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Is Obstructive Sleep Apnea a Risk Factor for Severe COVID-19?

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Background and Objective Obstructive sleep apnea (OSA) is a breathing disorder during sleep with an obstruction of the upper airway. Previous studies showed OSA as a risk factor for severe COVID-19. It is crucial to determine the risk factors for the severity of COVID-19 infection. We aim to clarify the relationship between COVID-19 severity, and OSA and its degree.

Methods Our case-control study included subjects diagnosed with OSA with polysomnography between January 2018 and November 2021, and a control group with a history of COVID-19 infection and without OSA diagnosis. The demographic data, comorbidities, apnea–hypopnea index, and oxygen desaturation index were recorded.

Results A total of 217 patients were included in our study. The degree of OSA was a risk factor in the OSA group ($p < 0.05$); on the other hand, the diagnosis of OSA by itself was not a risk factor. The apnea–hypopnea index and oxygen desaturation index were not related to the severity of COVID-19 infection ($p > 0.05$). Diabetes mellitus was associated with increased hospitalization in inpatient clinics ($p < 0.05$) and intensive care unit (ICU) ($p < 0.05$). Chronic obstructive pulmonary disease was a risk factor for admission to the ICU ($p < 0.05$).

Conclusions Our results showed that moderate-to-severe OSA patients are a vulnerable population to severe COVID-19 infection, although diagnosis of OSA by itself was not a risk factor.

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Keywords COVID-19 pandemic; Sleep apnea; Risk factors; Airway obstruction; Polysomnography; Index.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a viral infection caused by a betacoronavirus [1]. The COVID-19 pandemic has spread worldwide and can cause death by acute respiratory distress syndrome [2]. As another clinical aspect, post-COVID-19 syndrome is characterized by prolonged symptoms, such as fatigue, breathlessness, headaches, olfactory and gustatory dysfunctions, sleep difficulties, and anxiety after initial COVID-19 infection. These symptoms are related to the long-time process after COVID-19. Long-lasting symptoms seem to be related to the severity of the infection, hospitalization, and admission to the intensive care unit (ICU) [3]. Therefore, it is crucial to determine the risk factors for the severity of COVID-19 infection.

Some studies reported obstructive sleep apnea (OSA) as a risk factor for severe COVID-19 [1,2,4-6]. Conversely, there are also studies with implications that OSA is not associated with severe COVID-19 and poor outcomes [7-10].

Furthermore, post-COVID sleep disorders were reported in the current literature [11]. OSA is a breathing disorder during sleep with an obstruction of the upper airway. It was found as an independent risk factor for cardiac, neurologic, and perioperative morbidities [12].

Apnea–hypopnea index (AHI) and oxygen desaturation index (ODI) are the criteria mostly used in the diagnosis of OSA [1,13]. AHI is represented by the number of apnea and hypopnea events per hour of sleep. The ODI is presented by the number of episodes of oxygen desaturation per hour of sleep. Oxygen desaturation is defined as a decrease in blood oxygen saturation (SpO_2) to lower than 3% below baseline. ODI is increasingly recognized as a cardiovascular risk in OSA patients [13]. AHI is associated with the degree of airflow limitation with endothelial dysfunction, and also cardiovascular risk [14].

There are contrary findings in previous studies concerning the relationship between COVID-19 severity and AHI or ODI. Kravitz et al. [5] found that COVID-19 severity is related to the degree of OSA that is measured by the AHI and ODI. Ho et al. [1] found COVID-19 not to be associated with AHI and ODI, while it was related to OSA. Therefore the relationship between the degree of OSA and COVID-19 is unclear. We aim to clarify the relationship between COVID-19 severity, and OSA and its degree.

METHODS

Subjects

Our case-control study included subjects diagnosed with OSA with polysomnography between January 2018 and November 2021, and a control group with a history of COVID-19 infection, but without OSA diagnosis. The demographic data, comorbidities, AHI, and ODI were recorded. AHI was used to classify sleep apnea severity as mild ($5 \leq AHI < 15$ events per hour), moderate ($15 \leq AHI < 30$ events per hour), and severe ($AHI \geq 30$ events per hour) [14]. The patients were divided into two groups: mild and moderate-to-severe OSA. The inclusion criteria for the OSA group were OSA patients with a history of COVID-19 infection that was confirmed by the positivity of the polymerase chain reaction (PCR) test. Exclusion criteria were being vaccinated before COVID-19 infection, and the COVID-19 infection not being confirmed by a positive PCR test. The hospitalization caused by COVID-19 was used to classify the severity of the infection. Our study was approved by the Ahi Evran University Medical Faculty's ethical committee (21.12.2021-approval no: 2021-21/204).

Statistical Analysis

Data analysis was performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). The normality assumption of continuous variables was tested with Kolmogorov–Smirnov and Shapiro–Wilk tests. Descriptive statistics of the variables are given as the mean ± standard deviation, median (min–max), and frequency n (%). Univariate analyses of continuous variables in the study were performed using independent t-test and Kruskal–Wallis test, depending on the type of variable and the availability of assumptions. Univariate analyses of categorical data were performed according to the number of categories and expected values, using chi-square test, Fisher's exact test, and Fisher–Freeman–Halton exact test. A p-value of < 0.05 was accepted as significant.

RESULTS

A total 217 patients were included in our study. The OSA group included 109 patients (50.2%), and the control group 108 patients (49.8%). Subjects were 39.6% female and 60.4% male. Table 1 presents the descriptive statistics and comparison of the demographic data of the OSA and control groups. There was

Table 1. The descriptive statistics and the comparison of demographic data

	Total (n = 217)	Control (n = 108, 49.8%)	OSA (n = 109, 50.2%)	p-value
Age (yr)	54.3 ± 13.01	54.55 ± 13.32	54.04 ± 12.75	0.774*
Gender				0.542†
Female	86 (39.6)	45 (41.7)	41 (37.6)	
Male	131 (60.4)	63 (58.3)	68 (62.4)	
Hospitalization				0.280†
Yes	23 (10.6)	9 (8.3)	14 (12.8)	
No	194 (89.4)	99 (91.7)	95 (87.2)	
DM				0.364†
Yes	74 (34.1)	40 (37.0)	34 (31.2)	
No	143 (65.9)	68 (63.0)	75 (68.8)	
HTN				0.372†
Yes	135 (62.2)	64 (59.3)	71 (65.1)	
No	82 (37.8)	44 (40.7)	38 (34.9)	
IHD				0.006†
Yes	65 (30.0)	23 (21.3)	42 (38.5)	
No	152 (70.0)	85 (78.7)	67 (61.5)	
COPD				0.448†
Yes	30 (13.8)	13 (12.0)	17 (15.6)	
No	187 (86.2)	95 (88.0)	92 (84.4)	
Asthma				0.098†
Yes	37 (17.1)	23 (21.3)	14 (12.8)	
No	180 (82.9)	85 (78.7)	95 (87.2)	
Hypothyroidism				> 0.999‡
Yes	8 (3.7)	4 (3.7)	4 (3.7)	
No	209 (96.3)	104 (96.3)	105 (96.3)	

Values are presented as mean ± SD or n (%).
*Independent t-test; †Chi-square test; ‡Fisher's exact test.
OSA, obstructive sleep apnea; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease.

no significant difference between the age, gender, and other demographic data of the two groups.

COVID-19 and OSA

A total 10.6% of the total samples were hospitalized due to COVID-19 infection. The ratio of hospitalized patients was 12.8% (n = 14) in the OSA group and 8.3% (n = 9) in the control group. OSA was not a risk factor for severe COVID-19 ($p > 0.05$) (Table 1). The degree of OSA was a risk factor in the OSA group ($p < 0.05$) (Table 2); on the other hand, the diagnosis of OSA by itself was not a risk factor.

COVID-19 and AHI

Table 2 shows the descriptive and comparative analysis of the OSA group. The OSA patients were classified as 32.1% mild 67.9% moderate-to-severe, according to the AHI levels. A total 87.2% of patients were not hospitalized. Moderate-to-severe OSA was related to the severity of COVID-19 infection ($p < 0.05$). Even though the patients with admission to the ICU had the highest median AHI, there was no significant difference ($p > 0.05$) .

COVID-19 and ODI

Similarly, although the patients with admission to the ICU had the highest median ODI, there was no significant difference ($p > 0.05$) (Table 2).

Table 2. The descriptive and comparative analysis of OSA group

	Total (n = 109)	No hospitalization (n = 95, 87.2%)	Inpatient clinics (n = 10, 9.2%)	Intensive care unit (n = 4, 3.7%)	p-value
AHI, median (min–max)	28.35 (0.0–110.0)	15.9 (0.0–110.0)	30.5 (10.0–80.1)	35.4 (5.2–65.6)	0.221†
ODI, median (min–max)	37.49 (0.2–154.8)	19.8 (0.2–154.8)	37.7 (24.2–115.0)	58.9 (6.2–105.0)	0.082†
Age (yr), median (min–max)	54.04 (25.0–86.0)	54.0 (25.0–86.0)	64.5 (42.0–73.0)	64.5 (56.0–70.0)	0.127†
Degree of OSA					0.043*
Mild	35 (32.1)	34 (35.8)	0 (0.0)	1 (25.0)	
Moderate to severe	74 (67.9)	61 (64.2)	10 (100.0)	3 (75.0)	
Gender					0.724*
Female	41 (37.6)	36 (37.9)	3 (30.0)	2 (50.0)	
Male	68 (62.4)	59 (62.1)	7 (70.0)	2 (50.0)	
Hospitalization					0.040*
Yes	34 (31.2)	26 (27.4)	5 (50.0)	3 (75.0)	
No	75 (68.8)	69 (72.6)	5 (50.0)	1 (25.0)	
DM					0.178*
Yes	71 (65.1)	59 (62.1)	9 (90.0)	3 (75.0)	
No	38 (34.9)	36 (37.9)	1 (10.0)	1 (25.0)	
HTN					0.282*
Yes	42 (38.5)	34 (35.8)	6 (60.0)	2 (50.0)	
No	67 (61.5)	61 (64.2)	4 (40.0)	2 (50.0)	
IHD					0.014*
Yes	17 (15.6)	12 (12.6)	2 (20.0)	3 (75.0)	
No	92 (84.4)	83 (87.4)	8 (80.0)	1 (25.0)	
COPD					0.276*
Yes	14 (12.8)	13 (13.7)	0 (0.0)	1 (25.0)	
No	95 (87.2)	82 (86.3)	10 (100.0)	3 (75.0)	
Asthma					> 0.999*
Yes	4 (3.7)	4 (4.2)	0 (0.0)	0 (0.0)	
No	105 (96.3)	91 (95.8)	10 (100.0)	4 (100.0)	

Values are presented as median (min–max) or n (%).
*Fisher Freeman Exact Test; †Kruskal Wallis.
OSA, obstructive sleep apnea; AHI, apnea–hypopnea index; ODI, oxygen desaturation index; DM, diabetes mellitus; HTN, hypertension; IHD, ischemic heart disease; COPD, chronic obstructive pulmonary disease.

COVID-19 and Comorbidities

There was no significant difference between the two groups in comorbidities, except for ischemic heart disease. Diabetes mellitus (DM) was associated with increased hospitalization in inpatient clinics ($p < 0.05$) and ICU ($p < 0.05$). Chronic obstructive pulmonary disease was a risk factor for admission to the ICU ($p < 0.05$).

DISCUSSION

Maas et al. [2] compared the severity of 9405 OSA patients with all populations. The OSA group did not differ from all populations but had a higher ratio of male gender (45.9% vs. 41.7%; $p < 0.0001$). Male gender was reported as a risk factor for severe COVID-19 in the literature [15]. DM and hypertension were related to COVID-19 severity.

Kravitz et al. [5] studied 312 OSA patients in which the degree of OSA of 124 patients was not documented. Hospitalized patients were reported more likely to be severe sleep apnea (61.6% vs. 36.7%; $p < 0.05$). There was no control group in that study. On the other hand, sleep apnea severity was not associated with composite outcomes of mortality and ICU admission. DM, hypertension, and cardiovascular diseases were risk factors for hospitalization, while there was no association with composite outcomes. Pazarlı et al. [6] emphasized the implication that OSA is a risk factor for severe COVID-19 infection and explained their implication by the increased expression of angiotensin-converting enzyme (ACE) and dysregulation of the renin–angiotensin system in OSA patients due to chronic intermittent hypoxia [16,17].

Furthermore, the comorbidities are mostly seen in OSA, and determined as risk factors for COVID-19 [6]. Strausz et al. [4] studied a sample of 445 COVID-19 patients, of whom 38 patients had OSA diagnoses, and differed from the non-OSA group with the male gender ($p > 0.05$).

Ho et al. [1] retrospectively studied 137 OSA patients with a documented degree of AHI and ODI. The sample included 91 males (66.4%) and 46 (33.6%) females. There was no significant difference between the AHI and ODI levels of hospitalized and non-hospitalized patients.

On the other hand, Del Brutto et al. [8] conducted a population-based study including 180 OSA COVID-19 patients. There was no control group. OSA was not associated with the severity of COVID-19 infection.

Furthermore, Mashaqi et al. [10] performed a case-control study with 139 OSA COVID-19 and 1599 non-OSA COVID-19 patients. The two groups did not differ in gender, median age, or comorbidities. OSA patients had a degree of 22% mild, 27% moderate, and 51% severe. The authors found no association between OSA and severe COVID-19 after adjusting for age, gender, body mass index, and comorbidities.

Tufik [9] supported the implications of those studies and explained the previously reported association between COVID-19 and OSA by the comorbidities that are mostly seen in OSA patients and confounders of severe COVID-19 infection [18].

The common pathophysiological base of OSA and COVID-19 infection was explained by the increased expression of ACE and dysregulation of the renin–angiotensin system in OSA patients due to chronic intermittent hypoxia [16,19,20].

The studies that report OSA as a risk factor for severe COVID-19 are remarkable, in that some aspects of the design can affect the results. In Maas et al. [2], there was a higher male gender in the OSA group, and the male gender was reported as a risk factor for severe COVID-19 in the literature. There was no control group in Kravitz et al. [5], and the COVID-19 severity was not compared with another non-OSA group. In Strausz et al. [4], there was an inequality between the sample width and male gender ratio of the OSA and non-OSA groups.

Our study was designed similarly to Mashaqi et al. [10], and our results are consistent with their findings. Our study design was remarkable with a design that enabled clear implications as a case-control study, and with the aspect that there was no significant difference between the age, gender, and other demographic data of the two groups with equal sample width. Our results were consistent with the literature, and also clarify the controversial results of those studies. Similar to studies in the literature, our study found no association between the COVID-19 severity and AHI and ODI. When the possible worsening impact of OSA on the prognosis of COVID-19 was evaluated, it became nonsignificant after adjusting for age, gender, body mass index, and comorbidities [10]. This aspect emphasizes the existence of critical comorbidities and risk factors in OSA patients and its impact on poor outcomes, not because of the diagnosis of OSA. In addition, our results showed that moderate-to-severe OSA patients are a vulnerable population to severe COVID-19 infection, although diagnosis of OSA by itself was not a risk factor.

Considering the limitation of our study of being monocentric, a larger study sample could ensure more determinative implications.

As a result, our study showed that OSA by itself is not a risk factor for severe COVID-19 infection, but moderate-to-severe OSA was a risk factor associated with COVID-19 severity.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Author Contributions

Conceptualization: Nermin Zerman, Cihan Aydin. Data curation: Nermin Zerman. Formal analysis: Nermin Zerman, Cihan Aydin. Methodology: Cihan Aydin. Writing—original draft: Nermin Zerman, Cihan Aydin. Writing—review & editing: Cihan Aydin.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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None

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