



# Is Obstructive Sleep Apnea Associated with Higher Covid-19 Severity?

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## Abstract

**Objective** To investigate the associations between obstructive sleep apnea (OSA) and coronavirus disease 2019 (COVID-19) severity.

**Methods** Twelve individuals hospitalized in a Brazilian tertiary hospital diagnosed with COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) underwent respiratory polygraphy.

**Results** Polygraphic records identified seven participants without obstructive sleep apnea (OSA) (OSA-) and five with OSA (OSA+). The OSA+ group presented worse peripheral oxygen saturation ( $77.6\% \pm 7.89\%$ ) than the OSA- group ( $84.4\% \pm 2.57\%$ ) ( $p = 0.041$ ). Additionally, the OSA+ group showed greater COVID-19 severity (100%) than the OSA- group (28.57%) ( $p = 0.013$ ) and required longer oxygen therapy ( $p = 0.038$ ), but without difference in the length of hospitalization. The OSA+ group also presented higher rates of platelets ( $p = 0.008$ ) and D-dimer ( $1,443 \pm 897$ ) than the OSA- group ( $648 \pm 263$  ng/mL) ( $p = 0.019$ ).

**Conclusion** Obstructive sleep apnea in individuals hospitalized due to COVID-19 was associated with higher COVID-19 severity, worse peripheral oxygen saturation, longer oxygen therapy time, and higher platelet and D-dimer rates.

## Keywords

- ▶ COVID-19
- ▶ obstructive sleep apnea
- ▶ sleep
- ▶ polygraphy

## Introduction

The coronavirus disease 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still under investigation. The main risk factors associated with the most severe forms of SARS-CoV-2 manifestation are cardiovascular and metabolic diseases<sup>1,2</sup>

Overweight and obesity are also risk factors for severe pneumonia in individuals with COVID-19,<sup>3</sup> and great concern exists regarding the incidence of SARS-CoV-2 in patients who are overweight, obese, or both. Another factor is the relationship between obstructive sleep apnea (OSA) and major comorbidities associated with severe COVID-19.<sup>4,5</sup>

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Most clinical case series of patients with severe COVID-19 reported associations between OSA and male sex, obesity, age, and cardiometabolic disorders.<sup>6</sup> The low incidence of OSA diagnosis in high-risk populations is congruent with the underdiagnosis of this disease.<sup>7</sup>

Another important factor is that OSA is associated with reduced lung function and increased lung inflammation even when obesity is controlled. This partially explains why patients with OSA present a high risk of developing pneumonia, which plays a significant role in the progression of COVID-19 infection.<sup>8</sup>

Furthermore, unexplored mechanisms that may link the imbalance between angiotensin-II receptor, angiotensin-II converting enzyme (the entry receptor for SARS-CoV-2)<sup>9</sup> and severe COVID-19 infections may also be applied to OSA. Studies with patients with untreated OSA demonstrated increased angiotensin-converting enzyme<sup>9</sup> expression and dysregulation of the renin-angiotensin system mainly due to chronic intermittent hypoxia.<sup>10</sup>

Understanding the possible link between OSA and severe COVID-19 outcomes may generate important information and encourage investments in treating sleep disorders. Therefore, this study investigated OSA as a factor associated with COVID-19 severity.

## Materials and Methods

### Study Design

This descriptive observational study was conducted in a tertiary hospital in Ceará (Brazil) from April to May 2021. The data corresponded to the second wave of SARS-CoV-2 infection in Brazil.

### Participants

Participants were recruited by convenience from COVID-19 isolation wards at hospital discharge. We included individuals aged  $\geq 18$  years with clinical diagnosis of COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) and able to perform sleep polygraphy. Individuals on oxygen therapy, invasive or noninvasive mechanical ventilation, or tracheostomized were not included. The exclusion criteria were previous pulmonary disease causing significant obstructive or restrictive disorder, previous neuromuscular disease, or pulmonary hypoventilation by any cause.

The study followed the Declaration of Helsinki<sup>11</sup> and resolution 466/2012 of the National Health Council. Assessments were initiated after written informed consent and understanding about the protocol. The study was approved by the research ethics committee of the Hospital Universitário Walter Cantídio (CAAE: 40734920.8.3002.5045).

### Initial Assessment and Hospitalization Data

Data regarding laboratory and imaging examinations, length of hospital stay, need for invasive and noninvasive mechanical ventilation, need for oxygen therapy, and clinical complications were collected from medical records. Data from medical records refer to the worst clinical situation presented by the participants throughout the hospital stay.

Coronavirus disease 2019 severity was classified as mild (mild clinical symptoms and no signs of pneumonia on imaging examination), moderate (fever and respiratory symptoms with radiological evidence of pneumonia), severe (respiratory distress [ $> 30$  breaths/min], oxygen saturation  $< 93\%$  at rest, arterial partial pressure of oxygen/fraction of inspired oxygen of  $< 300$  mm Hg, or chest imaging showing lesion progression of  $> 50\%$  within 24–48 hours), or critical (respiratory failure and mechanical ventilation, shock, or other organ failure requiring intensive care unit [ICU]).<sup>12</sup>

### Quantitative Sleep Assessment

All participants underwent respiratory polygraphy at bedside using a type-III portable multichannel device (PolyWatch, BMC Medical, Beijing, China), which includes a nasal flow cannula, chest strap, and oximeter for recording peripheral oxygen saturation and heart rate. Participants also used the ActTrust2 Actigraph (Condor Instruments, Vila Madalena, SP, Brazil), a noninvasive method for monitoring rest and activity cycles. The actigraph was used to assess whether the participant was in a sleep state during polygraphy to attenuate the limitation of the type-III sleep study for diagnosing respiratory disorders. Thus, participants with short sleep time (according to the actigraph) were excluded from the study.

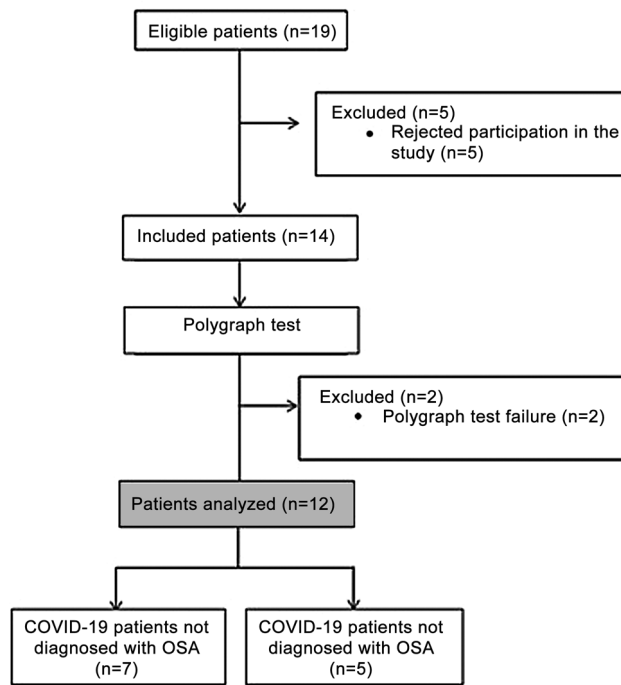
Before the exam, participants were instructed on the placement and maintenance of the devices, and recordings started only after answering the doubts of participants. Instructions were also given to stop recordings upon awakening in the morning by pressing a button on the polygraph monitor.

### Data Analysis

The PolyLogic Sleep Analysis software (BMC Medical) was used to analyze the respiratory variables of the polygraphy, while the ActStudio software (Condor Instruments) assessed the actigraphy records. For sleep staging, the polygraphy record was divided into time intervals of 30 seconds, and respiratory events were divided into 120 seconds. Two certified professional experts in sleep studies manually analyzed the data, and sleep and associated events were scored according to the AASM Manual for the Scoring of Sleep and Associated Events.<sup>13</sup> Obstructive sleep apnea severity was classified according to the respiratory event index as mild (between 5 and 14.9/hour), moderate (between 15 and 29.9/hour), or severe ( $\geq 30$ /hour). The respiratory event index and minimum oxygen saturation were analyzed as study outcomes. After these analyses, participants were divided into two groups based on the presence (OSA+) or absence (OSA-) of OSA.<sup>13</sup>

### Statistical Analysis

Data distribution was analyzed using the Shapiro-Wilk test, and results were presented as mean  $\pm$  standard deviation (SD). Continuous data were compared using the unpaired *t*-test while the  $\chi^2$  test analyzed categorical data. Qualitative variables were expressed in absolute and relative frequencies. Data were analyzed using the Statistical Package for Social Science, version 20.0 (IBM Corp., Armonk, NY, USA); significance was set at  $p < 0.05$ .



**Fig. 1** Flowchart of participant selection.

## Results

### Eligibility

Nineteen participants with COVID-19 meeting the eligibility criteria were contacted. Of these, five refused participation

when informed about using the devices for nighttime polygraphy, while two presented technical failures in the polygraph records. Thus, this study included 12 participants: 7 with OSA- and 5 with OSA+ (►Fig. 1).

### Sample Characteristics

►Table 1 presents the demographic data, symptoms, and comorbidities of participants. The most reported symptoms were dyspnea and cough; comorbidities (e.g., hypertension, diabetes, anemia, and heart failure) were similarly distributed in both groups.

### Polygraphic Characteristics

Polygraphic recordings showed a significantly lower oxygen saturation in the OSA+ than OSA- group ( $77.6\% \pm 7.89\%$  vs  $84.4\% \pm 2.57\%$ ;  $p = 0.041$ ) (►Fig. 1). However, no difference ( $p = 0.180$ ) was found in apnea duration between the OSA+ and OSA- groups ( $25.4 \pm 19.7$  second vs  $12.1 \pm 12.3$  seconds) (►Fig. 2 and 3).

►Table 2 presents the associations between COVID-19 severity and OSA diagnosis. Coronavirus disease 2019 was more severe in individuals from the OSA+ (100%) than OSA- group (28.57%) ( $p = 0.013$ ). The OSA+ group also received oxygen therapy for a longer time than the OSA- group ( $p = 0.038$ ). Regarding length of hospital stay, no significant difference was observed ( $p = 0.268$ ).

►Table 3 presents the comparisons between groups considering blood cell and biochemical variables. The OSA+ group presented a thrombocytosis profile ( $p = 0.008$ )

**Table 1** Demographic data, symptoms, comorbidities, and functioning according to groups.

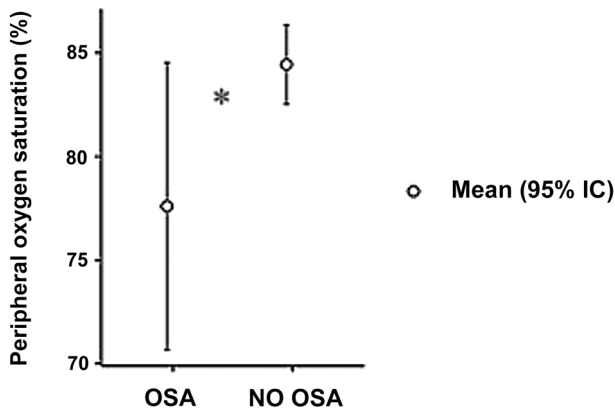
	Individuals with COVID-19		p-value
	OSA+ (n = 5)	OSA- (n = 7)	
Age, mean ( $\pm$ SD)	55 (13.5)	53.42 (10.43)	0.847 <sup>a</sup>
Sex, N (%)			
Male	3 (60)	3 (42.85)	0.558 <sup>a</sup>
Symptoms, N (%)			
Headache	1 (20)	2 (28.57)	0.734 <sup>b</sup>
Dyspnea	5 (100)	6 (85.71)	0.377 <sup>b</sup>
Fever	2 (20)	3 (42.85)	0.921 <sup>b</sup>
Myalgia	1 (20)	3 (42.85)	0.408 <sup>b</sup>
Cough	5 (100)	5 (71.42)	0.190 <sup>b</sup>
Comorbidities, N (%)			
SAH	1 (20)	1 (14.28)	0.793 <sup>b</sup>
DM	1 (20)	2 (28.57)	0.735 <sup>b</sup>
HF	1 (20)	1 (14.28)	0.793 <sup>b</sup>
Obesity	1 (20)	1 (14.28)	0.793 <sup>b</sup>
Anemia	1 (20)	1 (14.28)	0.793 <sup>b</sup>
No comorbidities	2 (40)	3 (42.85)	0.921 <sup>b</sup>

Abbreviations: DM: diabetes mellitus; HF, heart failure; OSA, obstructive sleep apnea; SAH, systemic arterial hypertension.

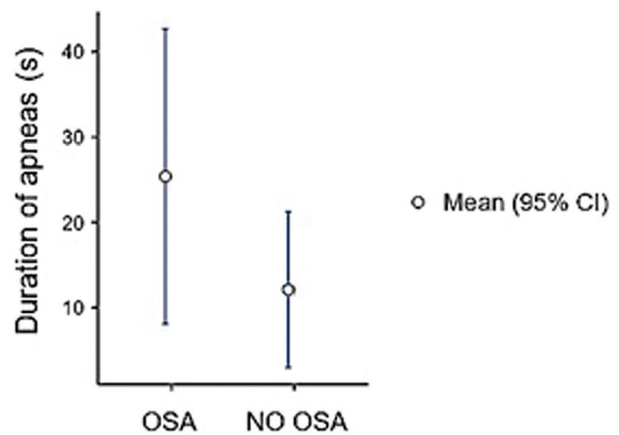
Data on age are presented as mean and standard deviation and other variables as absolute and relative values.

<sup>a</sup>Unpaired t-test.

<sup>b</sup>:  $\chi^2$  test.



**Fig. 2** Minimum oxygen saturation of individuals with COVID-19 in the OSA+ and OSA- groups. Abbreviation: OSA: obstructive sleep apnea. Unpaired *t*-test. \**p* = 0.041.



**Fig. 3** Apnea duration (in seconds) of individuals with COVID-19 in the OSA+ and OSA- groups. Abbreviation: OSA: obstructive sleep apnea. Unpaired *t*-test. \**p* = 0.180.

**Table 2** Associations between COVID-19 severity, OSA diagnosis, and clinical variables.

	Individuals with COVID-19		p-value
	OSA+ (n = 5)	OSA- (n = 7)	
<b>COVID-19 severity, N (%)</b>			
Moderate	0 (0.0)	5 (71.42)	*0.013 <sup>a</sup>
Severe	5 (100)	2 (28.57)	*0.013 <sup>a</sup>
<b>Clinical variables, mean (±SD)</b>			
Length of hospitalization (days)	15 (3)	12 (4)	0.268 <sup>b</sup>
Oxygen therapy time (days)	12 (4)	5 (2)	*0.038 <sup>b</sup>

Abbreviation: OSA, obstructive sleep apnea.

<sup>a</sup>:  $\chi^2$  test; <sup>b</sup>: Student's *t*-test.

\**p*-value < 0.05.

**Table 3** Comparison of laboratory variables and presence of obstructive sleep apnea.

	Individuals with COVID-19		p-value
	OSA+ (n = 5)	OSA- (n = 7)	
<b>Laboratory variables, mean (±SD)</b>			
RBCs (millions/ $\mu$ L)	4.28 (0.81)	4.77 (0.50)	0.242
Hemoglobin (g/ dL)	10.5 (3.53)	13.53 (1.18)	0.374
Hematocrit (%)	36.37 (7.25)	40.27 (3.80)	0.250
Neutrophil ( $\mu$ L)	67.08 (9.13)	64.23 (14.64)	0.710
Leukocyte ( $/\text{mm}^3$ )	11,846.80 (2,771.30)	8895.43 (2384.39)	0.076
Lymphocyte ( $/\text{mm}^3$ )	23.60 (0.39)	27.18 (13.36)	0.602
Platelets ( $/\text{mm}^3$ )	449,240 (75,503)	229,827 (132,865)	0.008*
PAT (s)	11.95 (1.02)	12.1 (2.54)	0.601
APTT (s)	29.35 (2.86)	24.25 (0.35)	0.500
PCr (mg/dL)	0.84 (0.73)	1.01 (0.91)	0.542
Urea (mg/dL)	40 (9)	51 (32)	0.394
Creatinine (mg/dL)	0.76 (0.09)	0.81 (0.20)	0.578
D-dimer (ng/mL)	1,443 (897)	648 (263)	0.019*
CPK (U/L)	228 (318)	61 (54)	0.458

Abbreviations: APTT, Activated partial thromboplastin time; CPK, creatine phosphokinase; CRP, C-reactive protein; PAT, prothrombin activity time; RBCs, red blood cells.

Unpaired *t*-test.

compared with the OSA- group. Higher rates of D-dimer were also found in the OSA+ ( $1443 \pm 897$  ng/ mL) compared with the OSA- group ( $648 \pm 263$  ng/ mL) ( $p = 0.019$ ).

## Discussion

The findings revealed that individuals hospitalized due to COVID-19 and with OSA presented more severe symptoms than those without OSA as well as higher platelet and D-dimer counts, longer oxygen therapy time, and worse peripheral oxygen saturation. Our results corroborate a previous study exploring the relationships between greater COVID-19 severity and OSA.<sup>14</sup>

Regarding clinical outcomes during hospitalization, our results can be compared with those of Mashaqi et al.,<sup>14</sup> who conducted a cohort analysis with 1,738 individuals with COVID-19 and OSA and 1,599 without OSA and observed a statistical significance in ICU admission. However, this association was attenuated when the model was adjusted for age, sex, body mass index (BMI), and comorbidities. A retrospective study by Cade et al.<sup>15</sup> with 443 patients also found that the increased risk of intubation, ICU admission, or hospitalization associated with OSA was attenuated after adjustment for demographic data, BMI, and comorbidities. Both studies reported OSA diagnosis by reviewing medical and health records.

Our study also revealed that individuals with OSA need oxygen therapy for longer, which may be associated with low nocturnal oxygen saturation due to apnea and hypopnea and high COVID-19 severity. In this context, oxygen therapy must be well evaluated, considering that continuous positive airway pressure is the gold standard for reversing apnea and hypopnea events and improving saturation.<sup>16</sup> In addition, prolonged and unnecessary administration of oxygen therapy may expose the patient to the harmful effects of oxygen.<sup>17</sup>

In contrast to Mashaqi et al.,<sup>14</sup> we found elevated platelet levels and higher D-dimer rates in individuals with OSA. These findings can be explained by the hypercoagulability of OSA<sup>18</sup> and characteristics of COVID-19, which may increase the risks of developing thrombotic conditions.

Previous studies investigating the influence of OSA on other lung injuries warned about the possible relationships with COVID-19 severity and increased risk of developing community-acquired pneumonia<sup>19</sup> and perioperative acute respiratory distress syndrome.<sup>20</sup> Pathophysiological mechanisms may explain the associations between greater disease severity and worse clinical outcomes. Untreated OSA progresses with repeated airway obstruction and generates negative intrathoracic pressure; thus, associated shear forces may favor inflammatory processes with worsening lung injury. Also, increased sympathetic outflow during OSA episodes promotes catecholamine release, which may increase the risk of cardiovascular complications (e.g., arrhythmias, cardiac ischemia, and hypercoagulability).<sup>18</sup>

Our study has clinical implications. Given the repercussions on the clinical outcome of individuals hospitalized due to COVID-19, the presence of OSA should be viewed as a potential comorbidity and risk factor for adverse COVID-19

outcomes. Patients with suspected OSA should be carefully evaluated and promptly treated. Considering the modulating and regulatory effects of sleep on the immune system,<sup>21</sup> adequate treatment may reduce the COVID-19 evolution or other lung lesions.

Some limitations also need to be highlighted. A small sample size increases the chances of  $\beta$  error and limits the external validity, while clinical data collected using medical records increases the risk of information bias. In addition, the cross-sectional design of the study hinders the capacity to infer associations, different from longitudinal studies. Another limiting factor was that the sample was composed of hospitalized individuals, which may impair polygraphic recordings because data were collected during sleep in the ward. We encourage longitudinal studies with a larger sample size to ensure the external validity of the results.

The greatest strength of our study is the use of type-III polygraphy, which enhances the precision and reliability of OSA diagnosis and enables the extraction of quantitative sleep data. In addition, we used actigraphy to ensure the adequacy and comparability of the polygraph recording time with the sleep time recorded by the actigraph.

## Conclusion

High COVID-19 severity was associated with OSA diagnosis. Also, individuals with COVID-19 and OSA presented longer oxygen therapy time, higher platelet count and D-dimer, and worse peripheral oxygen saturation than those without OSA.

### Authors' Contribution

LCZ: Preparation and planning of work, data acquisition, and manuscript drafting.

DMT: Data acquisition, data analysis, and interpretation. SCM, MASN: revised the work critically for important intellectual content.

CFL: drafted and made substantial contributions to the conception of the work and revised it critically.

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### Conflict of Interests

The authors have no conflict of interests to declare.

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