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Original Article

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Facility-measured nocturnal hypoxemia and sleep among adults with long COVID versus age- and sex-matched healthy adults: a preliminary observational study

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Abstract

Study Objectives: Persistent post-acute sequelae of SARS-CoV-2 infection, i.e. long COVID, impacts multiple organ systems. While lower blood oxygen is expected when SARS-CoV-2 infects the lungs, hypoxia without pulmonary symptoms may continue after the acute phase. Ventilation and blood oxygen are more vulnerable during sleep, but nocturnal hypoxemia hasn't been studied in people with long COVID in a facility setting using gold-standard polysomnography (PSG).

Methods: We conducted an observational study with 50 participants (25 long COVID, 25 age-sex-matched healthy controls) using in-laboratory overnight PSG. We calculated the average SpO_2, average SpO_2 after removing desaturations, the respiratory rate in different sleep periods, and the hypoxic costs using all desaturations.

Results: We found that average SpO_2 was lower in participants with long COVID: 1.0% lower after sleep onset ($p = .004$) and 0.7% lower during REM ($p = .002$); average SpO_2 after removing desaturations was also lower in participants with long COVID: 1.3% lower after sleep onset ($p = .002$), 0.9% lower during REM ($p = .0004$), and 1.4% lower during NREM ($p = .003$); and respiratory rate was 1.4/minute higher in participants with long COVID during REM ($p = .005$). There were no significant differences in SpO_2 and respiratory rate before sleep onset, the within-participant change from before to after sleep onset, or hypoxic costs.

Conclusions: The results suggest that long COVID had a persistent lower nocturnal blood oxygen saturation, and support the need for a large-scale study of nocturnal hypoxemia in people with long COVID compared to the general population.

Key words: long COVID; sleep; nocturnal hypoxemia; oxygen desaturation; SpO_2; polysomnography

Statement of Significance

Blood oxygen impairment can continue after the acute phase of COVID-19. While sleep is a state during which people are vulnerable to hypoxemia, nocturnal hypoxemia using gold standard polysomnography (PSG) has not been studied in people with long COVID. The study uses facility-obtained in-lab PSG to investigate the hypothesis that long COVID is associated with persistently lower blood oxygen levels during sleep. These findings highlight the need for further research to understand better how long COVID affects sleep and overall health.

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Ever since the COVID-19 pandemic, persistent post-acute sequelae of SARS-CoV-2 infection (PASC), i.e. long COVID, have imposed new challenges on our healthcare system [1–4]. While the acute phase of the infection primarily involves the respiratory system, old or new symptoms can persist months after the first infection [5], significantly impacting individuals' quality of life. Many symptoms of long COVID have been reported, where the primary ones include fatigue, brain fog, sleep complaints, post-exertional malaise, dizziness, and gastrointestinal symptoms [5–8]. The cause of long COVID remains unknown. The possible reasons include persisting low-grade viral infection, long-lasting impairment of the respiratory system [9], a hyperactive immune system leading to inflammation in organs [10], and an autoimmune response [11].

It has been observed that there may be long-lasting problems with blood oxygen associated with SARS-CoV-2 infection. For example, persistently low levels of oxygen saturation can be found in people with long COVID during exercise tests [12, 13] and under experimental upper arm cuffing [14]. Resting-state hypoxemia is independently associated with mortality in both non-COVID adults [15] and patients with COVID [16]. Sleep is a stage during which people are vulnerable to hypoxemia. In the Apple Heart & Movement Study [17], researchers conducted a cross-sectional analysis of 72 million 24-hour SpO_2 values from 33 080 participants using wearable devices and found a 0.8% decrease in the nocturnal oxygen saturation compared to daytime. The normal mild hypoventilation of sleep, as well as the effects of ventilation-perfusion mismatch due to gravitation and position, can amplify wake abnormalities in ventilation or gas exchange. Nocturnal hypoxemia can lead to persistent oxidative stress at the cellular level [18] and is related to unfavorable outcomes, including fatigue and daytime sleepiness [19], cardiovascular disorders due to diminished blood pressure dipping [20], and cognitive impairment [21], etc. Importantly, such hypoxemia might develop without proportional signs of respiratory distress [22]. However, an important aspect, nocturnal hypoxemia using polysomnography (PSG), has not been studied in patients with long COVID. PSG provides a high-quality research-standard approach for studying the multi-organ changes in patients with long COVID.

Here, we compared the nocturnal SpO_2 in participants with long COVID vs. age-sex-matched controls using facility-measured in-lab overnight PSG, which is the clinical gold standard in sleep recording. We hypothesized that the blood oxygen (measured by SpO_2) after sleep onset is lower in people with long COVID. We compared different SpO_2 parameters and respiratory rates in different sleep periods and stages.

Methods

Study design and cohort

This is a pilot observational study. Participants were recruited via advertisement postings on Craigslist and physical flyers in the Greater Boston Area, postings on ClinicalTrials.gov (NCT03377543 and NCT05606211), and referrals by clinicians at Beth Israel Deaconess Medical Center (BIDMC)'s Critical Illness and COVID-19 Survivorship Clinic. The long COVID inclusion criteria were (1) over 18 years of age, (2) confirmed history of SARS-CoV-2 infection based on medical documentation and/or COVID testing, and (3) PASC/long COVID consistent with diagnostic code ICD-10 U09.9: Post COVID-19 condition, unspecified. The long COVID exclusion criteria are (1) a history of chronic pain before SARS-CoV-2 infection, and (2) pregnant or nursing. These long COVID patients were enrolled between November 2022 through November 2023.

The control participants were a convenience sample of participants in past studies that enrolled and studied sleep in healthy people [23], hence having different exclusion criteria than the long COVID participants. Controls were 1:1 matched by sex and age (±5 years) to the long COVID participants. The inclusion criteria for control participants were (1) age between 18 and 65 years, (2) body mass index (BMI) between 18.5 and 35 kg/m2, (3) daily sleep duration between 7 and 9 hours, and a habitual sleep period starting within one hour of 11:00 pm verified by electronic sleep, and (4) negative toxicology screen for amphetamines, barbiturates, benzodiazepines, cocaine, opiates, and methadone. The exclusion criteria were (1) any active infection/disease, (2) lab values outside of the standard range, (3) pre-diabetes or diabetes (HbA1c > 5.7%), (4) history of neurological, chronic pain, immune/inflammatory, vascular/cardiovascular disorders (including hypertension and Raynaud syndrome), liver/kidney, metabolic disorders, gastrointestinal disorders, psychiatric disorders, sleep disorders, and lung diseases/pulmonary disorders, (5) personal or family history of stroke, (6) systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg, (7) symptoms or diagnosis of asthma or asthma medication within the year before enrollment, (8) intolerance or allergy to non-steroidal anti-inflammatory drugs, (9) pregnant or nursing, (10) medication other than oral contraceptives, and (11) current smoking. These control participants were enrolled between July 2018 and May 2022.

Measures of sleep and nocturnal oxygen saturation

Participants who passed the eligibility criteria stayed at the Clinical Research Center at BIDMC to undergo an attended overnight polysomnography. The recordings were conducted using equipment from Natus SleepWorks and Embla RemLogic and were scored by one sleep technologist following the AASM 2012 scoring manual [24]. The apnea–hypopnea index (AHI) was defined as per the same guideline [24]: the number of apneas regardless of desaturations or arousals, or hypopneas with >30% flow reduction and ≥3% oxygen desaturation or with arousal, divided by total sleep time in hours.

Standard overnight polysomnography included a fingertip pulse oximeter based on photoplethysmography (Nonin, Minnesota, USA) in both PSG hardware devices, providing oxygen saturation (SpO_2). The SpO_2 was measured continuously at 1 Hz (1 sample per second). We measured average SpO_2, average SpO_2 after removing desaturations, and average respiratory rate before and after sleep onset, and during REM and NREM. We also computed the within-participant difference from before sleep onset to after sleep onset. To obtain the average SpO_2 without desaturations, we first detected all desaturation events using a minimum decrease of 2% and a minimum duration of 5 seconds, and then we used linear interpolation to fill in the drop using the SpO_2 values at the start and the end of each desaturation event. We also extracted the hypoxic costs for all desaturations [25, 26], defined as the total area under all desaturations (apnea-independent) below the pre-event baseline divided by the total sleep time. Importantly, we conducted sensitivity analyses to account for the overestimation of SpO_2 in people with darker skin by about 1.1% [27], using both subset analysis and adjustment.

Statistical analysis

We used partial Spearman's correlation between the exposure and the outcome to obtain the p-value for comparing the two groups while adjusting for BMI since it is negatively associated

Table 1. Cohort Characteristics

Variable	Control (n = 25)	Long COVID (n = 25)^	P-value*
Demographics			
Age: year, mean (standard deviation [SD])	37.1 (11.6)	38.2 (10.9)	n.s.
Sex: n of female (%female)	17 (68%)	17 (68%)	n.s.
Body mass index: kg/m^2, mean (SD)	26.2 (4.4)	27.8 (6.3)	n.s.
Race: n (%)			.0009
Asian	1 (4%)	0 (0%)	
Black	10 (40%)	0 (0%)	
White	14 (56%)	21 (84%)	
More than one race	0 (0%)	4 (16%)	
Years since long COVID: median (min–max)	—	1.3 (0.8–3.6)	—
Sleep parameters			
Apnea–hypopnea index (AHI): /hour, mean (SD)	1.9 (1.9)	1.9 (2.6)	n.s.
Total sleep time: hour, mean (SD)	7.3 (0.6)	6.4 (1.3)	.003
Sleep efficiency: %, mean (SD)	90.7 (6.7)	78.3 (15.0)	.0004
Wake after sleep onset (WASO): minute, mean (SD)	28.2 (15.8)	42.1 (32.8)	n.s.
Sleep latency from lights off: minute, mean (SD)	14.3 (27.9)	43.7 (63.8)	.04
REM latency from lights off: minute, mean (SD)	104.0 (68.6)	177.2 (100.5)	.004
N1 time: minute, mean (SD)	37.2 (21.5)	37.2 (22.1)	n.s.
N2 time: minute, mean (SD)	224.4 (42.3)	189.1 (43.0)	.005
N3 time: minute, mean (SD)	74.7 (32.7)	84.2 (44.3)	n.s.
REM time: minute, mean (SD)	99.6 (36.0)	72.5 (38.1)	.01
N1 %: median (IQR)	6.1 (4.7–9.2)	6.5 (4.8–8.4)	n.s.
N2 %: median (IQR)	46.5 (38.8–53.2)	38.2 (34.3–46.6)	.006
N3 %: median (IQR)	16.4 (8.2–20.0)	17.9 (12.8–21.3)	n.s.
REM %: median (IQR)	19.6 (16.5–25.8)	14.7 (10.6–18.1)	.003
N1 % in the first half: median (IQR)	12.8 (8.3–19.3)	6.2 (0.0–13.8)	.007
N2 % in the first half: median (IQR)	6.2 (3.6–7.9)	5.7 (3.6–9.2)	n.s.
N3 % in the first half: median (IQR)	43.0 (39.0–52.0)	34.8 (29.5–39.3)	.006
REM % in the first half: median (IQR)	26.5 (15.2–30.8)	24.1 (17.6–31.9)	n.s.
N1 % in the second half: median (IQR)	28.1 (20.8–34.4)	20.1 (15.9–26.1)	.03
N2 % in the second half: median (IQR)	6.8 (4.6–12.5)	7.1 (5.2–9.9)	n.s.
N3 % in the second half: median (IQR)	47.8 (42.4–55.4)	46.1 (37.2–48.3)	n.s.
REM % in the second half: median (IQR)	7.5 (2.9–10.6)	10.2 (3.5–15.9)	n.s.
Daytime vital signs: mean (SD)			
Temperature (°F)	98.2 (0.6)	97.4 (3.6)	n.s.
Systolic blood pressure (mmHg)	113.9 (18.1)	122.3 (14.2)	n.s.
Diastolic blood pressure (mmHg)	72.2 (9.7)	79.1 (8.8)	.03
Resting heart rate (beat/minute)	71.8 (11.9)	81.9 (12.7)	.02
O_2 saturation (%)	99.2 (1.0)	98.0 (1.7)	.02

*t-test for a continuous variable, chi2 test for categorical variable. "n.s." stands for not significant, i.e. p-value > .05.
^ The medications, comorbidities before COVID infection, and long COVID symptoms of the long COVID group are shown in Table S1 in the supplementary material.

with SpO_2 [28]. The partial Spearman's correlation between group (categorical variable) vs. parameters (continuous variable) is a valid and robust approach to compare two groups while adjusting for covariates. We did not adjust for age and sex since they are matched by design (see Table 1). We did not adjust for AHI since there was no participant with high AHI (>10/hour), with no statistically significant difference. We used the Bonferroni multiple test correction to control the family-wise error rate, where the number of independent tests was 9:2 (SpO_2 and respiratory rate) × 4 (before sleep onset, after sleep onset, REM, NREM) + 1 (hypoxic costs). The significance was set at p-value < .05/9 = .00556. All analyses were done using Python 3.10.12.

Results

Cohort characteristics

The cohort contained 50 participants, including 25 long COVID and 25 age-sex-matched healthy controls. The cohort characteristics are shown in Table 1. Participants were 37–38 years old on average, and 68% female and 32% male. By study design, there were no differences in age and sex. There were no Black participants in the long COVID group. The median time since long COVID (index date) was 1.3 years. The long COVID group had about 12% lower sleep efficiency, about 1 hour shorter sleep duration, and three times longer sleep latency. The long COVID group

Table 2. SpO_2 and Respiration Parameters in Different Conditions

Condition	Parameter	Control (n = 25): median (IQR[+])	Long COVID (n = 25): median (IQR)	P-value[*]
Lights off until sleep onset (i.e. wake before sleep onset or sleep latency period)^	Average SpO_2 (%)	97.5 (97.0–97.9)	96.3 (95.4–97.0)	.01
	Average SpO_2 after removing desaturations (%)	97.5 (97.1–98.0)	96.5 (95.8–97.3)	.01
	Respiratory rate (/minute)	16.0 (13.7–17.7)	15.9 (14.5–17.6)	n.s.
After sleep onset until lights on	**Average SpO_2 (%)**	**96.1 (95.5–97.1)**	**95.1 (94.1–95.8)**	**.004**
	Average SpO_2 after removing desaturations (%)	**96.4 (95.9–97.2)**	**95.1 (94.2–95.9)**	**.002**
	Respiratory rate (/minute)	14.3 (13.8–15.5)	15.5 (14.4–16.2)	n.s.
REM	**Average SpO_2 (%)**	**96.4 (95.9–97.1)**	**95.7 (94.1–96.1)**	**.002**
	Average SpO_2 after removing desaturations (%)	**96.6 (96.3–97.4)**	**95.7 (94.4–96.3)**	**.0004**
	Respiratory rate (/minute)	**14.9 (13.4–15.5)**	**16.3 (15.3–17.3)**	**.005**
NREM	Average SpO_2 (%)	96.1 (95.3–97.1)	94.9 (93.8–95.6)	.006
	Average SpO_2 after removing desaturations (%)	**96.3 (95.7–97.2)**	**94.9 (94.1–95.7)**	**.003**
	Respiratory rate (/minute)	14.3 (13.8–15.4)	15.3 (14.1–16.2)	n.s.
Within-participant difference from before to after sleep onset	Average SpO_2 (%)	–0.7 (–1.1--0.2)	–1.2 (–2.1--0.4)	.05
	Average SpO_2 after removing desaturations (%)	–0.7 (–1.2--0.1)	–1.3 (–2.1--0.3)	.04
	Respiratory rate (/minute)	–0.4 (–2.0–0.9)	–0.5 (–1.2–0.7)	n.s.
Hypoxic costs	Hypoxic costs with desaturations (%×minute/hour)	9.1 (5.7–20.8)	9.7 (7.7–22.3)	n.s.

[*]The bolded parameters indicate statistical significance after Bonferroni correction; "n.s." stands for not significant, i.e. p-value > .05. ^ Lights off until sleep onset (i.e., wake before sleep onset or sleep latency period) had a mean duration of 14.3 minutes in the control group and 43.7 minutes in the long COVID group. [+] IQR stands for interquartile range.
The p-values are reported after adjusting for body mass index.

had higher diastolic blood pressure, systolic blood pressure, and lower O_2 saturation. PSGs for all long COVID patients and 11 controls were obtained using Natus PSG device, while PSGs for the remaining 14 controls were obtained using RemLogic PSG device. The medications, comorbidities before COVID infection, and long COVID symptoms of the long-COVID group are described in Table S1 in the supplementary material. Among the comorbidities before COVID infection, two diagnoses were significantly higher ($p < .05$) in the long COVID group: depression/anxiety and pain/inflammation. Three participants in the long COVID group had no active disease or medication and therefore may have qualified for the control group before SARS-CoV-2 infection/long COVID diagnosis.

Comparison results

In Table 2, we show the comparison results for the SpO_2 measurements in different conditions. The average SpO_2 was lower in individuals with long COVID: 1.0% lower after sleep onset until lights on ($p = .004$) and 0.7% lower during REM ($p = .002$). The average SpO_2 after removing desaturations was also lower in participants with long COVID: 1.3% lower after sleep onset until lights on ($p = .002$), 0.9% lower during REM ($p = .0004$), and 1.4% lower during NREM ($p = .003$). The respiratory rate was 1.4/minute higher in participants with long COVID during REM ($p = .005$). There was no statistical significance for parameters at lights off until sleep onset, in the difference from before to after sleep onset, or in hypoxic costs.

For sensitivity analysis, in Table S2 in the supplementary material, we show the results by excluding participants with darker skin approximated by the black race, and also excluding their matched pairs. The sample size was reduced to 15 in each group. There was no significance in terms of the SpO_2 measures. The respiratory rates after sleep onset, during REM, and during NREM were faster in the long COVID group. As another way to consider skin color tone, instead of excluding Black participants, in Table S3 we additionally adjusted for the Black race, there was also no significance in terms of the SpO_2 measures. The respiratory rates after sleep onset and during REM were faster in the long COVID group.

SpO_2 trace in participants with long COVID and controls

We visualized the overnight SpO_2 and respiratory rate traces, which provided temporal information. In Figure 1, we show three traces that are time aligned to sleep onset in each group: average SpO_2 with desaturations removed, difference between the two groups, and respiratory rate. The long COVID patients had lower SpO_2 after sleep onset. In Figure 2, we zoom in to show 15 minutes before and after the time-aligned sleep onset. The difference started to emerge around 5 to 10 minutes after sleep onset.

The respiratory rate trace in the long COVID group was slightly higher than that in the control group. Therefore, the average values of respiratory rate were not significant across groups both before and after sleep onset (Table 2). A less obvious observation from Figure 2 is the higher respiratory rate in REM since the traces are aligned to sleep onset, not REM onset.

Discussion

We found that patients with long COVID compared to healthy controls had a persistent lower nocturnal blood oxygen saturation i.e. the average SpO_2 after removing desaturations after sleep

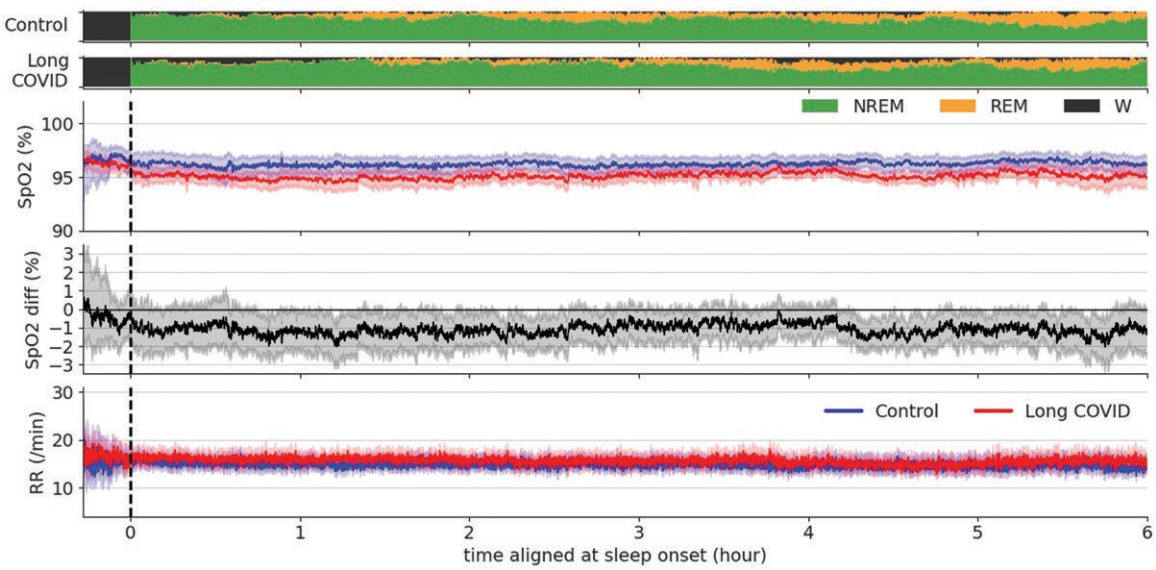

Figure 1. The first and second panels show the hypnograms of control and long COVID groups time-aligned to sleep onset. They are represented as the fraction (%) of participants who are at NREM (green), REM (orange), or wake (black) stage at each time. The third panel shows the group averaged SpO2 traces, time-aligned to sleep onset across the night. The fourth panel shows the difference in SpO2 traces, defined as the long COVID group minus the control group, hence negative value means long COVID has values lower than the control. The bottom panel shows the respiratory rate traces derived from the abdomen respiratory effort belt. For all traces, blue is for controls, and red is for long COVID.

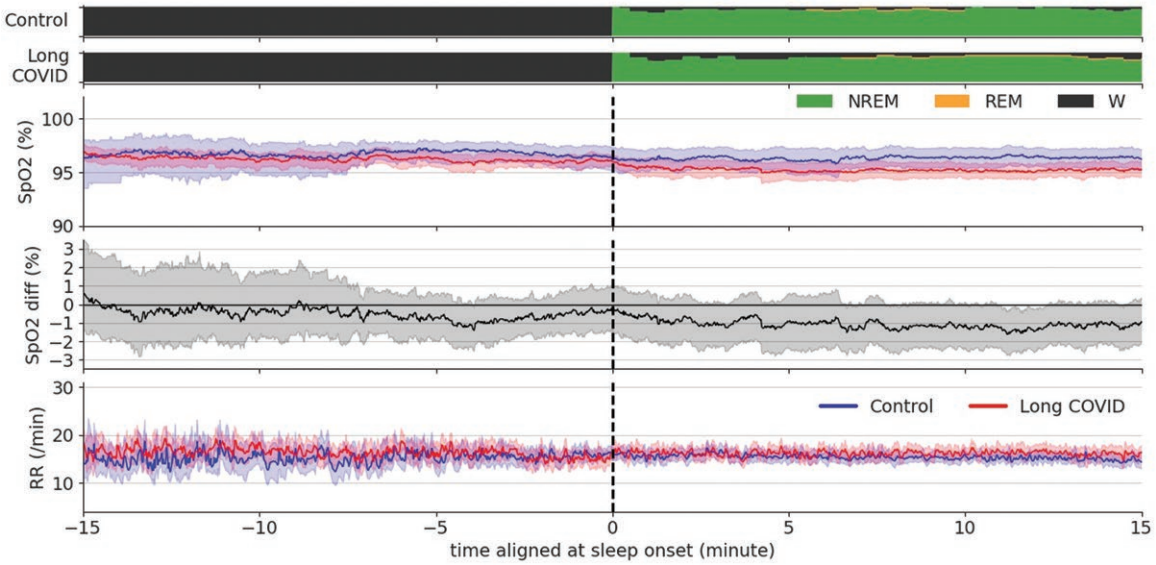

Figure 2. A zoom-in version at ±15 minutes around the time-aligned sleep onset. The legends are the same as in Figure 1.

onset, especially during REM sleep. This difference emerged as early as 5 to 10 minutes after sleep onset. There was no difference in hypoxic costs, indicating the depth and duration of episodic desaturations were similar in participants with long-term COVID compared to healthy controls. We also found that the long COVID participants had reduced sleep efficiency, longer sleep latency and REM latency, less REM and N2 sleep, and less N3 in the first half of the night (Table 1). It is unknown if such sleep architecture changes are related to the gas exchange pattern.

Possible explanations of the subclinical hypoxia include the subtle persistence of lung injury following COVID as supported by reports of shortness of breath in 10 out of 25 of our participants with long COVID (Table S1), and also many other factors, including endothelial functions. This could include mild levels of ventilation-perfusion mismatch or reduced gas diffusing capacity, due to possible etiologies such as residual inflammation of the lung parenchyma or small vessels, that become amplified during sleep. Along this line, micro-embolic [29] and endothelial dysfunction [30] have been observed in people with long COVID. The supine position during sleep may also contribute by reducing the functional residual capacity. Diaphragm dysfunction has been reported in COVID-19 infection [31] and would be amplified in the supine position and especially during REM sleep when there is respiratory muscle hypotonia.

The mild reduction in oxygen saturation observed during sleep in people with long COVID may provide a marker of long

COVID-related organ dysfunction. As oxygen saturations are easy to track even with consumer wearables or oximeters, tracking this mild hypoxia, even if not directly pathological, may provide prognostic information throughout residual disease or recovery.

In Table 2, the average SpO_2 in NREM was lower than in REM in both groups, which was unexpected. Further analysis showed that 17 (68%) long COVID participants and 20 (80%) control participants had an average SpO_2 in NREM lower than REM. The possible reasons include low AHI and differences in body position. However, this finding needs to be replicated.

There are several limitations in our study. First, due to the preliminary nature of the study, the sample size of 50 was small. We cannot exclude selection bias, where people with symptoms and better educated about long COVID may be more likely to be enrolled in our study. Second, pulmonary function or chest imaging were not routinely collected in this study and will be an important part of future studies. Third, the two groups were balanced for sex and age, but we could not match the two groups based on pre-COVID comorbidities and medications, which remain important confounders that might be addressed in large cohorts. Another important factor yet to consider is skin pigmentation, which is recognized to contribute to oximetry biases. Clearly, additional data are needed in more diverse samples and with instruments that are equally valid across groups. In addition to skin pigmentation, it is known that long COVID is more prominent in women [32], middle or old age, overweight or obese, and people with comorbidities [33]. Studies with larger sample sizes are needed, which may be implemented using home devices [34]. Next, the observed difference in SpO_2 at about 1% is small. It is necessary to discuss the small difference in a better context, such as comparing it to normative data at a given age. Last but not least, given that the patients were recruited/enrolled before the National Academies of Sciences, Engineering, and Medicine released a definition of Long COVID, we acknowledge the heterogeneous and evolving nature when applying the predefined inclusion criteria of the long COVID group. At the same time, only four control participants were enrolled during the COVID-19 pandemic. This could lead to misclassification bias so that the difference between the two groups was attenuated. Therefore, the actual effect size could be larger than what we observed.

The results call for a larger study to determine the normative ranges for oxygen saturation in health and correlations with future health outcomes, so that deviations from these normative data in diseases (such as long COVID and lung diseases) can be interpreted. Therefore, while the changes observed are small in magnitude, they suggest that patients with long COVID may experience persistent cardiopulmonary impairment even 1 year after their acute infection.

Supplementary material

Supplementary material is available at *SLEEP Advances* online.

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Disclosure Statement

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Author Contribution

Haoqi Sun (Formal analysis [Lead], Writing - original draft [Lead], Writing - review & editing [Lead]), Rammy Dang (Data curation [Lead], Resources [Lead], Writing - review & editing [Supporting]), Monika Haack (Conceptualization [Equal], Funding acquisition [Equal], Writing - review & editing [Equal]), Kristine Hauser (Data curation [Equal], Project administration [Equal], Writing - review & editing [Equal]), Jennifer Scott-Sutherland (Data curation [Equal], Project administration [Equal], Resources [Equal]), Brandon Westover (Conceptualization [Equal], Methodology [Equal], Writing - review & editing [Equal]), Sairam Parthasarathy (Conceptualization [Equal], Writing - review & editing [Equal]), Susan Redline (Conceptualization [Equal], Writing - review & editing [Equal]), Robert Thomas (Conceptualization [Equal], Data curation [Equal], Resources [Equal], Writing - review & editing [Equal]), and Janet Mullington (Conceptualization [Lead], Data curation [Equal], Funding acquisition [Equal], Methodology [Equal], Supervision [Equal], Validation [Equal], Writing - review & editing [Lead])

Data Availability

The code is available on GitHub https://github.com/Hockey86/long-covid-spo2-psg. The dataset is available upon reasonable request from the corresponding author(s).

References

1. Crook H, Raza S, Nowell J, Young M, Edison P. Long covid—mechanisms, risk factors, and management. *BMJ*. 2021;**374**:n1648. doi:10.1136/bmj.n1648
2. Reese JT, Blau H, Casiraghi E, *et al.*; N3C Consortium. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programs. *EBioMed* 2023;**87**:104413. doi:10.1016/j.ebiom.2022.104413
3. Nalbandian A, Sehgal K, Gupta A, *et al*. Post-acute COVID-19 syndrome. *Nat Med*. 2021;**27**:601–615. doi:10.1038/s41591-021-01283-z
4. Shah W, Hillman T, Playford ED, Hishmeh L. Managing the long term effects of covid-19: summary of NICE, SIGN, and RCGP rapid guideline. *BMJ*. 2021;**372**:n136. doi:10.1136/bmj.n136
5. Thaweethai T, Jolley SE, Karlson EW, *et al.*; RECOVER Consortium. Development of a definition of postacute sequelae of SARS-CoV-2 infection. *JAMA*. 2023;**329**:1934–1946. doi:10.1001/jama.2023.8823

6. Huang L, Yao Q, Gu X, *et al*. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet (London, England)*. 2021;**398**:747–758. doi:10.1016/S0140-6736(21)01755-4
7. Davis HE, Assaf GS, McCorkell L, *et al*. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMed*. 2021;**38**:101019. doi:10.1016/j.eclinm.2021.101019
8. Naik S, Haldar SN, Soneja M, *et al*. Post COVID-19 sequelae: a prospective observational study from Northern India. *Drug Dis Therap*. 2021;**15**:254–260. doi:10.5582/ddt.2021.01093
9. Böning D, Kuebler WM, Vogel D, Bloch W. The oxygen dissociation curve of blood in COVID-19–An update. *Front Med*. 2023;**10**(1098547):1098547. doi:10.3389/fmed.2023.1098547
10. Frere JJ, Serafini RA, Pryce KD, *et al*. SARS-CoV-2 infection in hamsters and humans results in lasting and unique systemic perturbations after recovery. *Sci Transl Med*. 2022;**14**:eabq3059. doi:10.1126/scitranslmed.abq3059
11. Chang SE, Feng A, Meng W, *et al*. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;**12**(5417):5417. doi:10.1038/s41467-021-25509-3
12. Guarnieri G, Lococo S, Bertagna De Marchi L, *et al*. Persistent oxygen desaturation during exercise in patients with long COVID. *Eur Respir J*. 2022;**60**(suppl 66):3725. doi:10.1183/13993003.congress-2022.3725
13. Guler SA, Ebner L, Aubry-Beigelman C, *et al*. Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J*. 2021;**57**:2003690. doi:10.1183/13993003.03690-2020
14. Schäfer H, Teschler M, Mooren FC, Schmitz B. Altered tissue oxygenation in patients with post COVID-19 syndrome. *Microvasc Res*. 2023;**148**(104551):104551. doi:10.1016/j.mvr.2023.104551
15. Vold ML, Aasebø U, Wilsgaard T, Melbye H. Low oxygen saturation and mortality in an adult cohort: the Tromsø study. *BMC Pulm Med*. 2015;**15**:1–12.
16. Xie, *J. et al*. Association between hypoxemia and mortality in patients with COVID-19. In: *Mayo Clinic Proceedings* **vol. 95**. Rochester, MN: Elsevier; 2020: 1138–1147.
17. Shapiro I, Stein J, MacRae C, O'Reilly M. Pulse oximetry values from 33,080 participants in the apple heart & movement study. *NPJ Digital Med*. 2023;**6**(134):134. doi:10.1038/s41746-023-00851-6
18. Eisele H-J, Markart P, Schulz R; & others. Obstructive sleep apnea, oxidative stress, and cardiovascular disease: evidence from human studies. *Oxid Med Cell Longevity*. 2015;**2015**(2015):608438. doi:10.1155/2015/608438
19. Vgontzas AN, Papanicolaou DA, Bixler EO, *et al*. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metabol*. 2000;**85**:1151–1158. doi:10.1210/jcem.85.3.6484
20. Perger E, Baillieul S, Esteve F, *et al*. Nocturnal hypoxemia, blood pressure, vascular status and chronic mountain sickness in the highest city in the world. *Ann Med*. 2022;**54**:1884–1893. doi:10.1080/07853890.2022.2091791
21. Naismith SL, Duffy SL, Cross N, *et al*. Nocturnal hypoxemia is associated with altered Parahippocampal functional brain connectivity in older adults at risk for dementia. *J Alzheimer's Dis*. 2020;**73**:571–584. doi:10.3233/JAD-190747
22. Dhont S, Derom E, Van Braeckel E, Depuydt P, Lambrecht BN. The pathophysiology of 'happy'hypoxemia in COVID-19. *Respir Res*. 2020;**21**:1–9.
23. Engert LC, Ledderose C, Biniamin C, *et al*. Effects of low-dose acetylsalicylic acid on the inflammatory response to experimental sleep restriction in healthy humans. *Brain Behav Immun*. 2024;**121**:142–154. doi:10.1016/j.bbi.2024.07.023
24. Berry RB, Budhiraja R, Gottlieb DJ, *et al*.; American Academy of Sleep Medicine. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events: deliberations of the sleep apnea definitions task force of the American academy of sleep medicine. *J Clin Sleep Med*. 2012;**8**:597–619. doi:10.5664/jcsm.2172
25. Azarbarzin A, Sands SA, Taranto-Montemurro L, Redline S, Wellman A. Hypoxic burden captures sleep apnoea-specific nocturnal hypoxaemia. *Eur Heart J*. 2019;**40**:2989–2990. doi:10.1093/eurheartj/ehz274
26. Esmaeili N, Labarca G, Hu W-H, *et al*. Hypoxic burden based on automatically identified desaturations is associated with adverse health outcomes. *Ann Am Thoracic Soc*. 2023;**20**:1633–1641. doi:10.1513/AnnalsATS.202303-248OC
27. Shi C, Goodall M, Dumville J, *et al*. The accuracy of pulse oximetry in measuring oxygen saturation by levels of skin pigmentation: a systematic review and meta-analysis. *BMC Med*. 2022;**20**(267):1.
28. Kapur VK, Wilsdon AG, Au D, *et al*. Obesity is associated with a lower resting oxygen saturation in the ambulatory elderly: results from the cardiovascular health study. *Respir Care*. 2013;**58**:831–837. doi:10.4187/respcare.02008
29. Canale MP, Menghini R, Martelli E, Federici M. COVID-19–associated endothelial dysfunction and microvascular injury: from pathophysiology to clinical manifestations. *Cardiac Electrophysiol Clinics*. 2021;**14**(21):21–28. doi:10.1016/j.ccep.2021.10.003
30. Nicolai L, Kaiser R, Stark K. Thromboinflammation in long COVID—the elusive key to postinfection sequelae? *J Thromb Haemost*. 2023;**21**:2020–2031. doi:10.1016/j.jtha.2023.04.039
31. Polkey MI. Diaphragm dysfunction as a contributor to breathlessness after COVID-19 infection. *Am J Respir Crit Care Med*. 2023;**207**:964–965. doi:10.1164/rccm.202301-0105ED
32. Shah DP, Thaweethai T, Karlson EW, *et al*.; RECOVER Consortium. Sex Differences in Long COVID. *JAMA Net Open*. 2025;**8**:e2455430. doi:10.1001/jamanetworkopen.2024.55430
33. Jeffrey K, Woolford L, Maini R, *et al*. Prevalence and risk factors for long COVID among adults in Scotland using electronic health records: a national, retrospective, observational cohort study. *EClinicalMed*. 2024;**71**:102590. doi:10.1016/j.eclinm.2024.102590
34. Mekhael M, Lim CH, El Hajjar AH, *et al*. Studying the effect of long COVID-19 infection on sleep quality using wearable health devices: observational study. *J Med Internet Res*. 2022;**24**:e38000. doi:10.2196/38000