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ORIGINAL ARTICLE

Sleep health and the circadian rest-activity pattern four months after COVID-19

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ABSTRACT

Objective: To describe the prevalence and severity of sleep disorders and circadian alterations in COVID-19 patients four months after the acute phase of the disease. **Methods:** This was a cross-sectional observational prospective study of patients with mild COVID-19, moderate COVID-19 (requiring hospitalization but no mechanical ventilation), or severe COVID-19 (with ARDS) four months after the acute phase of the disease. All patients underwent a home sleep apnea test and seven-day wrist actigraphy, as well as completing questionnaires to assess sleep quality and mental health. Differences among the three groups of patients were evaluated by ANOVA and the chi-square test. **Results:** A total of 60 patients were included in the study. Of those, 17 were in the mild COVID-19 group, 18 were in the moderate COVID-19 group, and 25 were in the severe COVID-19 group. Sleep quality, as assessed by satisfaction, alertness, timing, efficiency, and duration scale scores, was found to be impaired in all three groups, which also had a high prevalence of unhealthy sleep, as assessed by the Pittsburgh Sleep Quality Index. The prevalence of insomnia was increased in all three groups, as assessed by the Insomnia Severity Index. The home sleep apnea test showed that the overall prevalence of obstructive sleep apnea was 60%, and seven-day wrist actigraphy showed that total sleep time was < 7 h in all three groups. Changes in quality of life and in the circadian rest-activity pattern were observed in all three groups. **Conclusions:** Sleep-related symptoms, changes in the circadian rest-activity pattern, and impaired mental health appear to be common in COVID-19 patients four months after the acute phase of the disease, severe COVID-19 being associated with a higher prevalence of obstructive sleep apnea.

Keywords: Sleep apnea, obstructive; Sleep disorders, circadian rhythm; COVID-19.

INTRODUCTION

The current health emergency due to COVID-19 is the first pandemic of the 21st century.[1] It has spread across the world rapidly.[2,3] After the acute phase of the disease, current evidence indicates that clinical, physical, and mental health continues to be affected.[4-6] Novel research applies the term "long COVID-19 syndrome" to identify this subtype of patients with persistent symptoms during the recovery phase.[7] Previous studies have indicated that, after acute COVID-19 infection, the most common symptoms are anxiety, depression, fatigue, and impaired pulmonary function.[4] Moreover, other studies suggest that, during the recovery phase, COVID-19 patients report more posttraumatic stress symptoms and deterioration of preexisting psychiatric disorders.[6-9] However, most of the studies aiming to explore COVID-19 sequelae include clinical data, pulmonary function data, and health-related quality of life (HRQoL) data, excluding a comprehensive evaluation of sleep health and circadian rhythms.

The sleep-wake cycle is under a circadian rhythm, along with several other processes, including the control of body temperature and the secretion of hormones such as cortisol and melatonin.[10] COVID-19 and its associated context can, by affecting sleep, affect other circadian rhythms and sleep-related processes such as cognition and immune function.[8] Additionally, sleep disorders such as obstructive sleep apnea (OSA) can be linked to both processes.[11] Moreover, OSA has been linked to severe COVID-19 and worse outcomes during the recovery phase.[12] Therefore, it is necessary to investigate the relationship of sleep health and disruption of the circadian rest-activity pattern with the severity of COVID-19. The objective of the present study was to describe the prevalence and severity of sleep disorders and circadian alterations in COVID-19 patients four months after the acute phase of the disease.

METHODS

This was a cross-sectional observational prospective study including two hospitals in Chile (the *Hospital Regional Dr. Guillermo Grant Benavente* and the *Complejo Asistencial Dr. Víctor Ríos Ruiz*) and performed

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in accordance with current guidelines for reporting observational studies.[13] The study protocol was approved by the institutional review boards of the Biobío Health Service and the Concepción Health Service (Code CEC-SSC: 07-20-26).

We included patients ≥ 18 years of age with an RT-PCR–confirmed diagnosis of SARS-CoV-2 infection between April and July of 2020. We included COVID-19 patients with varying degrees of disease severity, in accordance with the WHO definitions[3]: severe COVID-19—severe hypoxemia and medical records of ARDS in accordance with the Berlin definition[14]; moderate COVID-19—clinical or radiographic evidence of lower respiratory tract disease; and mild COVID-19—mild symptoms (e.g., fever, cough, and loss of taste or smell, without dyspnea). The patients with severe COVID-19 required ICU admission; those with moderate COVID-19 required hospitalization but no mechanical ventilation; and those with mild COVID-19 received clinical outpatient monitoring and supportive care. All of the patients included in the study were evaluated four months after the acute phase of COVID-19.

We excluded patients with previous respiratory comorbidities (asthma, COPD, and other respiratory diseases); patients receiving oxygen supplementation or noninvasive mechanical ventilation after hospitalization for COVID-19; and patients over 70 years of age. We also excluded patients who were lost to follow-up, those who were transferred to other hospitals or towns after discharge, and those with mental disability that might prevent them from completing the evaluations.

After giving written informed consent, all participants underwent physical examination and blood sample collection for further analysis. We collected data on demographics (age, sex, level of education, and place of residence), as well as on BMI (in kg/m^2), waist circumference (in cm), neck circumference (in cm), hip circumference (in cm), and comorbidities at baseline.

Sleep health

At baseline, the study participants completed a self-report questionnaire including information on their sleep habits and sleep-related symptoms, similar to that employed by Mazzotti et al.[15] Furthermore, the study participants completed the Spanish versions of the following questionnaires:

1. The satisfaction, alertness, timing, efficiency, and duration (SATED) scale.[16] A SATED scale score of 10 indicates good sleep health.
2. The Pittsburgh Sleep Quality Index (PSQI). The PSQI ranges from 0 to 21. A score of 0 indicates no sleep difficulties, and a score of 21 indicates severe sleep difficulties. Participants with PSQI scores = 5 were classified as healthy in terms of sleep quality, whereas those with PSQI scores > 5 were classified as unhealthy.[17]
3. The Epworth Sleepiness Scale (ESS). An ESS score > 10 was considered indicative of daytime sleepiness, and an ESS score of ≤ 10 was considered indicative of no daytime sleepiness.[17]
4. The Insomnia Severity Index (ISI). The ISI evaluates the presence and severity of insomnia. An ISI score > 7 was used in order to indicate insomnia.[18]
5. The STOP-Bang questionnaire. The STOP-Bang questionnaire was used in order to assess the risk of OSA. Scores of 0-2 were considered indicative of a low risk of OSA; scores of 3 and 4 were considered indicative of an intermediate risk of OSA; and scores of 5-8 were considered indicative of a high risk of OSA.[19-21]
6. The Morningness-Eveningness Questionnaire (MEQ). The MEQ was used in order to assess chronotypes. MEQ scores of 16-30 were considered indicative of an extreme evening chronotype; MEQ scores of 31-41 were considered indicative of a moderate evening chronotype; MEQ scores of 42-58 were considered indicative of an intermediate chronotype; MEQ scores of 59-69 were considered indicative of a moderate morning chronotype; and MEQ scores of 70-86 were considered indicative of an extreme morning chronotype.[22]

Evaluation of OSA and the circadian rest-activity pattern

OSA was evaluated by means of a home sleep apnea test (HSAT). The HSAT was performed in accordance with the American Academy of Sleep Medicine recommendations.[23] The HSAT was manually scored by one researcher, who was blinded to the clinical and questionnaire data. The HSAT was performed with an ApneaLink Air™ home sleep testing device (ResMed, San Diego, CA, USA) between August and November of 2020. We collected data on the following variables: respiratory disturbance index (RDI—apneas or hypopneas associated with 3% oxygen desaturation per hour), mean SpO_2, nadir SpO_2, total time with SaO_2 below 90%, and oxygen desaturation index ≥ 3%. OSA was defined as an RDI ≥ 5 events/h, and non-OSA was defined as an RDI of ≤ 4 events/h.[23]

Seven-day wrist actigraphy was performed with an ActTrust 2 actigraph (Condor Instruments, São Paulo, Brazil) between August and November of 2020. The data collected by the actigraph were extracted with the use of ActStudio software (Condor Instruments).[24,25] We examined the following parameters: time in bed (in min); total sleep time (TST, in min), defined as the number of minutes spent asleep during the time spent in bed; sleep onset latency (in min), defined as the number of minutes between bedtime and the first minute scored as sleep; sleep efficiency (in %), defined as the ratio between TST and time spent in bed; wake after sleep onset (in min), defined as the number of minutes awake after sleep onset; and arousals (in n).[26]

To describe the shape and consistency of the 24-h rest-activity pattern, activity counts of 30-s epochs were obtained, and nonparametric circadian rhythm analysis was performed.[27] We extracted the following data: interdaily stability (IS), which ranges from 0 to 1, representing the synchronization between

the internal rest-activity rhythm and the different zeitgebers; intraday variability (IV), which ranges from 0 to 2, representing the fragmentation of the rest-activity rhythm within each 24-h period; the most active 10-h period (M10); the least active 5-h period (L5); relative amplitude, which ranges from 0 to 1, representing the difference in magnitude of activity between active and rest phases (M10 – L5/M10 + L5); and the circadian function index, which ranges from 0 to 1 and is calculated as the average between IS, IV, and relative amplitude (IV values were inverted and normalized between 0 and 1). Additionally, we extracted the following variables through cosinor analysis: mesor, which represents the mean activity; amplitude, which represents the difference in magnitude of activity between the highest value of activity and the mean activity; and acrophase, which represents the time of peak activity.[28,29]

Evaluation of mental health

HRQoL was assessed by the 12-Item Short-Form Health Survey (SF-12), and the results were presented in the domains of physical health and mental health.[30] Quality of life was measured by the Hospital Anxiety and Depression Scale (HADS). Scores of 0-7 indicated normal quality of life, scores of 8-10 indicated borderline abnormal quality of life, and scores of 11-21 indicated abnormal quality of life.[31] Depression was measured by the Beck Depression Inventory. Scores of 0-13 indicated minimal depression, scores of 14-19 indicated mild depression, scores of 20-28 indicated moderate depression, and scores of 29-62 indicated severe depression.[32] Finally, fatigue was assessed by the Chalder Fatigue Scale.[33,34]

Statistical analysis

In this study, we hypothesized that the severity of COVID-19 was associated with a risk of OSA and unhealthy sleep. On the basis of a study by Perger et al.,[35] who reported undiagnosed OSA in 75% of patients with severe COVID-19, a baseline OSA prevalence of 25% from Chile,[36] a power of 90%, and a p value of 0.05 (type I error), the estimated sample size was 16 per group.

Quantitative variables with normal or non-normal distribution were expressed as means and standard deviations. Qualitative variables were expressed as absolute and relative frequencies. The normality of the data distribution was examined with the Shapiro-Wilk test. The between-group differences established by the clinical variables were evaluated by the chi-square test and one-way ANOVA (for parametric variables) or by the Kruskal-Wallis test or Fisher's exact test (for nonparametric variables). ANCOVA was performed to analyze sleep questionnaire data and HSAT results. BMI and age were used as covariates. Factors associated with a higher probability of OSA were identified by logistic regression analysis. The analysis was adjusted for sex, age (19-36, 37-46, 47-56, and 57-69 years), and nutritional status. The results of the analysis were presented as ORs and their respective 95% CIs. An OR > 1 indicated a higher probability of having OSA, and an OR of < 1 indicated a lower probability of having OSA. For all tests, a p value < 0.05 was considered statistically significant. All statistical analyses were performed with the IBM SPSS Statistics software package, version 25 (IBM Corporation, Armonk, NY, USA).

RESULTS

Sociodemographic data and comorbidities

A total of 60 COVID-19 patients were included in the study. Of those, 17 had mild COVID-19, 18 had moderate COVID-19, and 25 had severe COVID-19. Table 1 presents sociodemographic, anthropometric, and comorbidity data, by COVID-19 severity. The patients with severe COVID-19 were older than those with mild or moderate COVID-19. The prevalence of obesity was 64.7% in the moderate COVID-19 group and 64% in the severe COVID-19 group. Additionally, the prevalence of central obesity was high in the mild, moderate, and severe COVID-19 groups (66.7%, 82.4%, and 76.0%, respectively). The prevalences of diabetes mellitus, insulin resistance, and hypertension were highest in the moderate COVID-19 group (35.2%, 29.4%, and 47.0%, respectively).

Sleep health and the circadian rest-activity pattern in COVID-19 patients during the recovery phase

Table 2 shows the self-report data on sleep-related symptoms. Excessive daytime sleepiness and daytime tiredness were more prevalent in the mild COVID-19 group than in the moderate and severe COVID-19 groups, although the difference was not significant. In the moderate COVID-19 group, there was a high prevalence of difficulty falling asleep, difficulty maintaining sleep, and waking up too early. In the severe COVID-19 group, there was a high prevalence of difficulty maintaining sleep and waking up too early. The mean number of hours of sleep as reported by patients ranged from 6.4 h to 6.9 h.

The risk of OSA as assessed by the STOP-Bang questionnaire was higher in the severe and moderate COVID-19 groups ($p = 0.038$). The prevalence of OSA as assessed by the HSAT was 60% (27.8%, 64.7%, and 80.0% for the mild, moderate, and severe COVID-19 groups, respectively; Table 3). The logistic regression analysis showed that COVID-19 patients in the 57- to 69-year age bracket had a higher probability of having OSA than did those in the 19- to 36-year age bracket ($OR = 22.709$; $p = 0.003$). Neither nutritional status nor sex increased the probability of having OSA (Figure 1).

Sleep quality was found to be impaired in all three groups of COVID-19 patients. Mean SATED scale scores were 6.3 ± 3.0 in the mild COVID-19 group, 5.2 ± 2.3 in the moderate COVID-19 group, and 6.1 ± 2.2 in the severe COVID-19 group. Moreover, the PSQI showed that all three groups had a high prevalence of unhealthy sleep. An ESS score > 10 was found in

Table 1. Baseline characteristics of the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Age, years	39.8 ± 13.8[a]	47.6 ± 11.3[a]	50.2 ± 10.6[b]	0.020
Sex				
Male	33.3%	64.7%	60.0%	0.121
Female	66.7%	35.7%	40.0%	
Level of education, no. of years of schooling				0.230
< 8 years	22.2%	29.4%	56.0%	
8-12 years	33.3%	17.6%	16.0%	
> 12 years	44.5%	52.9%	28.0%	
Living in a nonurban area	5.6%	17.6%	8.0%	
Anthropometry				
BMI	29.5 ± 5.1	31.3 ± 2.6	32.1 ± 5.9	0.238
Normal	16.7%	0%	8.0%	0.271
Overweight	44.4%	35.3%	28.0%	
Obesity	38.9%	64.7%	64.0%	
Hip circumference, cm	98.1 ± 13.4	104.6 ± 9.8	107.0 ± 13.2	0.072
Central obesity, n (%)	6 (33.3%)	3 (17.6%)	6 (24.0%)	0.557
Neck circumference, cm	40.1 ± 5.5	42.5 ± 3.9	42.8 ± 5.7	0.212
Waist circumference, cm	107.8 ± 8.8	106.6 ± 8.6	110.4 ± 10.4	0.415
Comorbidities				
Hypertension	11.1%	47.0%	36.0%	0.350
Diabetes mellitus	5.5%	35.2%	20.0%	0.030
Insulin resistance	0%	29.4%	4.0%	0.020
Smoking status				
Nonsmoker, n (%)	17 (66.6)	20 (52.9)	20 (58.8)	0.480
Current smoker, n (%)	4 (22.2)	1 (5.8)	3 (8.8)	0.240
Former smoker, n (%)	2 (11.1)	7 (38.8)	11 (32.3)	0.280
Smoking history, pack-years	5.6 ± 7.5	8.1 ± 9.3	8.6 ± 9.3	0.470

[a]Data expressed as %, n (%), or mean ± SD. *One-way ANOVA and the chi-square test, with ANOVA being adjusted for confounding variables (age, sex, and BMI). Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). A value of $p < 0.05$ was considered significant for all analyses.

38.9% of the patients in the mild COVID-19 group, in 47.1% of those in the moderate COVID-19 group, and in 36.0% of those in the severe COVID-19 group. The prevalence of insomnia as assessed by the ISI was increased in all three groups (50.0%, 82.4%, and 56.0% in the mild, moderate, and severe COVID-19 groups, respectively).

Actigraphy revealed a TST of < 7 h in all three groups (5 h 47 min and 54 s in the mild COVID-19 group, 6 h 04 min and 06 s in the moderate COVID-19 group, and 6 h 25 min and 30 s in the severe COVID-19 group). Sleep efficiency ranged from 86.3% to 87.4%. Circadian function was found to be impaired in all three groups. We found significant differences among the three groups regarding IV, which was higher in the moderate COVID-19 group than in the mild and severe COVID-19 groups (0.72 ± 0.11, 0.62 ± 0.09, and 0.64 ± 0.11, respectively). However, there were no significant differences among the three groups regarding the remaining variables. The acrophase was 15:33:05 (time) in the mild COVID-19 group, 15:44:00 (time) in the moderate COVID-19 group, and 15:17:33 (time) in the severe COVID-19 group.

Clinical and mental health

Table 4 shows the results related to fatigue, HRQoL, mood, and depression, by COVID-19 severity. We found significant differences between the moderate COVID-19 group and the other groups regarding HADS anxiety domain scores. The mean HADS anxiety domain score in the moderate COVID-19 group was 8.6 ± 3.8, and 47% of the patients in that group reported abnormal values, in comparison with 16.7% and 12% of those in the mild and severe COVID-19 groups, respectively. With regard to HRQoL, we found significant differences among the groups; mental health was found to be better in the mild COVID-19 group than in the moderate and severe COVID-19 groups. Furthermore, severe fatigue was found in all three groups (in 61.1% of the patients in the mild COVID-19 group, in 88.2% of those in the moderate COVID-19 group, and in 72.0% of those in the severe COVID-19 group).

DISCUSSION

The main findings of the present study are as follows: 1) Sleep health is severely impaired four

Table 2. Self-report data on sleep-related symptoms in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Excessive daytime sleepiness	52.9%	23.5%	24.0%	0.15
Falling asleep involuntarily during the day	52.9%	35.3%	28.0%	0.25
Dozing off while driving	5.9%	5.9%	8.00%	0.95
Difficulty falling asleep	41.2%	70.6%	36.0%	0.07
Difficulty maintaining sleep	47.1%	64.7%	56.0%	0.58
Waking up too early	35.3%	58.8%	52.0%	0.36
Taking a nap	17.6%	5.9%	24.0%	0.30
Daytime tiredness	58.8%	64.7%	48.0%	0.54
Heavy nocturnal sweating	47.1%	47.1%	52.0%	0.93
Observed apneas	11.8%	17.6%	20.0%	0.78
Morning headaches	47.1%	52.9%	36.0%	0.53
Number of hours of sleep (on weekdays)	6.9 ± 0.9	6.4 ± 1.4	6.7 ± 1.9	0.58
Number of hours of sleep (on weekends)	8.2 ± 1.5	6.7 ± 1.5	7.6 ± 2.4	0.09
Nocturia	41.2%	70.6%	64.0%	0.17
Apnea during the night	23.5%	35.3%	36.0%	0.66
Restless legs syndrome	47.1%	47.1%	52.0%	0.93
Severe snoring	23.5%	23.5%	28.0%	0.92
Taking sleeping pills	17.6%	35.3%	24.0%	0.48

[a]Data expressed as % or mean ± SD. *One-way ANOVA and the chi-square test. A value of $p < 0.05$ was considered significant for all analyses.

months after the acute phase of COVID-19. 2) The overall prevalence of OSA was 60%, being as high as 80% in the severe COVID-19 group. 3) With regard to the circadian rest-activity pattern, the moderate COVID-19 group had higher IV and lower circadian function index, M10, L5, IS, mesor, and amplitude, as well as worse sleep quality as assessed by the PSQI. Moreover, the moderate COVID-19 group had a higher prevalence of insomnia, an intermediate chronotype (as determined by the MEQ), and higher anxiety (as assessed by the HADS).

After the acute phase of COVID-19, all three groups had poor sleep quality, low TST values, and prevalent insomnia. With regard to SF-12 scores, the moderate and severe COVID-19 groups had lower quality of physical and mental health than did the mild COVID-19 group. Recent evidence has shown that patients with severe COVID-19 have similar risk factors for OSA.[37] We have previously shown that undiagnosed sleep-disordered breathing is associated with severe COVID-19 during the acute phase.[12] Current evidence suggests that OSA is an independent risk factor for severe COVID-19 presentations and an increased risk of hospitalization.[12]

The present study confirmed the physical and psychological consequences of COVID-19. The symptoms of the acute phase, four months after medical discharge, may be more significant than those thought to be essentially disorders associated with sleep. We investigated respiratory sleep disturbances, sleep quality disturbances, and sleep patterns in COVID-19 patients four months after discharge, providing prospective evidence of the relationship between sleep-disordered breathing and the severity of COVID-19. In addition, we found that all of the patients with COVID-19 in the present study had sleep disturbances, regardless of the severity of the disease. This evidence can contribute to a more precise profile of the sequelae of COVID-19 and to the development of comprehensive, long-term intervention programs covering these health problems.

In our study, we explored different parameters of circadian rest-activity rhythms. In the group of patients with moderate COVID-19, we found significant fragmentation of the rest-activity rhythm, as assessed by IV. This finding can be explained by the high prevalence of comorbidities in the moderate COVID-19 group. Circadian and sleep disorders have been associated with harmful health outcomes in non-COVID-19 patients, including cardiometabolic and cognitive disorders.[37] Interruptions in the sleep-wake cycle can influence circadian rhythms and homeostasis.[38]

Recent evidence indicates that people who recover from COVID-19 continue to experience symptoms for months (long COVID-19 syndrome). In the present study, the prevalence of sleep disorders was found to be high. To our knowledge, this is the first study to describe sleep health after acute COVID-19. Moreover, we found symptoms associated with mental health (depression and anxiety), fatigue, and impaired HRQoL.[6]

Our study showed a high prevalence of poor sleep quality and insomnia in all three groups of patients with COVID-19, as well as a decrease in the number of hours of sleep (which were below the recommended for optimal health).[39] In addition, our study showed a low quality of life in the physical and mental health

Table 3. Sleep questionnaire data and home sleep apnea test results in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Sleep questionnaires				
SATED scale score	6.3 ± 3.0	5.2 ± 2.3	6.1 ± 2.2	0.470
PSQI score	8.5 ± 4.2[a]	12.3 ± 4.4[b]	9.3 ± 4.5[a]	0.049
Healthy sleep (≤ 5)	16.7%	11.8%	12.0%	0.883
Unhealthy sleep (> 5)	83.3%	88.2%	88.0%	
ESS score	7.5 ± 5.5	9.2 ± 5.2	8.2 ± 5.1	0.511
Nonsleepy (≤ 10)	61.1%	52.9%	64.0%	0.768
Sleepy (> 10)	38.9%	47.1%	36%	
ISI	8.2 ± 6.9	12.9 ± 6.2	9.4 ± 6.1	0.082
Without insomnia	50%	17.6%	44.0%	0.108
With insomnia	50%	82.4%	56%	
STOP-Bang questionnaire score	2.2 ± 1.7[a]	3.5 ± 2.2[a]	3.6 ± 1.6[b]	0.047
No risk of OSA	27.8%	0%	4.0%	0.038
Low risk of OSA	27.8%	41.2%	16.0%	
Intermediate risk of OSA	33.3%	35.3%	48.0%	
High risk of OSA	11.1%	23.5%	32.0%	
MEQ score	54.1 ± 8.7	55.2 ± 7.9	59.5 ± 7.4	0.208
Home sleep apnea test				
RDI	7.3 ± 10.2	12.2 ± 10.5	12.6 ± 9.5	0.779
0-4 events/h (non-OSA)	72.2%	35.3%	20.0%	0.002
≥ 5 events/h (OSA)	27.8%	64.7%	80.0%	
Obstructive apneas, events/h	1.79 ± 2.87	1.41 ± 2.70	2.89 ± 5.53	0.686
Central apneas, events/h	2.3 ± 4.5	3.8 ± 7.8	2.1 ± 3.5	0.595
Hypopnea index, events/h	4.92 ± 7.16	6.91 ± 8.59	7.12 ± 5.18	0.747
ODI ≥ 3%	7.2 ± 11.7	11.2 ± 11.9	11.6 ± 9.7	0.489
Snoring events	608.6 ± 950.8	966.8 ± 1,591.9	958.7 ± 1,207.2	0.499
T90%	2.4 ± 5.6	7.5 ± 14.6	12.1 ± 22.0	0.352
Mean SpO_2	95.2 ± 1.2[a]	93.9 ± 1.5[b]	93.6 ± 1.8[b]	0.041
Nadir SpO_2	85.8 ± 7.6	83.9 ± 5.6	82.4 ± 5.6	0.475
Actigraphy				
Time in bed, min	400.9 ± 101.0	410.1 ± 96.2	434.5 ± 99.4	0.445
Total sleep time, min	347.9 ± 105.3	364.1 ± 96.3	385.5 ± 90.6	0.399
Sleep onset latency, min	2.0 ± 1.5	2.1 ± 1.7	2.2 ± 2.3	0.965
Sleep efficiency, %	87.4 ± 5.7	86.3 ± 8.4	86.9 ± 6.2	0.912
WASO, min	42.2 ± 20.0	42.9 ± 19.2	47.2 ± 26.0	0.759
Arousals	7.7 ± 3.9	7.1 ± 3.6	7.3 ± 4.3	0.948
Circadian rhythm				
CFI	0.73 ± 0.06	0.71 ± 0.05	0.73 ± 0.06	0.520
M10	6,371.0 ± 1,170.3	6,024.0 ± 1,237.6	6,227.1 ± 1,629.6	0.794
L5	79.9 ± 48.5	62.0 ± 27.3	69.6 ± 36.7	0.435
RA	0.98 ± 0.01	0.98 ± 0.01	0.97 ± 0.02	0.959
IS	0.5 ± 0.1	0.4 ± 0.1	0.5 ± 0.1	0.428
IV	0.62 ± 0.09[a]	0.72 ± 0.11[b]	0.64 ± 0.11[a]	0.030
Mesor	3,012.5 ± 635.3	2,777.8 ± 785.4	2,789.8 ± 701.7	0.593
Amplitude	2,417.7 ± 682.5	2,162.7 ± 585.2	2,416.0 ± 688.8	0.441
Acrophase	15:33:05	15:44:00	15:17:33	

SATED: satisfaction, alertness, timing, efficiency, and duration; PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale; ISI: Insomnia Severity Index; OSA: obstructive sleep apnea; MEQ: Morningness-Eveningness Questionnaire; RDI: respiratory disturbance index; ODI: oxygen desaturation index; T90%: total time with SaO_2 below 90%; WASO: wake after sleep onset; CFI: circadian function index; M10: the most active 10-h period; L5: the least active 5-h period; RA: relative amplitude; IS: interdaily stability; and IV: intraday variability. [a]Data expressed as mean ± SD or %. *One-way ANOVA and the chi-square test. Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). ANCOVA was performed to analyze sleep questionnaire data and home sleep apnea test results. BMI and age were used as covariates. A value of $p < 0.05$ was considered significant for all analyses.

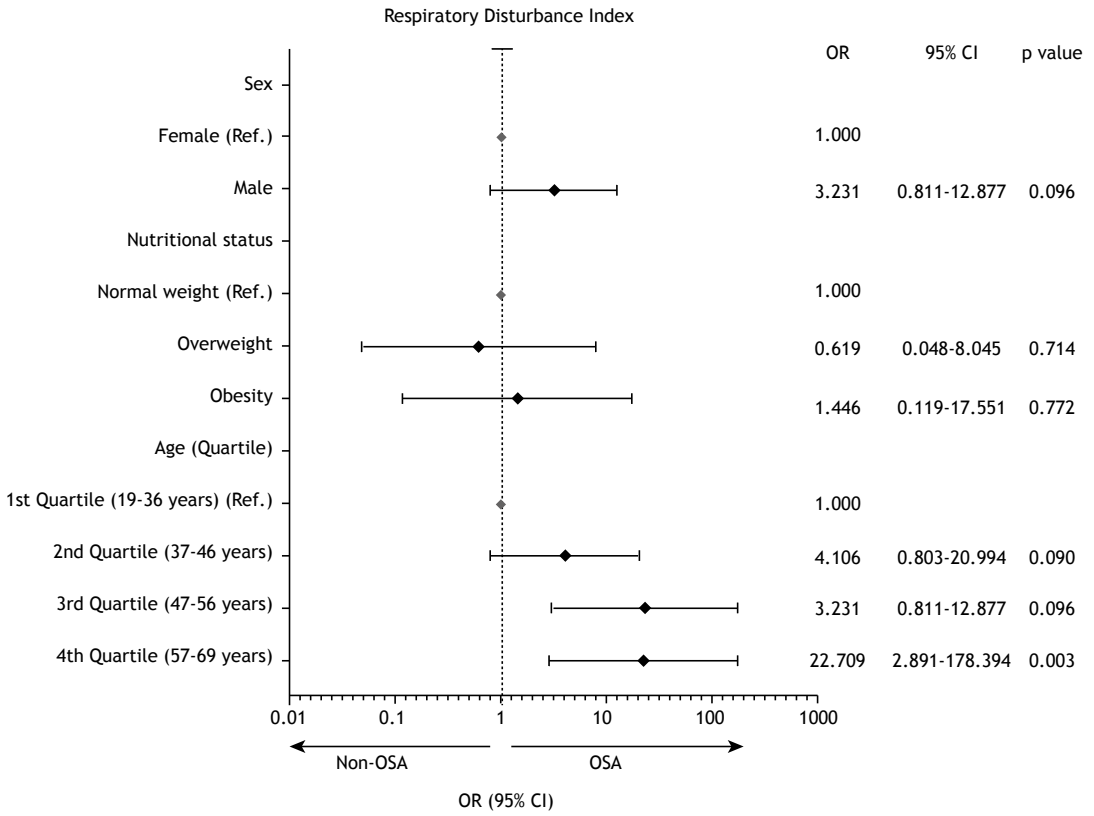

Figure 1. Logistic regression analysis of the probability of obstructive sleep apnea (OSA) in COVID-19 patients four months after the acute phase of the disease. The results were presented as ORs and their respective 95% CIs. The analysis was adjusted for sex, age, and nutritional status. An OR > 1 indicated a higher probability of having OSA, and an OR of < 1 indicated a lower probability of having OSA. A value of $p < 0.05$ was considered statistically significant.

domains of the SF-12, as well as a high prevalence of severe fatigue.

Previous studies have evaluated the risk of sequelae after COVID-19, focusing on clinical parameters, pulmonary function tests, and quality of life parameters.[3-6] Our study opens up another dimension to explore during the recovery phase of COVID-19 infection (i.e., sleep health), and our results are relevant to current clinical practice.

One of the limitations of the present study is that the sample size was small (60 patients). Future studies exploring COVID-19 symptoms in larger cohorts should include sleep health in their evaluations. Another limitation is the lack of a control group, meaning that we were unable to compare the effects of COVID-19 severity on the study variables.

We found a high prevalence of sleep-related symptoms in the group of patients with moderate COVID-19. Future studies investigating such patients should examine the psychological and sleep sequelae of COVID-19. The patients with moderate COVID-19 in the present study had worse sleep quality and higher anxiety than did those with mild or severe COVID-19. This might be due to the high prevalence of insulin resistance, diabetes mellitus, and hypertension in the moderate COVID-19 group. It has recently been shown that a high burden of comorbidities is associated with low sleep quality and high anxiety.[39,40]

Yet another limitation is that we used subjective measures of different sleep parameters. However, the prevalence of sleep disorders in the present study was high in all three groups of patients.

In conclusion, our findings show several sleep-related symptoms, as well as changes in the circadian rest-activity pattern, together with impaired mental health, in COVID-19 patients four months after the acute phase of the disease. Further studies are needed to confirm these findings and understand the underlying mechanisms.

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AUTHOR CONTRIBUTIONS

GL: study design and guarantor of the article; MH-B, JL, DE, IC, and EN-L: data extraction and analysis; GL, IC, and MH-B: statistical analysis; MH-B, IC, EN-L, GL, AT, and FB: drafting of the manuscript; GL, EN-L, AT,

Table 4. Health-related quality of life, mood, depression, and fatigue in the study population (N = 60).[a]

Variable	COVID-19			p*
	Mild (n = 18)	Moderate (n = 17)	Severe (n = 25)	
Mental health				
HADS-A score	5.6 ± 4.6[a]	8.6 ± 3.8[b]	5.6 ± 3.7[a]	0.042
Normal	77.8%	47.1%	72.0%	0.067
Borderline abnormal	5.6%	5.9%	16.0%	
Abnormal	16.7%	47.1%	12.0%	
HADS-D score	5.0 ± 4.6	5.9 ± 3.6	3.4 ± 2.9	0.096
Normal	72.2%	70.6%	84.0%	0.305
Borderline abnormal	11.1%	11.8%	16.0%	
Abnormal	16.7%	17.6%	0%	
BDI score	8.2 ± 9.4	12.1 ± 8.1	8.9 ± 6.8	0.308
No depression	77.8%	76.5%	72.0%	0.744
Mild depression	11.1%	5.9%	20.0%	
Moderate depression	5.6%	11.8%	8.0%	
Severe depression	5.6%	5.9%	0%	
Health-related quality of life				
SF-12, mental health score	50.26 ± 7.77[a]	40.37 ± 11.44[b]	41.21 ± 10.09[b]	0.005
SF-12, physical health score	45.0 ± 11.06	43.33 ± 12.44	49.86 ± 8.93	0.123
Fatigue				
Chalder Fatigue Scale score	4.4 ± 3.4	6.6 ± 2.3	5.1 ± 2.7	0.079
Total score	13.3 ± 10.2	19.8 ± 6.9	15.4 ± 8.0	0.079
Severe fatigue	61.1%	88.2%	72.0%	0.189

HADS-A: Hospital Anxiety and Depression Scale, anxiety domain; HADS-D: Hospital Anxiety and Depression Scale, depression domain; BDI: Beck Depression Inventory; and SF-12: 12-Item Short-Form Health Survey. [a]Data expressed as mean ± SD or %. *One-way ANOVA and the chi-square test. Different letters in the same row indicate significant differences between groups (one-way ANOVA and post hoc analysis with the Bonferroni test). A value of $p < 0.05$ was considered significant for all analyses.

and FB: critical revision of the manuscript for important intellectual content; MH-B, GL, IC, DE, JL, EN-L, AT, and FB: approval of the final version.

CONFLICTS OF INTEREST

None declared.

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