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Brief Research Report

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Impact of sleep disruption on cognitive function in patients with postacute sequelae of SARS-CoV-2 infection: initial findings from a Neuro-COVID-19 clinic

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Abstract

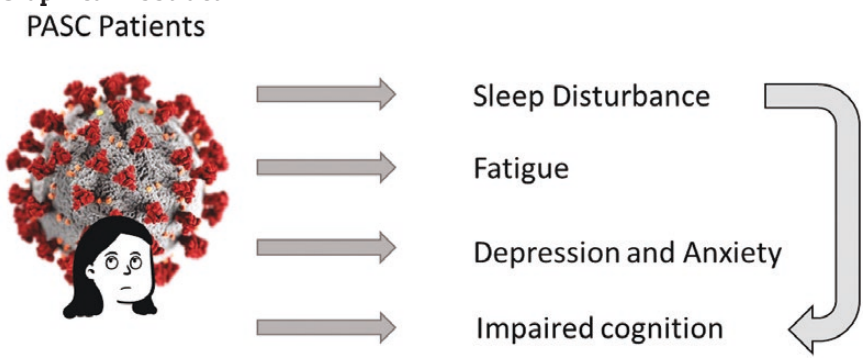
Introduction: Fatigue, brain fog, and sleep disturbance are among the most common symptoms of postacute sequelae of SARS-CoV-2 infection (PASC). We sought to determine the impact of sleep disruption on cognition and quality of life in patients with neurologic manifestations of PASC (Neuro-PASC).

Methods: Thirty-nine patients were recruited from Neuro-COVID-19 clinic. Mean age was 48.1 years, 71.8% were female, and 82% were never hospitalized for COVID-19. Patients were evaluated via clinical assessment, quality-of-life measures in domains of cognitive function, fatigue, sleep disturbance, anxiety, and depression, NIH Toolbox cognitive tests, and 7 days of wrist actigraphy.

Results: The median number of neurologic symptoms attributed to PASC was 6, with brain fog being the most common in 89.7%. Regarding non-neurologic symptoms, 94.9% complained of fatigue and 74.4% of insomnia. Patients reported significant impairment in all quality-of-life domains and performed worse in a task of attention compared to a normative US population. Actigraphy showed Neuro-PASC patients had lower sleep efficiency, longer sleep latency (both $p < 0.001$), and later sleep midpoint ($p = 0.039$) compared to 71 age-matched healthy controls with no PASC history. Self-reported cognitive symptoms correlated with the severity of fatigue ($p < 0.001$), anxiety ($p = 0.05$), and depression ($p < 0.01$). Objective evidence of sleep disruption measured by wakefulness after sleep onset, sleep efficiency, and latency were associated with decreased performance in attention and processing speed.

Conclusion: Prospective studies including larger populations of patients are needed to fully determine the interplay of sleep disruption on the cognitive function and quality of life of patients with PASC.

Graphical Abstract



Key words: post-acute sequelae of SARS-CoV-2 infection; neurology; sleep; cognition; insomnia; fatigue; COVID-19; long COVID

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Statement of Significance

Sleep disturbance is frequent in patients affected by neurologic manifestations of postacute sequelae of SARS-CoV-2 infection (Neuro-PASC). Patients commonly complain of fatigue (94.9%), brain fog (89.7%), and insomnia (74.4%) and have objective evidence of sleep disruption and cognitive dysfunction. Compared to age- and sex-matched healthy controls with no history of PASC, patients had significantly later sleep timing, longer sleep latency, and lower sleep efficiency, including 50% having a sleep efficiency of ≤85%. Impaired attention and processing speed on the NIH Toolbox were associated with poor sleep continuity measures. Strategies to improve sleep in individuals affected by PASC may help improve their quality-of-life and cognition.

Introduction

More than 100 million people in the United States have been infected by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) [1]. While COVID-19 was initially identified primarily as a respiratory disease, neurologic, pulmonary, cardiac, and gastrointestinal symptoms may linger [2–7]. This persistent multisystem dysfunction occurring in patients with both severe (i.e. hospitalized with pneumonia/hypoxemia) and mild (e.g. non-hospitalized with transient cough and fever) COVID-19 constitutes the "long COVID" syndrome, also called "postacute sequelae of SARS-COV-2 infection" (PASC) [8, 9].

Fatigue, cognitive impairment, and insomnia are among the most common symptoms in patients with neurologic manifestations of PASC (Neuro-PASC) [10]. There is ample evidence that sleep disturbance is linked with fatigue, cognitive impairment, poor physical health, and reduced quality of life [11]. Therefore, sleep dysfunction may be a modifiable factor in the development and persistence of PASC. The aim of this pilot study was to assess the impact of sleep disturbance on cognition using objective measures of sleep–wake activity and cognitive function in patients presenting to a Neuro-COVID-19 Clinic. We tested the hypothesis that sleep disruption is associated with cognitive dysfunction and impaired quality-of-life in Neuro-PASC patients.

Methods

Participants were recruited from the ambulatory Neuro-COVID-19 Clinic at Northwestern Memorial Hospital between October 2021 and July 2022. Forty adults provided written informed consent to participate in this study, including 32 who had mild initial COVID-19 and were never hospitalized for pneumonia or hypoxemia. Patients were invited to participate if they met the following criteria: at least 18 years old and had a previous diagnosis of SARS-CoV-2 infection confirmed by laboratory testing. Participants who were unable to understand English and/or had substantial cognitive impairment that would preclude the use of study assessment instruments were not included. Control data from 71 adults for wrist actigraphy (age and gender matched with a 2:1 ratio when possible) were taken from two ongoing studies of healthy participants (exclusions for these two studies included: unstable medical condition, diabetes, gastric surgery, weight management, pregnancy, and hormone replacement therapy) with no history of PASC using identical actigraphy procedures. These studies were approved by the Northwestern University Institutional Review Board (STU00215411, STU00206038, and STU00206014) and all participants gave written informed consent.

Patients were evaluated via clinical assessment/history, chart review, patient-reported outcomes for symptom severity, and cognitive performance tests, and were sent home to record 7 days of wrist actigraphy with a sleep log. Upon completing actigraphy and the sleep log, materials were returned via courier to the study team. Basic demographics (gender, race, and ethnicity), height, weight, and COVID-19 hospitalization status were also recorded from the medical record.

Symptom burden was measured with questionnaires including the Epworth Sleepiness Scale (ESS), STOP-BANG, the Micro-Munich Chronotype Questionnaire (MCTQ) [12–14], and the computer-adapted test format version of the following Patient-Reported Outcomes Measurement Information System (PROMIS) questionnaires: Fatigue, Sleep-Related Impairment, Sleep Disturbance, Cognitive Function, Psychosocial Illness Impact and General Life Satisfaction [15, 16]. Performance on cognitive function was objectively assessed using the NIH Toolbox Fluid Cognition Battery. Participants completed the Flanker Inhibitory Control and Attention Test (attention and executive function), the Dimensional Change Card Sort Test (executive function), the List Sorting Working Memory Test (working memory), and the Pattern Comparison Speed Test (processing speed) [17, 18]. Both PROMIS and NIH Toolbox results are expressed as adjusted T-scores, with a score of 50 representing the normative mean/median of the United States reference population with a SD of 10. Lower cognition T-scores indicate worse performance while higher fatigue, sleep disturbance, anxiety, and depression T-scores indicate greater severity.

Sleep–wake/rest–activity patterns were assessed using wrist actigraphy and a sleep log. Prior to leaving the clinic, participants were instructed to wear the wrist actigraphy monitor (Actiwatch Spectrum Plus, Philips Respironics) on their nondominant wrist free of binding sleeves and jewelry and to press the marker when initiating sleep and at waking, and to complete a daily sleep diary (Sleep Foundation Sleep Diary [19]) for 7 consecutive days. Within 1 hour of waking, participants were instructed to complete the sleep diary and report the time when they got into bed, when they tried to go to sleep, how long it took them to fall asleep, when they woke, and the number and duration of awakenings. Wrist activity and light data were collected in 30-second epochs, with default settings (medium threshold and 10-minute immobile/mobile time). Rest intervals were set manually based on criteria described previously, using a combination of marker, sleep log, activity, and light levels in a hierarchical manner. The following variables were calculated using Actiware-Sleep software (Philips Respironics 6.0.9): time in bed, total sleep time (TST), sleep latency, sleep efficiency, wakefulness after sleep onset (WASO), and the number of awakenings [20].

Data analysis

Data were summarized as number of patients (frequency), mean (SD) for normally distributed variables, and median (interquartile range [IQR]) for non-normally distributed variables. Group differences were assessed using Fisher's exact test, unpaired *t* test, and Wilcoxon rank sum test. Age and gender were not significantly

different between groups. Correlations between variables were assessed with Pearson's or Spearman's correlation tests, as appropriate. We used linear regression models to assess for associations between cognitive performance on NIH Toolbox tests and actigraphy-derived sleep variables, adjusting for age and history of COVID-19-related hospitalization. To determine if the results of PROMIS and NIH Toolbox domains differed from expected, patient group T-scores were compared to the demographic-matched normative US population median of 50 using one-sample Wilcoxon signed rank tests. Midpoint timing difference was tested using the Watson-Wheeler test. Two-sided $p \leq 0.05$ was considered significant and all analyses were performed in R version 4.2.2 including packages "nparACT" for calculation of nonparametric actigraphy measures, "nonlinearTseries" for detrended fluctuation analysis of power law characteristics, and "circular" for the circular version of the Pearson's product–moment correlation and Watson-Wheeler test, consistent with our prior work [21]. Study data were collected and managed using REDCap electronic data capture tools.

Results

Thirty-nine Neuro-PASC participants provided sufficient data for analysis including 38 actigraphy records suitable for interpretation (Figure 1). Thirty-two participants (82%) were never hospitalized for COVID-19 pneumonia or hypoxemia. Demographic characteristics and reported symptoms for the Neuro-PASC patients are provided in Table 1. Mean age was 48.1 years and 71.2% were female. Patients were evaluated an average of 12.1 months after COVID-19 onset and felt 59.5% recovered compared to their pre-COVID-19 baseline. More than 80% of the sample had at least 1 comorbid condition. The median number of discrete neurologic symptoms attributed to PASC was 6 with 87% reporting ≥4 neurologic symptoms, with brain fog being the most frequent (89.7%). In addition, fatigue (94.9%) and insomnia (74.4%) were the most common non-neurologic symptoms.

Self-reported quality-of-life measures and sleep questionnaires

Patients reported significantly impaired quality-of-life in all PROMIS domains examined compared to the normative US population ($p < 0.0001$ for all; Figure 2). The median (IQR) Epworth sleepiness scale score was 9 (2.5, 12) and 35% of the PASC patients had an ESS ≥10, the conventional threshold for moderate-to-severe daytime sleepiness [22]. The median (IQR) for the STOP-BANG was 2 (2–3), a score of 2 is considered low risk

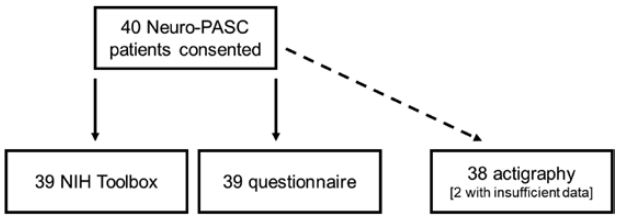


Figure 1. Neuro-PASC patient flow diagram. A total of 40 patients were consented, of these 39 contributed NIH Toolbox data, 39 contributed questionnaire data, and 38 contributed actigraphy data (two subjects were excluded due to insufficient wear time). Solid line indicates measures conducted at clinic visits and dashed line indicates measures collected at home starting immediately after the clinic visit.

Table 1. Demographics, comorbidities in Neuro-PASC patients.

Demographics and comorbidities	Overall
n	39
Age, years, mean (1 SD)	48.1 (16.5)
Gender	
Male, *n* (%)	11 (28.2)
Female, *n* (%)	28 (71.8)
Race, *n* (%)	
White	30 (76.9)
Black or African American	4 (10.3)
Asian	1 (2.6)
American Indian/Alaskan Native	0 (0)
Native Hawaiian/Other Pacific Islander	1 (2.6)
Other	2 (5.1)
Multiracial	0 (0)
Not specified	1 (2.6)
Ethnicity, *n* (%)	
Not Hispanic or Latino	32 (82.1)
Hispanic or Latino	5 (12.8)
Not specified	2 (5.1)
Visit type, *n* (%)	
In-person	28 (71.8)
Televisit	11 (28.2)
SARS-CoV-2 RT-PCR, *n* (%)	
Positive	33 (84.6)
Negative	4 (10.3)
Not performed	2 (5.1)
SARS-CoV-2 serology, *n* (%)	
Positive	7 (17.9)
Negative	3 (7.7)
Not performed	29 (74.4)
Positive RT-PCR and serology, *n* (%)	4 (10.3)
Any positive SARS-CoV-2 test (Reverse transcription polymerase chain reaction, serology, or antigen), *n* (%)	39 (100)
Any pre-existing comorbidity, *n* (%)	32 (82.1)
Depression/anxiety	20 (51.3)
Dyslipidemia	11 (28.2)
Neuropsychiatric disease [a]	11 (28.2)
Hypertension	8 (20.5)
Gastrointestinal disease [b]	7 (17.9)
Autoimmune disease [c]	6 (15.4)
Headache	6 (15.4)
Lung disease [d]	5 (12.8)
Cancer	4 (10.3)
Other endocrine disorders [e]	4 (10.3)
Cardiovascular disease [f]	3 (7.7)
Insomnia	2 (5.1)
Type 2 diabetes	2 (5.1)
Traumatic brain injury	2 (5.1)
Dysautonomia	1 (2.6)

Table 1. Continued

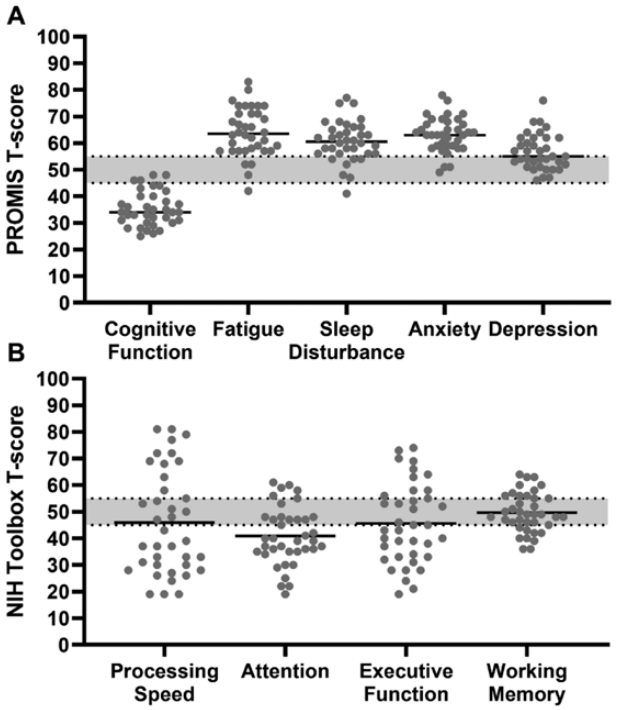
Demographics and comorbidities	Overall
Cerebrovascular disease	1 (2.6)
Neuromuscular disease [g]	1 (2.6)
Other [h]	5 (12.8)
Neurologic signs and symptoms	
Time from symptom onset to clinic visit, months, mean (1 SD)	12.1 (7.0)
Self-reported impression of recovery compared to pre-COVID-19 baseline, mean % (1 SD)	59.5 (17.3)
Number of neurologic manifestations/symptoms attributed to COVID-19, median (IQR)	6 [5–7.5]
Neurologic symptom, *n* (%)	
≥4	34 (87.1)
Brain fog	35 (89.7)
Headache	34 (87.1)
Anosmia	30 (76.9)
Dysgeusia	28 (71.8)
Dizziness	23 (59.0)
Myalgia	22 (56.4)
Numbness/tingling	21 (53.8)
Pain other than chest	14 (35.9)
Tinnitus	14 (35.9)
Blurred vision	15 (38.5)
Other symptom, *n* (%)	
Fatigue	37 (94.9)
Insomnia	29 (74.4)
Depression/anxiety	27 (69.2)
Shortness of breath	21 (53.8)
Dysautonomia[i]	16 (41.0)
Chest pain	15 (38.5)
GI symptoms[j]	15 (38.5)

[a]Bipolar (2), RLS (1), akathisia (1), parkinsonism (1), spinal stenosis (1), meningioma (1), ADHD (3), fibromyalgia (2), OCD (1), ME/CFS (1), and carpal tunnel (1).
[b]GERD (6), Barrett's esophagus (1), IBS (1), fatty liver (1), and Barrett's esophagus (1).
[c]Rheumatoid arthritis (4), Sjögren's syndrome (1), type 1 diabetes (1), psoriasis (1), and Raynaud's.
[d]Asthma (4) and obstructive sleep apnea (1).
[e]Hyperthyroid (1), osteoporosis (1), hypothyroid (2), and hyperparathyroid (1).
[f]Coronary artery disease (3).
[g]Lumbar stenosis (1).
[h]Thrombocytopenia (1), IgA deficiency (1), spherocytosis (1), anemia (1), and transaminitis (1).
[i]Self-reported other nondefined attributed to variation of heart rate and blood pressure (9), variation of heart rate (5), variation of blood pressure (2), and POTS (1).
[j]Nausea (7), not specified (3), diarrhea (8), vomiting (2), and constipation.

for obstructive sleep apnea [13]. The microMCTQ indicated that PASC patients had a mid-sleep on free days corrected for sleep debt over the work week (MSFsc) of 03:42 (±00:20), which is within a normal range [23].

Objective evaluation of cognitive performance

Neuro-PASC patients performed significantly worse in a task of attention ($p < 0.0001$), and there was a trend for worse executive function ($p = 0.09$), compared to normative US population (Figure 2).



Assessment Domain	T-score	*p*, norm[a]
PROMIS Quality of Life (median (IQR))		
Cognitive Function	34 (30.8-40)	**<0.0001**
Fatigue	63.5 (57-71)	**<0.0001**
Sleep Disturbance	60.5 (56-65.3)	**<0.0001**
Anxiety	63 (59-67.3)	**<0.0001**
Depression	55 (51.8-62)	**<0.0001**
NIH Toolbox (median (IQR))		
Processing Speed	41 (30-61.8)	0.23
Attention	39.5 (35-47.8)	**<0.0001**
Executive Function	44 (33.3-55.8)	0.09
Working Memory	49 (45.3-55.8)	0.77

[a]norm: against normative population median T-score of 50

Figure 2. Quality of Life and cognitive function results from the PROMIS Questionnaires and NIH Toolbox in Neuro-PASC patients. Neuro-PASC patients reported worse quality of life in cognition, fatigue, sleep disturbance, anxiety, and depression domains. Neuro-PASC patients had worse performance on the attention task compared to the US normative population.

Wrist actigraphy

Sleep metrics derived from wrist actigraphy showed Neuro-PASC patients had lower sleep efficiency, longer sleep latency ($p < 0.001$) and later midpoint of sleep ($p = 0.039$) but similar WASO, number of awakenings, and TST compared to age-matched healthy controls (Table 2). The median (IQR) for the power law exponent from detrended fluctuation analysis was 0.94 (0.92–0.97) in the Neuro-PASC patients. Examples of activity monitoring from patients with normal and poor sleep quality are presented in Figure 3. Examples of two patients with poor quality-of-life measures in domains of fatigue and sleep disturbance that also had objective sleep disruption on actigraphy are provided in Figure 3 (panel A and B), these individuals showed evidence of sleep fragmentation, and difficulty falling asleep.

Association between measures of sleep, cognition and quality-of-life

After adjustment for age and history of COVID-19-related hospitalization, lower performance on NIH Toolbox attention test

Table 2. Actigraphy-based sleep characteristics in Neuro-PASC patients and controls.

Sleep variable (Mean ± SD)	Neuro-PASC (*N* = 38)	Controls (*N* = 71)	*P*-value
Total sleep time (minutes)	412 ± 64	410 ± 39	0.85
Sleep efficiency (%)	83.1 ± 6.9	89.5 ± 4.0	**<0.001**
Sleep onset latency (minutes)	23.5 ± 21.8	7.2 ± 5.5	**<0.001**
Wake after sleep onset (minutes)	42.4 ± 22.8	40.0 ± 17.8	0.52
Number of awakenings (#)	35.8 ± 12.8	33.2 ± 9.3	0.28
Sleep midpoint (hours:minutes)	03:41 (00:20)	03:15 (00:14)	**0.039**

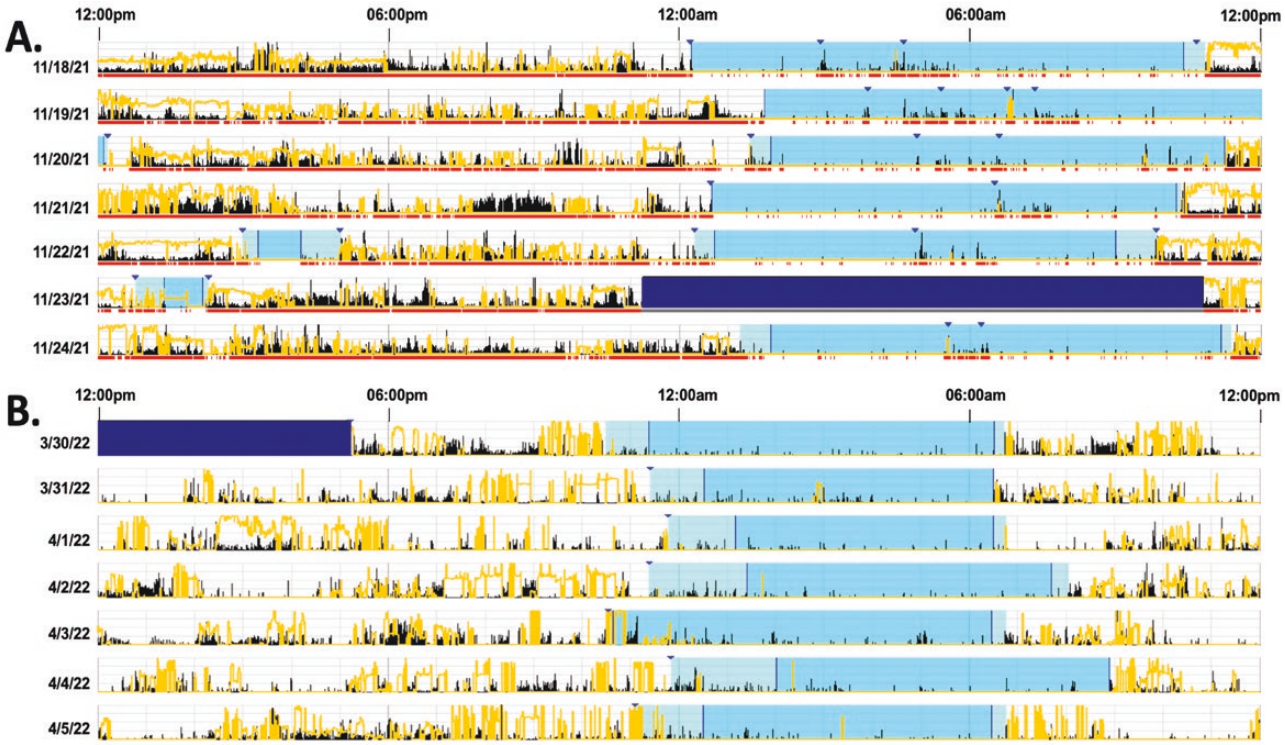


Figure 3. Example Actograms from Neuro-PASC patients, including two participants with high PROMIS fatigue and sleep scores and poor sleep based on actigraphy. The participant in the left panel (A) has poor sleep continuity, while the participant in image (B) takes more than 30 minutes to fall asleep. Black line indicates activity level, yellow line indicates light level, small blue triangles indicate participant marker usage for initiation or termination of the rest/sleep period, light and medium blue indicate rest and sleep intervals, and dark blue indicates device removed.

was associated with lower sleep efficiency ($\beta = 0.55$, $p = 0.039$) and a near-significant trend with longer sleep latency ($\beta = -1.55$, $p = 0.058$), while lower processing speed was associated with lower sleep efficiency ($\beta = 1.27$, $p = 0.004$), longer sleep latency ($\beta = -0.31$, $p = 0.027$), more WASO ($\beta = -0.31$, $p = 0.025$), and more awakenings ($\beta = -0.56$, $p = 0.016$). Similarly, we found a relationship between lower processing speed and attention performance and lower power law exponent from detrended fluctuation analysis ($\beta = 234$, $p = 0.011$, and $\beta = 102$, $p = 0.06$, respectively). Greater self-reported cognitive symptoms were correlated with greater severity of fatigue ($\rho = -0.66$, $p < 0.001$), anxiety ($\rho = 0.31$, $p = 0.058$), and depression ($\rho = -0.43$, $p = 0.007$), but not with self-reported sleep disturbance ($\rho = 0.00$, $p = 0.98$). The midpoint of sleep from self-reported sleep/wake times was correlated with the midpoint of sleep obtained by actigraphy measurement (circular version of the Pearson's product–moment correlation, $\rho = 0.87$, $p = 0.003$). There were no associations between actigraphy-measured sleep metrics and any of the PROMIS measures.

Discussion

Neuro-PASC patients presenting to a post-COVID clinic have a significant burden of self-reported symptoms of sleep disturbance, fatigue, and cognitive impairment along with objective evidence of cognitive dysfunction and sleep disruption compared to population controls. Many patients are still experiencing PASC long after the infection, with the average of 1 year between COVID-19 onset and the clinic visit. As has been previously reported, patients were presented to the clinic with many neurologic symptoms [10], including sleep disturbance, which is of particular interest for this study. While only 2% of patients endorsed insomnia prior to COVID-19, close to 75% reported insomnia at the time of their clinic visit. This self-reported symptom is supported by both PROMIS sleep disturbance scores and actigraphy that are significantly abnormal compared to population norms or matched controls. When measured objectively, patients took longer to fall asleep, had less efficient sleep, and had a later sleep timing compared to age- and gender-matched healthy controls.

Trouble falling asleep and staying asleep are key symptoms of insomnia [24]. In fact, 50% of the Neuro-PASC patients had sleep efficiencies <85% (compared to 7% of controls), which are likely to be primarily driven by the longer sleep onset latencies. The type of sleep disturbance observed in this sample is similar to that reported previously following severe COVID-19. In one study of adults 3 months after ICU discharge for COVID-19, 55% had sleep efficiencies of <85% and 72% had wake after sleep onset of ≥40 minutes using actigraphy [25]. Even though both self-reported and objective measures of sleep were reported to be worse in Neuro-PASC patients, there were no significant associations between self-reported sleep complaints (PROMIS) and sleep–wake patterns recorded with wrist actigraphy, although discordance between self-reported sleep complaints and objective sleep measured with either polysomnography or wrist actigraphy is not unusual [26–28].

Most Neuro-PASC patients reported brain fog and self-reported cognitive impairment, which was reflected as poor performance in a validated task of attention. Sleep disturbance is known to impact cognitive function, and in this study, that was also the case with objective measures of difficulty initiating and maintaining sleep being associated with worse performance in attention and processing speed. Lower power law exponents indicate degradation of the ultradian activity rhythms toward irregular disruption and randomness, and lower power law exponents have been associated with worsening dementia over time and greater cognitive disruption during acute illness [21, 29, 30]. Our findings extend those observations into the Neuro-PASC population. Interestingly, self-reported cognitive symptoms were not associated with self-reported sleep complaints. These findings suggest that objective measures of sleep and cognition should be used when examining the relationship between these two complaints.

The strengths of this study include the use of both objective and self-reported measures of sleep and cognitive function. This study also has limitations including a relatively small number of patients and convenience control sample. It is also possible that the difference in sleep efficiency between patients and controls is driven by the difference in sleep onset latency, which is considered to be less reliable from actigraphy, this is tempered by routine use of markers and sleep logs to indicate rest start/end times in this sample. In addition, while 82% of patients had mild COVID-19 and never required hospitalization, 18% were previously hospitalized for COVID-19 pneumonia. However, this ratio of nonhospitalized/posthospitalization Neuro-PASC patients is representative of the Neuro-COVID-19 clinic population during the period of observation. Of note, a previous study of the first 600 Neuro-PASC patients evaluated at our clinic, including 100 posthospitalization and 500 nonhospitalized patients, showed no significant differences between those two groups in the prevalence of insomnia prior to COVID-19, and insomnia, fatigue, and brain fog at the time of the clinic visit. However, posthospitalization patients had broader cognitive dysfunction and decreased insight into their cognitive abilities [10]. It is, therefore, possible that additional associations between sleep and cognition may exist in this category of patients.

Taken together, this study demonstrates both objective impairment in sleep and cognition in Neuro-PASC patients, and sleep impairment is related to poor performance in tasks of attention and processing speed. As such, interventions to improve sleep could benefit cognitive performance in PASC patients. Prospective studies including larger populations of posthospitalization and nonhospitalized patients are needed to fully determine the interplay of sleep/circadian rhythm disruption on the cognitive function and quality of life in patients with PASC.

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Disclosure Statement

KJR, LTI, MJ, ZSO, SMA, DG, KLK, PCZ, IJK, and MBM have no relevant financial disclosure.

Author Contributions

Kathryn Reid (Conceptualization [equal], Data curation [equal], Formal analysis [supporting], Methodology [supporting], Project administration [supporting], Writing—original draft [lead], Writing—review & editing [lead]), Louis Ingram (Data curation [supporting], Writing—original draft [supporting]), Millenia Jimenez (Data curation [supporting]), Zachary Orban (Data curation [supporting], Visualization [supporting], Writing—review & editing [supporting]), Sabra Abbott (Data curation [supporting], Writing—review & editing [supporting]), Daniela Grimaldi (Data curation [supporting], Writing—review & editing [supporting]), Kristen Knutson (Data curation [supporting], Writing—review & editing [supporting]), Phyllis Zee (Conceptualization [supporting], Funding acquisition [lead], Resources [lead], Writing—review & editing [supporting]), Igor Koralnik (Conceptualization [equal], Investigation [equal], Resources [supporting], Visualization [equal], Writing—review & editing [supporting]), and Matthew Maas (Conceptualization [equal], Data curation [equal], Formal analysis [equal], Writing—original draft [supporting], Writing—review & editing [supporting]).

Data Availability Statement

The data underlying this article will be shared with qualified investigators on reasonable request to the corresponding author at k-reid@northwestern.edu.

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