoms compared to individuals not having OSA.⁹⁻¹¹ A retrospective analysis of medical records showed that around 10% to 12% of COVID-19 patients had been previously diagnosed with OSA.^{12,13} The mortality rate of patients with COVID-19 diagnosed with OSA was higher than that of controls, as reported by Cade et al.¹¹

Determining the actual occurrence of OSA in patients with COVID-19 is challenging because conducting polysomnography (PSG) during an active infection is not practical. In our previous study, we performed a longitudinal, questionnaire-based study among adults with COVID-19 pneumonia in 2020 and estimated the occurrence of high-risk OSA at 38% using the Berlin Questionnaire (BQ).¹³ Because obesity and hypertension are known comorbidities that negatively impact the prognosis of COVID-19, we modified the BQ scoring system to exclude these diseases.¹⁴ The modified BQ (mBQ) indicated that the prevalence of OSA was 22%. Our analysis proposed that patients identified as high-risk for OSA using the modified criteria experienced worse prognoses compared with those with low-risk OSA, regardless of sex, age, and other concomitant diseases.¹⁴

The primary engagement of the upper airway system and the lungs has made chest computed tomography (CT) imaging an essential tool for diagnosing, initially evaluating, and monitoring patients with COVID-19 throughout the pandemic.^{15,16} During these demanding times, it is vital to quickly and accurately determine disease severity. Artificial intelligence (AI) systems enable the rapid assessment of large numbers of patients, evaluation of disease severity, prediction of prognosis, and assessment of treatment response.¹⁷

In our previous research, we investigated the relationship between AI-assisted CT-based severity scores (SS) and short-

term sequels.¹⁸ Through receiver operating characteristics curve analysis, we discovered a total opacity score (TOS) of 2.65 on CT scans that resulted in 81% sensitivity and 56% specificity regarding the requirement for supplemental oxygen. Moreover, a multivariate logistic regression analysis indicated that a TOS >2.65 was linked to a nearly fourfold increase in the need for extra oxygen support and a 2.4-fold increase in the risk of hospitalization.¹⁸

In a subsequent study, we found a significant relationship between TOS and high-risk OSA and adverse COVID-19 outcomes. We now address the association between TOS severity and OSA severity in terms of apnea-hypopnea index (AHI) based on PSG data.¹⁹

MATERIAL AND METHODS

Study Design, Participants, and Ethics Approval

As illustrated in Figure 1, this study included 320 adults with COVID-19 infection in 2020 as the initial OSA COVID-19 study.⁹ Patients were, then, randomly invited for an overnight PSG in-hospital study at a median of 406 days [interquartile range (IQR) 379-475 days] after the initial COVID-19 onset. Participants without PSG and eligible CT scans as well as the ones with primary and metastatic lung malignancies and history of tuberculosis were excluded with remaining 56 participants for the current study protocol (Figure 1).

The study protocol was approved by the Koç University Committee on Human Research (approval no: 2021.231. IRB2.049, date: 06.05.2021). Written informed consent was obtained from all participants. The initial OSA COVID-19 study was registered at ClinicalTrials.gov (NCT04363333).

Data Collection and Definitions

The diagnosis of COVID-19 was based on positive polymerase chain reaction analysis of nasopharyngeal samples, clinical symptoms, and radiological findings. All patients completed

Main Points

- We previously demonstrated that artificial intelligence-guided chest computed tomography-based total opacity scores (TOS) are linked to high-risk obstructive sleep apnea (OSA) based on the Berlin Questionnaire.
- Our results suggest that the severity of TOS is associated with the severity of OSA based on objective polysomnography findings.
- These results further support the link between OSA and poor outcomes in patients with Coronavirus disease-2019 pneumonia.

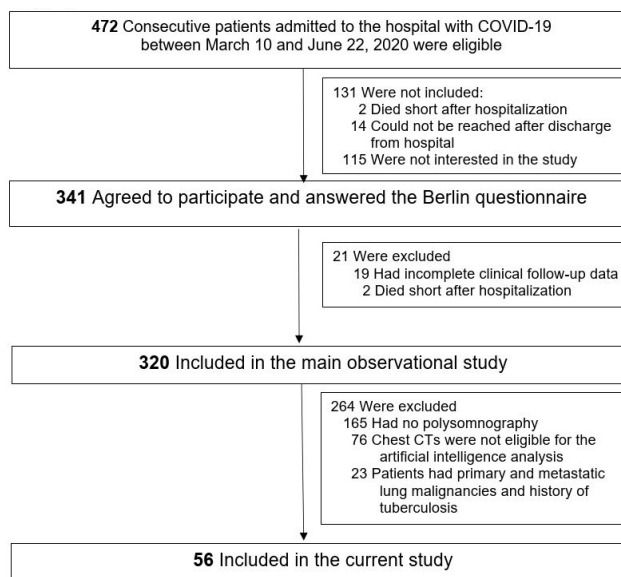


Figure 1. Flow of patients through the study

COVID-19: Coronavirus disease-2019, CT: computed tomography

a survey regarding sleep habits and sleep-related symptoms according to clinical routines. Demographics, concomitant diseases, and physical examination findings were documented. A BMI 30 kg/m² was defined as obesity.²⁰

Chest Computed Tomography Protocol and Assessment

A 64-detector row CT scanner (Somatom® Definition AS; Siemens Healthineers, Forchheim, Germany) was used to scan each patient. After a full inspiratory breath-hold, a supine scan was performed, covering the lung apices to the costophrenic angles. Protocols for low radiation doses were used, and the scanner automatically selected X-ray tube parameters based on the size of the patient. No intravenous contrast agent was used.

Siemens Healthineers (Forchheim, Germany) supplied the automated lung opacity analysis application “CT Pneumonia Analysis,” which was used to analyze images and determine the severity of pneumonia. High-opacity regions, like consolidations and ground glass opacities, which are frequently observed in lung infections, can be automatically identified and quantified using this technique. The technique computes the volumes of lobes, total lung volume, and areas with high opacity, including ground glass and consolidation, based on 3D segmentations of lesions, lungs, and lobes. The ratio of the volume of high opacity areas to the entire lung volume was used to estimate the degree of lung parenchyma involvement, which was defined as the percentage of total opacity. Figures 2A and 2B illustrate two examples of AI and CT images showing TOS values of 1.1 and 17.2, respectively.

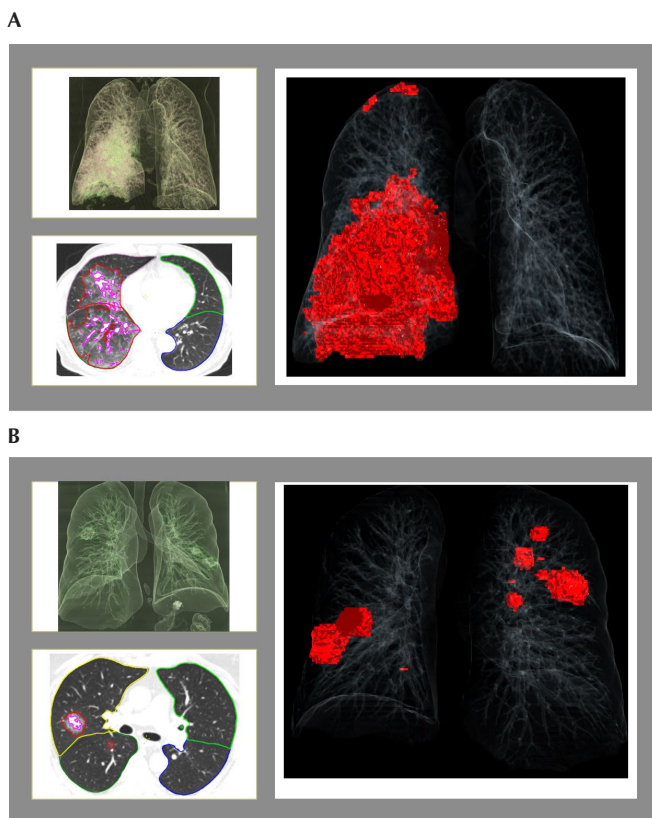


Figure 2. 360° volume rendering overview showing the affected areas and depiction of segmented lung lobes and high-density areas of a patient with (A) total opacity score of 19.3 and (B) total opacity score of 1

Sleep Studies

PSG (NOX-A1 system; Nox Medical Inc., Reykjavik, Iceland) was used in the Koç University Hospital sleep laboratory for this study. Electroencephalography, electrooculography, chin- and leg-electromyograms, nasal airflow, snoring intensity, thoracoabdominal and leg movements, body posture, heart rate (HR), oxygen saturation, and video recording were all measured as part of the PSG. According to the guidelines provided in The American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events 2.5,²¹ sleep stages and arousals were evaluated using 30-s intervals. Hypopnea was defined as a decrease in nasal pressure amplitude of >30% and/or thoracoabdominal movement of >30% for ≥10 seconds if there was significant oxygen desaturation (reduction by ≥3% from the immediately preceding baseline value) and/or an arousal. Apnea was defined as a nearly complete (>90%) cessation of airflow.²² The oxygen desaturation index (ODI) was calculated as the number of major desaturations per hour of total sleep time, and the total number of significant desaturations was also recorded. The lowest SpO₂ and amount of time below 90% SpO₂ (TS90%) were recorded. According to the most recent International Classification of Sleep Disorders-3,²² OSA was classified as an AHI ≥15 episodes per hour of total sleep time when OSA-related symptoms were missing. A professional sleep technician blind to the mBQ categorizations graded each PSG recording manually in a mixed order.

Statistical Analysis

For continuous variables, the mean with standard deviation or median with 25th and 75th percentiles was displayed, and for categorical categories, counts with percentages were used to represent the anthropometric traits and PSG results of the study population. The Shapiro-Wilk test was used to assess normalcy. The Student's t-test or Mann-Whitney rank-sum test was used to compare continuous variables between the OSA and no-OSA groups, and the χ^2 test or Fisher's exact test was used to compare categorical variables. All tests were conducted at the 5% significance level. IBM Statistical Package for the Social Sciences (SPSS) 26.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS

A total of 56 patients (mean age 56±11.5) years; 71.4% males were included (Figure 1). The median BMI was 29.3 (27.0-31.4) kg/m², and 35.7% of the entire population were obese and 39.2% were hypertensive. In total, 21 and 35 patients had OSA (AHI ≥15 events/h), and 35 had no OSA (AHI <15 events/h) (Table 1). The patients with OSA were older than the participants without OSA, but the other baseline characteristics, demographics, and comorbidities were similar, except for the need for supplemental oxygen, which was more common among the OSA patients, who also had significantly longer hospitalization duration during the initial period (Table 1).

As shown in Table 2, sleep efficiency and the proportion of slow-wave sleep were significantly lower in the OSA group than in the non-OSA group. The proportion of rapid eye movement sleep was similar in both groups. The AHI and oxygenation indices were more severe in the OSA group per definition.

Table 1. Baseline characteristics and demographics of COVID-19 patients with and without OSA

	OSA n = 21	No OSA n = 35	P value
Demographic characteristics			
Age, y	60.0 (56.5-66.0)	53.0 (45.0-60.0)	0.007
Age >65 years	4 (19.0)	4 (11.4)	0.456
Male sex	17 (81.0)	23 (65.7)	0.222
BMI, kg/m ²	30.4 (28.1-33.9)	28.1 (26.9-31.2)	0.135
Comorbidities			
Hypertension	10 (47.6)	12 (34.3)	0.323
Obesity	7 (33.3)	13 (37.1)	1.000
Diabetes mellitus	4 (19.0)	5 (14.3)	0.715
Coronary artery disease	1 (4.8)	3 (8.6)	1.000
COPD	0 (0.0)	0 (0.0)	1.000
Asthma	1 (4.8)	0 (0.0)	0.375
Current smoking	2 (9.5)	3 (8.8)	1.000
Hospitalization and intensive care unit			
Hospitalization	17 (81.0)	27 (77.1)	0.737
ICU ward	3 (14.3)	2 (5.7)	0.352
Supplemental oxygen	13 (61.9)	8 (22.9)	0.003
In-hospital days	13.0 (4.5-17.5)	6.0 (3.0-8.0)	0.005

COVID-19: Coronavirus disease-2019, OSA: obstructive sleep apnea, y: year, BMI: body mass index, COPD: chronic obstructive pulmonary disease, ICU: intensive care unit

Table 2. Polysomnographic characteristics of patients with COVID-19 with and without OSA

	OSA n = 21	No OSA n = 35	P value
TST, min	382 (340-422)	398 (347-418)	0.571
Sleep efficiency, %	80 (71-85)	87 (77-92)	0.036
Slow wave sleep, % TST	17.2 (14.2-22.9)	30.6 (22.5-34.1)	<0.001
REM sleep, % of TST	16.1 (11.8-20.2)	18.4 (15.2-20.0)	0.290
AHI, events/h	21.8 (17.8-33.0)	6.8 (3.0-8.8)	<0.001
ODI, events/h	18.2 (14.8-27.7)	4.9 (2.3-6.7)	<0.001
Mean SpO ₂ , %	92.4 (91.5-93.4)	94.2 (92.9-95.0)	<0.001
SpO ₂ <90%, min	20.8 (8.9-61.0)	1.0 (0.2-5.7)	<0.001

COVID-19: Coronavirus disease-2019, OSA: obstructive sleep apnea, REM: rapid eye movement, AHI: apnea-hypopnea index, ODI: oxygen desaturation index

As illustrated in Figure 3, the median TOS was 10.5 (IQR 1.6-21.2) in the OSA group and 2.8 (IQR 1.4-9.0) in the no-OSA group ($P = 0.047$) (Figure 3), and the TOS was significantly correlated with AHI ($r = 0.33$, $P = 0.014$) as well as with ODI ($r = 0.31$, $P = 0.020$) in the entire cohort (Figure 4).

As shown in Table 3, OSA, AHI, and ODI were significantly associated with severe TOS after adjusting for age, male sex, BMI, and hypertension.

DISCUSSION

The main finding of our study was that AI-guided CT-based TOS severity was significantly associated with OSA severity in terms of AHI and ODI.

To the best of our knowledge, this is the first study to investigate the association between radiological severity of COVID-19 infection and OSA severity based on PSG findings. Previous studies addressing the prevalence of OSA in patients with COVID-19 infection were retrospective in nature and based

on diagnostic codes because of the inability to perform PSG during the active infectious periods. A retrospective study reported that 9.5% of individuals with COVID-19 pneumonia had a documented OSA diagnosis.²³ Another study showed that COVID-19 patients, with confirmed OSA diagnoses had higher mortality rates (12.3%) than the control group.¹¹

In our first study, we prospectively calculated the prevalence of OSA using the BQ among 320 patients with COVID-19 in the acute phase of infection.¹³ We found that 38% of the study population had a high-likelihood of OSA based on the questionnaire, which was much higher than the anticipated 14% prevalence in a nationwide study involving 5.021 adults in Türkiye.²⁴ As previously discussed in detail elsewhere,¹⁴ we modified the BQ scoring system by excluding obesity and

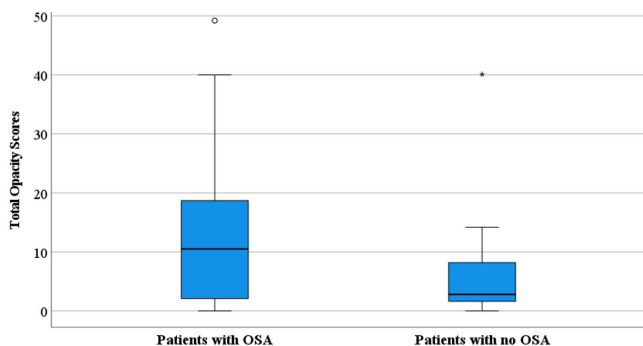


Figure 3. Comparison of total opacity scores among the study groups
OSA: obstructive sleep apnea

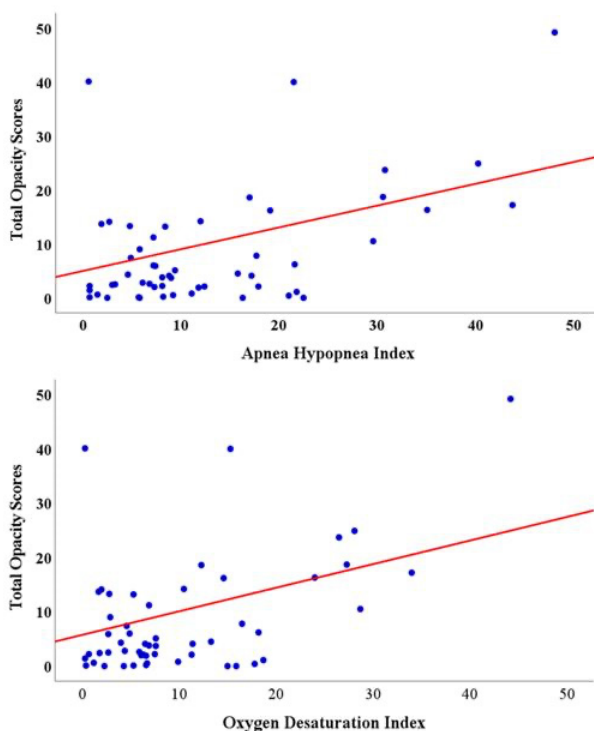


Figure 4. Linear association between total opacity scores and AHI and ODI
AHI: apnea-hypopnea index, ODI: oxygen desaturation index

Table 3. Regression analysis of variables associated with severe opacity score (TOS ≥15)

	Variables	Odds ratio	95% confidence interval		P
			Lower	Upper	
Model 1	Constant	0.016			0.256
	Age	0.978	0.885	1.082	0.669
	Male sex	2.030	0.251	16.396	0.669
	BMI	1.074	0.933	1.236	0.320
	Hypertension	1.743	0.277	10.960	0.554
	OSA	10.704	1.632	70.221	0.014
Model 2	Constant	0.050			0.428
	Age	0.964	0.868	1.070	0.491
	Male sex	0.904	0.107	7.663	0.926
	BMI	1.076	0.931	1.244	0.014
	Hypertension	1.401	0.213	9.200	0.725
	AHI	1.100	1.019	1.186	0.014
Model 3	Constant	0.013			0.243
	Age	0.982	0.889	1.085	0.724
	Male sex	1.197	0.150	9.579	0.866
	BMI	1.097	0.953	1.263	0.196
	Hypertension	1.299	0.219	7.718	0.774
	ODI	1.083	1.003	1.169	0.042

BMI: body mass index, OSA: obstructive sleep apnea, AHI: apnea-hypopnea index, ODI: oxygen desaturation index, TOS: total opacity scores

hypertension to better assess the prognosis of COVID-19 in individuals with high-risk OSA. The prevalence of high-risk OSA (22% in the study population) according to the mBQ.¹³

In the following validation study,¹⁴ the participants completed the surveys again and attended the PSG. People were classified as having OSA if their AHI was 15 occurrences per hour. With a sensitivity of 89%, specificity of 93%, predictive value of 89%, and negative predictive value of 93%, the mBQ demonstrated an accuracy of 91%. With an area under the curve of 0.91, the mBQ was a reliable method for diagnosing OSA. The method showed excellent diagnostic accuracy, specificity, and sensitivity in patients with a history of COVID-19. After removing the confounding effects of obesity and hypertension, the mBQ may be used as a screening tool for high-risk OSA and as a predictive tool in clinical cohorts.¹⁴

Chest CT scans play an important role in hospital settings for various purposes, such as patient prioritization and diagnosis support. Additionally, it could help quantify the severity and progression of diseases as well as monitor the response to treatment. AI algorithms based on CT scans improve diagnostic accuracy by reducing false-negative results and predicting disease outcomes. They also enable the analysis of large image datasets quickly and at a faster speed for chest CT scans.²⁵⁻²⁹

In a research conducted by Kardos et al.³⁰ involving 1,259 patients it was found that 51.5% of the samples were positive for reverse transcription-polymerase chain reaction (RT-PCR). In the test group of patients evaluated using deep learning technology, CT severity scoring compared to RT-PCR results showed sensitivity at 68%, specificity at 55%, accuracy at 58%, and positive predictive value of 58.9%, respectively. This standardized scoring system for COVID-19 pneumonia helps in diagnosis and clinical decision-making. Furthermore, it is suggested that the deep learning-based CT SS can identify lung abnormalities linked to COVID-19 even before a positive result from RT-PCR testing.³⁰

Chrzan et al.³¹ suggested that AI-based automated assessment of CT scans in individuals with COVID-19 pneumonia might serve as a tool in COVID-19 pneumonia to evaluate clinical severity and determining the optimal treatment plan. In addition, AI analysis can eventually become a routine diagnostic imaging approach. They also verified that the possibility of being admitted to the intensive care unit or experiencing a fatal outcome was highly correlated with the number of lung abnormalities detected by AI on CT scans during COVID-19. A connection was also observed regarding the extent of inflammation measured in laboratory tests.³¹

The application of AI in analyzing chest CT scans has proven valuable for predicting results and evaluating the severity of illnesses. Following the research findings of Chrzan et al.³¹ and Kardos et al.,³⁰ who highlighted the effectiveness of AI programs in examining extensive image datasets and connecting lung abnormalities with clinical outcomes, our research further supports the idea of combining AI-generated TOS with conventional clinical evaluation techniques. The AI-powered method enhances the precision of risk assessment, which can play a role in making clinical decisions easier by

identifying patients at higher risk of needing intensive care or extra oxygen support.

SS calculated by AI might serve as a valuable indicator of the need for additional oxygen support or admission to a hospital in patients with COVID-19 pneumonia. Higher SS values indicate more severe symptoms and possible outcomes. These findings emphasize the ability of AI to improve risk evaluation and guide treatment decisions. The integration of AI-based SS with traditional clinical parameters can enhance patient medical evolution. The findings of this research emphasize the growing significance of AI in diagnosis and patient care practices. The proposed method also aligns with current diagnostic methods and has the potential to greatly improve patient treatment quality and healthcare delivery standards overall.^{32,33}

In this context, we also applied the AI-guided scoring systems to the short-term outcomes described in our first study.¹⁸ As previously reported, a TOS >2.65 was significantly associated with an increased risk of extra oxygen need and hospitalization.¹⁸ Moreover, based on the severity of mBQ and TOR, we have also defined TOR thresholds [no or mild TOR (<5), moderate TOR (≥5 & <15), and severe TOR (≥15)] and showed a significant relationship between HR-OSA and TOR thresholds.¹⁹ Our current findings support this relationship and suggest that the severity of TOR (with a TOR score of ≥15) is associated with OSA severity, as objectively determined by AHI values.

The link between the severity of COVID-19 and OSA could be connected to the diversity of factors. Our initial research findings showed that individuals with more intense snoring experience worse outcomes.¹³ It is uncertain whether snoring is a direct manifestation of OSA or an indicator of OSA. We postulated that those who snore more loudly may be more vulnerable to COVID-19, most likely as a result of the strain placed on the upper airway muscles.¹³ Furthermore, it is possible that COVID-19 infection could increase the collapsibility of the upper airway muscles, leading to the initiation or worsening of OSA symptoms. This suggests a two-way relationship between OSA and COVID-19. There may be other mechanisms linking OSA with an increased risk of COVID-19 infection and adverse outcomes.^{9,10} In particular, OSA, when associated with obesity, might worsen hypoxemia and the cytokine storm observed in patients with COVID-19.¹⁰ Additionally, OSA might trigger COVID-19 infection and worsen outcomes in patients with hypertension and diabetes.³⁴ Some studies have suggested a connection between the development of pulmonary fibrosis and an increased risk of future OSA development in patients with COVID-19.³⁴ The inflammation caused by OSA, especially when combined with obesity or other health conditions, can worsen the cytokine storm seen in severe cases of COVID-19. Our findings support this hypothesis and offer further evidence that the severity of OSA as measured by specific PSG parameters is significantly correlated with the radiological severity of COVID-19.

This study has several implications for patient care in the medical field regarding COVID-19 infection and OSA. It is crucial to monitor COVID-19 patients with OSA, especially when TOS severity indicates significant lung abnormalities

on CT. Incorporating AI-assisted imaging analysis and tools like the mBQ can provide a more comprehensive approach to managing COVID-19 patients efficiently and effectively.

We acknowledge a certain limitations to our research. First, the sample size was small, which might limit the generalizability of the findings. Second, the study population was derived from near central districts of İstanbul, which might have limited the generalizability of the results to urban districts. Third, AI-based CT analysis might not be appropriate for all situations, such as the occurrence of concomitant lung cancer, fibrosis, and tuberculosis. Furthermore, the association between acute COVID-19 severity and chronic OSA may be affected by the post hoc study design, specifically the interval between the COVID-19 diagnosis and PSG.

CONCLUSION

AI-guided CT-based TOS severity in patients with COVID-19 pneumonia was associated with OSA severity based on PSG recordings. Moreover, the need for supplemental oxygen was more common in the OSA group, who had a longer hospitalization duration during the initial period. These results further support the association between OSA and poor outcomes in COVID-19 pneumonia.

Ethics

Ethics Committee Approval: The study protocol was approved by the Koç University Committee on Human Research (approval no: 2021.231.IRB2.049, date: 06.05.2021).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Concept: Z.A., Y.Ç., Ç.A., Y.P., Design: Z.A., Y.Ç., Ç.A., Y.P., Data Collection or Processing: Z.A., Y.Ç., Analysis or Interpretation: Z.A., Y.Ç., Ç.A., Y.P., Literature Search: Z.A., Y.Ç., Ç.A., Y.P., Writing: Z.A., Y.Ç., Ç.A., Y.P.

Conflict of Interest: Yüksel Peker reports grants from ResMed Inc and ResMed Foundation outside the submitted work. Zeynep Atçeken, Yeliz Çelik and Çetin Atasoy have nothing to declare.

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