

Sleep Disturbance Severity and Correlates in Post-acute Sequelae of COVID-19 (PASC)



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INTRODUCTION

Post-acute COVID-19 syndrome (PASC) is a global public health crisis in which patients experience lingering and debilitating symptoms beyond 4 weeks after the acute onset of SARS-CoV-2 infection.¹ Sleep disturbance has a reported prevalence of 34–50% in PASC,^{2,3} but only a few studies have identified associated risk factors, and these have primarily described sleep quality and not symptom severity.^{3,4} Likewise, studies to date have not investigated the interaction of mood disorders and fatigue with sleep disturbance severity or the association of objective sleep study indices in PASC.

METHODS

Patients with PASC¹ were evaluated at the Cleveland Clinic ReCOVer Clinic between February 2021 and April 2022. Patients ≥ 18 years old who completed Patient-Reported Outcomes Measurement Information System (PROMIS)⁵ Sleep Disturbance within 90 days or during their initial ReCOVer clinic visit were prospectively examined. Demographics and clinical characteristics were extracted from the COVID-19 Cleveland Clinic Registry. In a subset with pre-infection sleep studies available, Apnea Hypopnea Index (AHI) and hypoxia measures (mean oxygen saturation [SaO₂%] and percentage of time spent $< 90\%$ oxygen saturation [T90]) were extracted. Patient-reported outcomes collected during the initial ReCOVer clinic visit from the Electronic Medical Record included PROMIS Sleep Disturbance, Fatigue, and Global Health (PROMIS-GH) v1.2, Generalized Anxiety Disorder (GAD)-2, Patient Health Questionnaire (PHQ)-2, and the Quality of Life in Neurological Disorders (Neuro-QoL) v1.0 Cognitive Function. PROMIS scores were standardized on a *T*-scale with mean 50 (SD 10)⁶, with established cut-points at > 55 , > 60 , and > 70 for mild, moderate, and severe sleep disturbance respectively.⁶ Multivariable models were constructed to identify independent predictors of moderate to severe sleep disturbances based on clinically relevant variables determined a priori. Interactions between

mood disorders and fatigue using PROMIS Fatigue, PHQ-2, and GAD-2 scores were tested.

RESULTS

A total of 962 of 1660 patients completed the PROMIS Sleep Disturbance; 565 (58.7%) had normal to mild sleep disturbance and 397 (41.3%) had moderate to severe sleep disturbance with characteristics shown in Table 1. After adjustment (Table 2), Black race (OR = 1.84, 95%CI: 1.10–3.08, $p = 0.020$), hospitalization for COVID-19 (OR = 1.59, 95%CI: 1.10–2.32, $p < 0.015$), greater anxiety severity (OR = 1.31, 95%CI: 1.18–1.45, $p < 0.001$), and moderate to severe fatigue (OR = 2.03, 95%CI: 1.33–3.11, $p = 0.001$) were significantly associated with moderate to severe sleep disturbance. Statistical interactions of anxiety severity and moderate to severe fatigue were not significant ($p = 0.84$).

Forty-eight patients had pre-COVID-19 sleep testing conducted 2.6 ± 2.1 years prior to the initial ReCOVer Clinic appointment. AHI, the primary measure of obstructive sleep apnea (OSA) severity, was 15.4 ± 18.9 with mean SaO₂ of $92 \pm 2.3\%$ and a median T90% of 12.1 [2.8, 73.3] (Table 1). OSA (AHI: 18.7 ± 24.4 vs 12.4 ± 11.8 , $p = 0.27$) and hypoxia measures (mean SaO₂%; 91.5 ± 2.8 vs 92.5 ± 1.6 , $p = 0.14$; median T90% 16.5 [3.5, 83.2] vs 9.3 [1.8, 44.3], $p = 0.32$) were not statistically different between normal to mild and moderate to severe sleep disturbance.

DISCUSSION

Novel findings include a high prevalence of 41.3% of moderate to severe sleep disturbance in PASC associated with Black race, hospitalization for COVID-19, anxiety severity, and moderate to severe fatigue. There was no significant interaction between anxiety severity and moderate to severe fatigue; further studies are needed to investigate the interplay between mental and sleep disturbances in PASC physiologic pathways. Likewise, there was no association between objective sleep study measures of antecedent sleep apnea and hypoxia with sleep disturbance. This may be explained by the small sample size, testing indication biases, or limitations of sleep study type (i.e., home sleep apnea test), precluding assessment of objective sleep quality or quantity measures. With 58% of PASC patients completing PROMIS Sleep Disturbance, our study may suffer from selection bias. However, we observed that among patients of Black race who did not complete PROMIS Sleep Disturbance, 60% completed mood and fatigue questionnaires. As such, it is possible that the

Table 1 Patient Characteristics Stratified by Normal/Mild Versus Moderate/Severe Sleep Disturbance

Characteristic	Total (N=962)	Normal/mild sleep distur- bance (N=565)	Moderate/severe sleep distur- bance (N=397)	p-value
Age	49.6 ± 13.7	50.0 ± 14.5	49.1 ± 12.5	0.31 ^{a2}
Gender				0.41 ^c
Female	721 (74.9)	418 (74.0)	303 (76.3)	
Male	241 (25.1)	147 (26.0)	94 (23.7)	
Race				0.003 ^c
White	788 (81.9)	483 (85.5)	305 (76.8)	
Black	125 (13.0)	60 (10.6)	65 (16.4)	
Other	49 (5.1)	22 (3.9)	27 (6.8)	
BMI (kg/m ²)*	31.6 ± 7.7	31.2 ± 7.5	32.1 ± 8.0	0.11 ^{a1}
Time since positive test, (months)	6.7 ± 4.2	6.8 ± 4.2	6.5 ± 4.2	0.28 ^{a1}
Comorbidities				
Asthma	149 (15.5)	79 (14.0)	70 (17.6)	0.12 ^c
Chronic fatigue	4 (0.42)	2 (0.35)	2 (0.50)	0.99 ^d
COPD	21 (2.2)	12 (2.1)	9 (2.3)	0.88 ^c
Coronary artery disease	28 (2.9)	12 (2.1)	16 (4.0)	0.083 ^c
Dementia	1 (0.10)	0 (0.00)	1 (0.25)	0.41 ^d
Diabetes	77 (8.0)	38 (6.7)	39 (9.8)	0.081 ^c
Heart failure	13 (1.4)	8 (1.4)	5 (1.3)	0.84 ^c
Hypertension	202 (21.0)	118 (20.9)	84 (21.2)	0.92 ^c
Interstitial lung disease	3 (0.31)	0 (0.00)	3 (0.76)	0.070 ^d
Obesity	85 (8.8)	52 (9.2)	33 (8.3)	0.63 ^c
Pulmonary embolism	21 (2.2)	12 (2.1)	9 (2.3)	0.88 ^c
Pulmonary hypertension	5 (0.52)	5 (0.88)	0 (0.00)	0.081 ^d
Systemic lupus erythematosus	9 (0.94)	3 (0.53)	6 (1.5)	0.17 ^d
COVID-19 severity				
Hospitalization				0.017 ^c
Missing	16 (1.7)	10 (1.8)	6 (1.5)	
No	683 (71.0)	420 (74.3)	263 (66.2)	
Yes	263 (27.3)	135 (23.9)	128 (32.2)	
Intensive care unit stay				0.98 ^c
Missing	13 (1.4)	8 (1.4)	5 (1.3)	
No	898 (93.3)	527 (93.3)	371 (93.5)	
Yes	51 (5.3)	30 (5.3)	21 (5.3)	
Mechanical ventilation				0.99 ^c
Missing	14 (1.5)	8 (1.4)	6 (1.5)	
No	929 (96.6)	546 (96.6)	383 (96.5)	
Yes	19 (2.0)	11 (1.9)	8 (2.0)	
Patient-reported outcomes				
GAD-2*	2.2 ± 2.0	1.7 ± 1.7	3.0 ± 2.1	<0.001 ^{a2}
PHQ-2*	2.1 ± 1.9	1.6 ± 1.6	2.7 ± 2.0	<0.001 ^{a2}
PROMIS Global Mental Health†*	41.5 ± 9.2	44.0 ± 8.8	37.9 ± 8.6	<0.001 ^{a1}
PROMIS Global Physical Health†*	39.7 ± 8.6	42.1 ± 8.3	36.2 ± 7.7	<0.001 ^{a1}
PROMIS fatigue*	62.7 ± 9.1	60.2 ± 8.8	66.2 ± 8.2	<0.001 ^{a1}
Moderate/severe fatigue*	593 (67.2)	294 (57.1)	299 (81.5)	<0.001 ^c
Severe fatigue*	192 (21.8)	64 (12.4)	128 (34.9)	<0.001 ^c
PROMIS Sleep Disturbance	57.8 ± 8.4	52.3 ± 5.3	65.5 ± 5.3	<0.001 ^{a1}
Neuro-QoL Cognitive Function*	39.4 ± 10.0	41.6 ± 10.0	36.4 ± 9.2	<0.001 ^{a1}
Sleep study variables (N=48)				
Study type				0.61 ^d
Home sleep apnea test	44 (91.7)	22 (95.7)	22 (88.0)	
Polysomnogram	4 (8.3)	1 (4.3)	3 (12.0)	
AHI total	15.4 ± 18.9	18.7 ± 24.4	12.4 ± 11.8	0.27 ^{a2}
Mean oxygen saturation (%)*	92.0 ± 2.3	91.5 ± 2.8	92.5 ± 1.6	0.14 ^{a2}
% Sleep time O ₂ < 90 (T90)*	12.1 [2.8,73.3]	16.5 [3.5, 83.2]	9.3 [1.8, 44.3]	0.32 ^{a2}

BMI, body mass index; COPD, chronic obstructive pulmonary disease; GAD-2, Generalized Anxiety Disorder-2; PHQ-2, Patient Health Questionnaire-2; PROMIS, Patient-Reported Outcomes Measurement Information System

*Data not available for all subjects. Missing values: BMI (kg/m²)=90; GAD-2=136; PHQ-2=135; PROMIS Global Mental Health=38; PROMIS Global Physical Health=30; PROMIS Fatigue=80; moderate/severe fatigue=80; severe fatigue=80; Neuro-QoL Cognitive Function=126; mean oxygen saturation (%)=1; sleep time O₂ under 90 (%)=2

†Higher scores indicate better health/functioning

Comparisons across sleep disturbance categories were made using Pearson's chi-square test or Fisher's exact test for categorical variables and *t*-test for continuous variables

Statistics presented as mean ± SD, *N* (column %). *p*-values: a1 = *t*-test, a2 = Satterthwaite *t*-test, c = Pearson's chi-square test, d = Fisher's exact test

Table 2 Multivariable Logistic Regression Model for Predicting Moderate/Severe Sleep Disturbance

Predictor	Odds ratio (95% CI)	p-value
Age (per decade)	1.00 (0.88, 1.14)	0.97
Female	0.95 (0.64, 1.39)	0.78
Race (reference = White)		
Black	1.84 (1.10, 3.08)	0.020
Other	1.93 (0.95, 3.93)	0.069
BMI (per 5 kg/m ²)	1.05 (0.94, 1.17)	0.41
Hospitalization for COVID-19	1.59 (1.10, 2.32)	0.015
PHQ-2	1.08 (0.96, 1.21)	0.20
GAD-2	1.31 (1.18, 1.45)	<0.001
Moderate/severe fatigue	2.03 (1.33, 3.11)	0.001
Neuro-QoL Cognitive Function	0.99 (0.96, 1.01)	0.21

CI, confidence interval; BMI, body mass index; PHQ-2, Patient Health Questionnaire-2; GAD-2, generalized anxiety disorder-2

magnitude of association between Black race and moderate to severe sleep disturbances is even stronger. Study findings emphasize the importance of identification of sleep disturbance in PASC considering its impact on patients' quality of life, daytime functioning, and medical health status. Results inform risk stratification and highlight the need to elucidate contributions of structural racism and socioeconomic inequities to PASC-related sleep disturbances with the goal of developing interventions to reduce PASC disparities.


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Data Availability The data that support the findings of this study are available on request from the corresponding author.

Declarations

Conflict of Interest The authors have no financial conflicts of interest.

Cinthyia Pena-Orbea, MD¹ 

Brittany Lapin, PhD^{2,3}

Yadi Li, MD^{2,3}

Kristin Englund, MD⁴

Catherine Heinzinger, MD¹

Nancy Foldvary-Schaefer, DO, MS¹

Reena Mehra, MD, MS^{1,5}

¹Sleep Disorders Center, Neurological Institute, Cleveland Clinic, OH, Cleveland, USA;

²Neurological Institute Center for Outcomes Research & Evaluation, Cleveland Clinic, Cleveland, OH, USA;

³Department of Quantitative Health Sciences, Cleveland Clinic, Cleveland, OH, USA;

⁴Department of Infectious Disease, Respiratory Institute, Cleveland Clinic, Cleveland, OH, USA;

⁵Respiratory Institute, Heart and Vascular Institute and Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Corresponding Author: Cinthyia Pena-Orbea, MD; Sleep Disorders Center, Neurological Institute, Cleveland Clinic, OH, Cleveland, USA (e-mail: penac@ccf.org).

REFERENCES

1. Nalbandian A, Sehgal K, Gupta A, et al. Post-acute COVID-19 Syndrome. *Nat Med*. 2021;27(4):601-615. <https://doi.org/10.1038/S41591-021-01283-Z>
2. Nowakowski S, Kokonda M, Sultana R, et al. Association Between Sleep Quality and Mental Health Among Patients at a Post-COVID-19 Recovery Clinic. *Brain Sci*. 2022;12(5):586. <https://doi.org/10.3390/brainsci12050586>
3. Fernández-de-las-Peñas C, Gómez-Mayordomo V, de-la-Llave-Rincón AI, et al. Anxiety, Depression and Poor Sleep Quality as Long-Term Post-COVID Sequelae in Previously Hospitalized Patients: a Multicenter Study. *J Infect*. 2021;83(4):496. <https://doi.org/10.1016/j.jinf.2021.06.022>
4. Kalamara E, Pataka A, Boutou A, et al. Persistent Sleep Quality Deterioration Among Post-COVID-19 Patients: Results from a 6-Month Follow-up Study. *J Pers Med*. 2022;12(11). <https://doi.org/10.3390/jpm12111909>
5. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) Developed and Tested Its First Wave of Adult Self-reported Health Outcome Item Banks: 2005-2008. *J Clin Epidemiol*. 2010;63(11):1179-1194. <https://doi.org/10.1016/j.jclinepi.2010.04.011>
6. PROMIS. Accessed February 4, 2023. <https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/promis-score-cut-points>

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