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ORIGINAL COMMUNICATION

# Longitudinal analysis and treatment of neuropsychiatric symptoms in post-acute sequelae of COVID-19

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## Abstract

**Background** Persistent neuropsychiatric symptoms following acute COVID-19 infection are frequently reported. These include anxiety, depression, difficulty concentrating, fatigue, and insomnia. The longitudinal evolution of this neuropsychiatric burden is poorly understood and clinical guidelines concerning treatment are lacking.

**Objective** We sought to describe the longitudinal evolution of neuropsychiatric symptoms in the post-acute sequelae of COVID-19 (PASC) syndrome and examine symptom treatment at a single center.

**Methods** Consecutive participants experiencing persistent neurologic symptoms after acute COVID-19 infection were recruited from October 2020 to July 2022. Data collected included COVID-19 infection history, neurological exam and review of systems, Montreal Cognitive Assessment (MoCA), and self-reported surveys concerning neuropsychiatric symptoms and treatment. Data were collected at baseline and at 1-year follow-up.

**Results** A total of 106 participants (mean age 48.6, females 67%) were included in the study. At 1-year follow-up, 72.5% of participants reported at least one neuropsychiatric symptom. Over half (52.5%) of participants reported persistent fatigue. At baseline, 38.8% of all participants had met the established MoCA cut-off score of < 26 for mild cognitive impairment; this decreased to 20.0% at 1 year. COVID-19 infection severity was associated with neuro-PASC symptoms (including fatigue and anxiety) at 1 year. Overall, 29% of participants started at least one new medication for COVID-19-associated neuropsychiatric symptoms. Of the participants who started new medications, fatigue was the most common indication (44.8%) followed by insomnia (27.6%).

**Conclusions** Neuropsychiatric symptoms related to neuro-PASC improve over time but can persist for over a year post-recovery. Most treatment modalities targeted neuro-PASC fatigue.

**Keywords** COVID-19 · Long COVID · PASC · Post-COVID syndrome

## Introduction

The COVID-19 pandemic has greatly impacted human health, with consequences expected over the next several decades. In addition to acute pulmonary and systemic symptoms from COVID-19 infection and mental health problems arising from quarantine and isolation, one area of significant concern is the increasingly recognized post-acute sequelae of COVID-19 (PASC) syndrome, which may be characterized by long-term pulmonary, cardiac, psychiatric, and/or neurological symptoms [1].

There is increasing evidence that a significant proportion of COVID-19 survivors experience persistent neuropsychiatric symptoms long after recovery from their acute infection [2–4]. A meta-analysis of 31 studies ($n = 5153$ participants)

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found that following COVID-19 infection, the pooled prevalence for depression was 45%, the pooled prevalence of anxiety was 47%, and the pooled prevalence of sleep disturbances was 34% [2]. A study of over 200,000 patients found that a third (33.62%) of COVID-19 patients had been diagnosed with neurological or psychiatric disorders, including anxiety, depression, post-traumatic stress disorder (PTSD), and psychosis, during the 6-month period following a COVID-19 infection [3]. In a psychiatric screening of 408 adult patients surveyed 1-month after hospitalization for COVID-19 infection, 56% scored in the pathological range in at least one clinical dimension for PTSD, depression, anxiety, obsessive–compulsive symptoms, and insomnia [4]. In addition to the prevalence of various neuropsychiatric symptoms following COVID-19 infection, potential predictors of long COVID include age, body mass index, and female sex [5].

Despite the high prevalence of neuropsychiatric symptoms in PASC syndrome, there is still much to understand regarding of the longitudinal evolution of these symptoms and the clinical management of these symptoms. We have previously described neurological symptoms and selected phenotypes from a prospective cohort of neuro-PASC patients at 6-month follow-up [6]. In this current study, we sought to evaluate the longitudinal pattern of neuropsychiatric burden in PASC patients at 1-year follow-up and examine current treatment patterns for patients with PASC symptoms.

## Methods

### Study design

This study leveraged a parent prospective cohort study of neurological complications of COVID-19 at the University of California San Diego [6]. Participants completed self-reported, previously validated surveys and interviews at several time points: baseline (i.e., after resolution of their acute COVID-19 infection), 6-month, and 1-year follow-up. The 6-month and 1-year time points were measured from the initial baseline visit. This study was approved by the UCSD Institutional Review Board, and participants provided written informed consent.

### Participants

Consecutive patients meeting clinical diagnostic criteria for acute COVID-19 infection and reporting neurological or neuropsychiatric symptom post-infection were recruited from October 2020 to July 2022. Recruitment was conducted through the UCSD Neurology Clinic, Infectious Disease Clinic, Neuropsychology Clinic, and direct referrals to UCSD subspecialty clinics. Almost all participants had PCR confirmed infections, though a few were included from very early in the pandemic before testing was widely available. Participants were excluded from this study if they (1) did not have record of either a positive COVID-19 test result or clinically confirmed COVID-19 infection or (2) could not provide informed consent. Participants were divided into two cohorts. Cohort 1 consisted of participants who had been diagnosed with a neurological disease prior to COVID-19 infection. Cohort 2 consisted of participants who had never been diagnosed with a neurological disease.

### Demographics and medical history

We collected general demographic and clinical data regarding our participants including gender, age, tobacco use, height, weight, BMI, employment status, and past medical history. Participants were queried on their medical history and medications including determination of prior neurological conditions such as Guillain–Barre syndrome, multiple sclerosis (MS), Alzheimer's disease, migraine headaches, autoimmune encephalitis, narcolepsy, and Parkinson's disease.

### Instruments

We applied validated questionnaires to capture neuropsychiatric symptoms at baseline, 6 months, and 1 year. The PROMIS-29 form assessed seven health domains including pain interference, physical function, fatigue, sleep disturbance, depression, anxiety, and ability to participate in social roles in activities [7]. Domains were evaluated using four items per category and a 0–10 numeric rating for each item. The Impact of Events Scale—Revised (IES-R) measured participants' subjective response to a traumatic event (COVID-19 infection) using three subscales: intrusion, avoidance, and hyperarousal [8]. This validated survey was used to assess participants' level of distress following their COVID-19 infection with a maximum total score of 88. Score interpretation included— between 24 and 32: PTSD is a clinical concern; above 33: best cut-off for a probable diagnosis of PTSD [9, 10].

Modified Fatigue Impact Scale (MFIS) measured the impact of fatigue on physical, cognitive, and psychosocial functioning with a maximum total score of 84 [11]. The Epworth Sleepiness Scale (ESS) is a self-reported questionnaire used to assess daytime sleepiness with a maximum score of 24 [12]. The Montreal Cognitive Assessment (MoCA) is a screening test administered by healthcare providers to measure cognitive abilities including short-term memory, attention, language, and executive function; the MoCA has a maximum score of 30 points with a score of $< 26$ generally considered to be the threshold for mild cognitive impairment [13]. The MoCA score was adjusted

for education level with one point added to the total score for individuals with 12 years or less of education. The Neurological Review of Systems (ROS) was adapted from standard clinical ROS templates used to assess the presence and severity of various neurological symptoms. In this study, only 1-year outcomes were reported as the 6-month results were previously published [6]. Cumulative baseline data (including participants from our previous study examining 6-month outcomes and all individuals who enrolled since) were reported for reference.

### Data collection procedures

Data were collected through a secure REDCap electronic capture system. The PROMIS-29, IES-R, MFIS, and ESS questionnaires were sent electronically to participants via REDCap. The neurological ROS and MoCA were conducted during one-on-one visits with participants. To comprehensively analyze treatment received for COVID-19-related symptoms, chart review was conducted in addition to collecting self-reported medications from participants. Chart review included extraction of new medications started for neuropsychiatric symptoms that were considered related to an individual's COVID-19 infection by his or her treating physician. Medications that individuals were taking prior to their COVID-19 infection for a previously diagnosed or unrelated neuropsychiatric condition were not included in analyses.

### Statistical analysis

Descriptive analyses of frequencies, means, and standard deviation were reported as appropriate. Paired t-tests were used to compare differences in reported symptoms at baseline and at 1-year follow-up. Welch independent sample *t* tests were used to compare cohort 1 and cohort 2 at baseline and at 1-year follow-up. All statistical analyses were performed with R software version 4.2.1 (R Foundation for Statistical Computing), and $p$ values $< 0.05$ were considered significant. To assess the relationship between MoCA scores and self-reported neurological symptoms at baseline, point-biserial correlations were employed using MoCA score as a continuous variable and the neurological ROS metrics of encephalopathy (altered mental status), memory difficulties, and trouble concentrating as dichotomous variables. We used a binary ("Yes" or "No") classification for neurological ROS score and then used a point-biserial correlation to examine the relationship between each ROS score and each MOCA score for each patient across cohorts.

The association between initial COVID-19 infection severity (mild, moderate, severe) and clinical outcomes of interest utilized multivariable linear regression adjusting for age, sex, and time from acute infection. Pairwise differences between degrees of COVID-19 infection severity were compared using one-way ANOVA adjusting for multiple comparisons using the Tukey method.

## Results

### Participants

A total of 106 participants were included in the analysis, with 30 participants in cohort 1 (known prior neurologic condition) and 76 participants in cohort 2 (no known prior neurologic condition). Table 1 summarizes the demographic and clinical characteristics. The mean age at time of infection was 48.6 years (SD 12.6) and 67.0% of the participants were female. All participants reported experiencing acute COVID-19 infection symptoms; no participants had asymptomatic PCR testing. Of those recruited, 40 individuals completed their 1-year follow-up neurological ROS. Response rate varied for self-reported surveys (Tables 2, 3).

### COVID-19 infection severity

Participants self-reported the severity of their acute COVID-19 infection based on the symptom severity and duration. Infection severity was reported as follows—asymptomatic: 0%, mild: 34.7%, moderate: 39.6%, and severe: 25.7%. The median duration of acute COVID-19 infection was 14 days (IQR 11). Overall, 12.5% of participants reported hospitalization for their acute COVID-19 infection.

### Neurological review of systems and MoCA

Responses to the neurological ROS demonstrated a persistence of neuropsychiatric symptoms evaluated 1 year from baseline (Tables 2, 3). At baseline, fatigue was the most common symptom (69.9%). At 1 year, there was slight improvement in overall persistence and prevalence of individual symptoms but 72.5% of individuals still reported at least one neuropsychiatric symptom. Fatigue remained the most prevalent symptom (52.5%).

At baseline, 38.8% of all participants met the established MoCA cut-off score of $< 26$ for mild cognitive impairment. This percentage decreased to 20.0% at 1 year, and the mean MoCA score increased from 25.9 ($\pm 3.1$) to 27.6 ($\pm 2.6$) during this same time period. The point-biserial correlations for MoCA score and encephalopathy (altered mental status) was $-0.31$ ($p = 0.0058$); for memory difficulties $-0.21$ ($p = 0.064$); and for trouble concentrating $-0.13$ ($p = 0.24$).

**Table 1** Baseline demographics and clinical characteristics

| | Cohort 1 ($n=30$) | Cohort 2 ($n=76$) | Total ($n=106$) |
|---|---|---|---|
| Demographics | | | |
| Mean age at infection (SD) | 48.2 (10.4) | 49.1 (13.5) | 48.6 (12.6) |
| Female (%) | 73.3 | 64.5 | 67.0 |
| White (%) | 92.3 | 78.9 | 82.3 |
| Hispanic ethnicity (%) | 14.8 | 21.2 | 19.3 |
| Body mass index (mean, kg/m$^2$) | 26.3 | 28.2 | 27.7 |
| BMI category (%) | | | |
| Underweight (< 18.5) | 3.6 | 1.5 | 2.2 |
| Normal (18.5–24.9) | 42.9 | 32.8 | 35.8 |
| Overweight (25.0–29.9) | 28.5 | 34.3 | 32.6 |
| Obese (> 30) | 25.0 | 31.3 | 29.4 |
| Prior tobacco use (%) | 31.0 | 16.6 | 21.0 |
| Annual household income (%) | | | |
| < 15,000 | 7.7 | 3.1 | 4.4 |
| 15,000–24,999 | 0 | 3.1 | 2.2 |
| 25,000–34,999 | 3.8 | 1.7 | 2.2 |
| 35,000–49,999 | 0 | 6.3 | 4.4 |
| 50,000–74,999 | 15.4 | 15.6 | 15.6 |
| 75,000–99,999 | 11.5 | 10.9 | 11.1 |
| 100,000–149,999 | 26.9 | 18.8 | 21.1 |
| 150,000–199,999 | 15.4 | 17.2 | 16.7 |
| > 200,000 | 19.2 | 23.4 | 22.2 |
| COVID-19 infection history | | | |
| Test confirmed COVID-19 infection (%)[a] | 93.1 | 89.1 | 90.2 |
| Suspected COVID-19 infection (%) | 6.9 | 10.9 | 9.8 |
| Median time: acute COVID-19 infection to baseline assessment (days) | 73 | 175 | 134 |
| Median duration of acute COVID-19 infection [days (IQR)] | 14 (13) | 14 (18) | 14 (11) |
| COVID-19 infection severity (%)[b] | | | |
| Asymptomatic | 0 | 0 | 0 |
| Mild | 44.8 | 30.6 | 34.7 |
| Moderate | 41.4 | 38.9 | 39.6 |
| Severe | 13.8 | 30.6 | 25.7 |
| Requiring hospitalization for acute infection ($n$) | 10.3 | 13.3 | 12.5 |
| Vaccination status (%) | | | |
| Zero vaccine doses | 18.5 | 16.9 | 17.4 |
| Single vaccine doses | 3.7 | 8.5 | 7.0 |
| Two or more vaccine doses | 77.8 | 74.6 | 75.6 |

[a]COVID-19 infection was either PCR or antigen test confirmed

[b]COVID-19 infection severity was assessed as previously in Shanley et al. 2022. Severity was assessed via patient report, given the options: asymptomatic, mild, moderate, or severe. Patient self-assessment of infection severity was cross-referenced with reported acute viral symptom profile

## Validated instrument responses

The overall pooled percentage of participants meeting the best cut-off for a probable diagnosis of PTSD per the IES-R decreased from 21.9 to 12.5% from baseline to 1-year follow-up (Tables 2, 3). In an analysis of intra-participant changes from baseline to 1 year, we found a mean decrease in IES-R score of − 2.71 ($p=0.14$, 95% CI [− 6.40, 0.97]).

The average total MFIS score for all participants decreased from 39.4 at baseline to 27.9 at 1-year (Tables 2, 3). Additionally, using the Flachenecker et al. recommended cut-off score of 38 to distinguish fatigued individuals from non-fatigued individuals, we observed a decrease in

**Table 2** Baseline self-report clinical questionnaires, MoCA, and neurological review of systems findings

| | Cohort 1 | Cohort 2 | Total |
|---|---|---|---|
| Revised impact of events scale (mean, SD) | $n=22$ | $n=51$ | $n=73$ |
| Intrusion | 5.5 (7.3) | 8.1 (7.5) | 7.3 (7.5) |
| Avoidance | 4.2 (5.7) | 6.7 (6.7) | 6.0 (6.5) |
| Hyperarousal | 4.3 (6.0) | 5.5 (6.1) | 5.1 (6.1) |
| Total | 14.0 (16.3) | 20.3 (18.1) | 18.4 (17.7) |
| Participants for which PTSD is of clinical concern[a], *n* (%) | 2 (9.1) | 4 (7.8) | 6 (8.2) |
| Participants that meet the best cutoff for a probable diagnosis of PTSD[b] *n* (%) | 3 (13.6) | 13 (25.5) | 16 (21.9) |
| PROMIS-29 neuropsychiatric only (mean, SD) | n = 23 | n = 51 | n = 74 |
| Anxiety | 8.0 (4.4) | 8.6 (4.0) | 8.4 (4.1) |
| Depression | 8.1 (4.4) | 7.0 (3.5) | 7.4 (3.8) |
| Fatigue | 12.8 (5.4) | 12.1 (4.8) | 12.3 (5.0) |
| Sleep disturbance | 10.9 (5.2) | 11.4 (4.7) | 11.3 (4.8) |
| Ability to participate in social roles and activities | 13.1 (4.5) | 13.4 (4.8) | 13.3 (4.6) |
| Modified Fatigue Impact Scale (mean, SD) | $n=23$ | $n=55$ | $n=78$ |
| Physical | 19.3 (10.3) | 17.1 (10.1) | 17.7 (10.2) |
| Cognitive | 16.6 (10.9) | 18.9 (11.1) | 18.3 (11.0) |
| Psychosocial | 3.5 (2.4) | 3.6 (2.6) | 3.6 (2.5) |
| Total | 38.5 (20.8) | 10 (43.5) | 39.8 (22.5) |
| % of participants meeting the established cutoff for "fatigued"[c], *n* (%) | 32 (58.1) | 39.4 (21.9) | 42 (53.8) |
| MoCA (mean, SD) | $n=21$ | $n=59$ | $n=80$ |
| Total score | 25.9 (2.5) | 25.9 (3.4) | 25.9 (3.1) |
| % < 26, *n* (%) | 10 (47.6) | 21 (35.6) | 31 (38.8) |
| Epworth Sleepiness Scale (mean, SD) | $n=23$ | $n=55$ | $n=78$ |
| Total score | 7.2 (5.6) | 6.7 (4.7) | 6.3 (4.9) |
| Neurological Review of Systems: symptom presence, *n* (%) | $n=31$ | $n=72$ | $n=103$ |
| Encephalopathy | 10 (32.3) | 37 (51.4) | 47 (45.6) |
| Memory difficulties | 14 (45.2) | 46 (63.9) | 60 (58.3) |
| Trouble concentrating | 18 (58.1) | 41 (56.9) | 59 (57.3) |
| Insomnia | 13 (41.9) | 40 (55.6) | 53 (51.5) |
| Fatigue | 24 (77.4) | 48 (66.7) | 72 (69.9) |
| Neurological Review of Systems: severity score (1–10), mean (SD) | | | |
| Encephalopathy | 5.6 (2.7) | 5.5 (2.3) | 5.5 (2.4) |
| Memory difficulties | 6.2 (2.8) | 5.2 (2.5) | 5.5 (2.5) |
| Trouble concentrating | 5.4 (2.9) | 5.5 (2.3) | 5.5 (2.4) |
| Insomnia | 5.8 (2.3) | 5.4 (2.7) | 5.8 (2.6) |
| Fatigue | 6.4 (2.7) | 5.7 (2.9) | 5.9 (2.9) |

[a]Asukai et al. [9], score of 24–32

[b]Creamer et al. [10], score of 33 or above

[c]Flachenecker et al. [14], score of 38 or greater

percentage of participants meeting this cut-off from 53.8 to 37.8% from baseline to 1 year [14]. When analyzing intra-participant changes, we filtered for patients who have completed both time points (baseline and 1 year) across both cohorts ($n=27$). The mean MFIS score decreased by − 4.45 points ($p=0.12$, 95% CI [− 10.17, 1.20]).

We compared scores from cohort 1 and cohort 2 to assess potential differences between participants with and without prior neurologic diseases. At baseline, there were no significant differences between the two cohorts in any of the neuropsychiatric PROMIS-29 metrics: anxiety, depression, fatigue, sleep disturbance, and ability to participate in social roles and activities (Table 2). In contrast, at 1-year, we found that cohort 2 (participants without prior neurological disease) reported a significantly greater ability to participate in social roles and activities (cohort 1: $14.3 \pm 4.9$, cohort 2: $18.2 \pm 3.4$, $p=0.033$; Table 3). Additionally, at the 1-year time point, we observed a

**Table 3** One-year self-report clinical questionnaires, MoCA, and neurological review of systems findings

| | Cohort 1 | Cohort 2 | Total |
|---|---|---|---|
| Revised impact of events scale (mean, SD) | $n=11$ | $n=21$ | $n=32$ |
| Intrusion | 7.5 (7.0) | 3.2 (5.7) | 4.7 (6.4) |
| Avoidance | 6.1 (6.7) | 1.7 (3.2) | 3.2 (5.1) |
| Hyperarousal | 4.2 (4.6) | 2.0 (4.5) | 2.7 (4.6) |
| Total | 17.7 (17.9) | 6.9 (12.4) | 10.6 (15.1) |
| % of participants for which PTSD is of clinical concern[a] *n* (%) | 0.0 (0.0) | 2 (9.5) | 2 (6.3) |
| % of participants that meet the best cutoff for a probable diagnosis of PTSD[b] n(%) | 3 (27.3) | 1 (4.8) | 4 (12.5) |
| PROMIS-29 (neuropsychiatric only) (mean, SD) | $n=11$ | $n=20$ | $n=31$ |
| Anxiety | 8.8 (4.1) | 6.3 (3.0) | 7.1 (3.6) |
| Depression | 7.8 (3.9) | 5.4 (2.5) | 6.2 (3.2) |
| Fatigue | 11.4 (5.2) | 8.2 (5.5) | 9.4 (5.4) |
| Sleep disturbance | 10.5 (4.4) | 8.8 (4.9) | 9.5 (4.6) |
| Ability to participate in social roles and activities | 14.3 (4.9) | 18.2 (3.4)* | 16.7 (4.3) |
| Modified Fatigue Impact Scale (mean, SD) | $n=11$ | $n=26$ | $n=37$ |
| Physical | 13.1 (11.8) | 10.4 (10.5) | 11.2 (10.8) |
| Cognitive | 17.5 (13.6) | 12.8 (11.0) | 14.3 (11.8) |
| Psychosocial | 3.1 (2.9) | 1.7 (2.3) | 2.1 (2.6) |
| Total | 33.6 (27.7) | 5 (45.5) | 25.4 (22.3) |
| % of participants meeting the established cutoff for "fatigued"[c], n(%) | 9 (34.6) | 27.9 (24.0) | 14 (37.8) |
| MoCA (mean, SD) | $n=13$ | $n=22$ | $n=35$ |
| Total score | 27.9 (2.5) | 27.4 (2.7) | 27.6 (2.6) |
| % < 26, *n* (%) | 2 (15.4) | 5 (22.7) | 7 (20.0) |
| Epworth Sleepiness Scale (mean, SD) | $n=11$ | $n=26$ | $n=37$ |
| Total score | 7.7 (6.7) | 6.2 (4.5) | 6.6 (5.2) |
| Neurological Review of Systems: symptom presence, *n* (%) | $n=14$ | $n=26$ | $n=40$ |
| Encephalopathy | 6 (42.9) | 10 (38.5) | 16 (40.0) |
| Memory difficulties | 6 (42.9) | 13 (50.0) | 19 (47.5) |
| Trouble concentrating | 5 (35.7) | 12 (46.2) | 17 (42.5) |
| Insomnia | 4 (28.6) | 10 (38.5) | 14 (35.0) |
| Fatigue | 9 (64.3) | 12 (46.2) | 21 (52.5) |
| Neurological Review of Systems: score, mean (SD) | | | |
| Encephalopathy | 5.5 (1.0) | 5.0 (2.5) | 5.2 (2.1) |
| Memory difficulties | 5.5 (3.2) | 4.8 (2.7) | 5.1 (2.8) |
| Trouble concentrating | 6.4 (1.1) | 5.3 (2.7) | 5.6 (2.4) |
| Insomnia | 7 (3.6) | 4.5 (2.2) | 5.2 (2.8) |
| Fatigue | 6.7 (2.0) | 5.8 (2.6) | 6.1 (2.4) |

*Cohort 2 reported a significantly greater ability to participate in social roles and activities at 1 year, $p=0.03$

[a]Asukai et al. [9], score of 24–32

[b]Creamer et al. [10], score of 33 or above

[c]Flachenecker et al. [14], score of 38 or greater

trend towards a lower severity of depression and anxiety symptoms in cohort 2 compared to cohort 1, although these results did not reach nominal statistical significance (cohort 1: $7.8 \pm 3.9$, cohort 2: $5.4 \pm 2.5$, $p=0.083$ and cohort 1: $8.8 \pm 4.1$, cohort 2: $6.3 \pm 3.0$, $p=0.092$, respectively).

## Correlation between COVID-19 severity and PASC symptoms

In an adjusted multivariable regression model, COVID-19 infection severity (mild, moderate, or severe) was not associated with baseline MoCA or 1-year MoCA score (Table 4).

**Table 4** Association between initial COVID-19 infection severity and 1-year neuropsychiatric outcomes

| Outcome scores at 1 year | Adjusted $\beta$ (95% CI, $p$ value)[a] |
|---|---|
| MoCA | |
| Baseline | − 0.48 (− 1.38, 0.42) $p=0.29$ |
| One-year | − 0.58 (− 1.99, 0.82) $p=0.41$ |
| PROMIS-29 at 1 year | |
| Physical function | − 3.47 (− 5.12, − 1.84) $p=0.0002$ |
| Anxiety | 3.10 (1.21, 4.99) $p=0.02$ |
| Depression | 2.68 (0.88, 4.47) $p=0.005$ |
| Fatigue | 6.27 (3.74, 8.80) $p=0.00003$ |
| Sleep disturbance | 4.22 (1.73, 6.7) $p=0.002$ |
| Ability to participate in social roles and activities | − 4.54 (− 6.73, − 2.34) $p=0.003$ |

[a]Multivariable regression model for MOCA score at baseline adjusted for age and sex. Multivariable regression models for 1-year outcomes adjusted for age, sex, and time from acute infection

On ANOVA analysis, there were no pairwise differences between the degrees of COVID-19 infection severity and baseline MoCA scores, but there was a pairwise difference between severe and moderate infections (− 3.54, 95% CI − 6.91, − 0.17). COVID-19 severity was associated with 1-year PROMIS scores for physical function, anxiety, depression, fatigue, sleep disturbance, and ability to participate in social roles and activities after adjusting for age, sex, and time from acute infection (Table 4). On ANOVA analysis, there were significant pairwise differences between severe vs. mild infections and severe vs. moderate infections for physical function; severe vs. mild infection and severe vs. moderate infection for physical function; all pairwise comparisons for fatigue; severe vs. mild infection for sleep disturbance, and all pairwise comparisons for ability to participate (Fig. 1).

### Treatment

Out of 106 total study participants, 100 were evaluated for PASC treatment exposures with six excluded due to lack of electronic medical chart access. We found that out of these 100 participants, 29 individuals (29%) started treatment (medications, supplements, therapy, etc.) for neuropsychiatric symptoms attributable to neuro-PASC (Table 5). Of the 29 individuals who started new treatment, 12 were trialed on more than one medication for a single indication. Indications for starting new medications included anxiety, depression, trouble concentrating, insomnia, PTSD, migraine, neuropathy, mood disorder, and myoclonus. Out of the participants who started new medications, fatigue was the most common indication (44.8%) followed by insomnia (27.6%). The most common medication used for fatigue was amantadine (53.8% of prescriptions for fatigue). Overall, there was a large spectrum of medications and supplements used to treat the conditions listed. Generally, there was not a consistent pattern or drug-of-choice for neuro-PASC symptoms.

## Discussion

Our study demonstrates that while neuro-PASC symptoms overall improve after 1-year post-infection, the majority of participants report persistent symptoms, the most common being fatigue, memory difficulties, trouble concentrating, and insomnia. At 1 year, approximately half of the participants reported experiencing fatigue; additionally, memory difficulties remained in approximately half of the participants at 1 year. We found that participants without prior neurological disease reported a significantly greater ability to participate in social roles and activities at 1 year, despite no difference at baseline. MoCA score was found to be correlated with self-reported ROS symptoms, specifically encephalopathy (altered mental status). Additionally, acute COVID-19 infection severity was associated with 1-year PROMIS scores for physical function, anxiety, fatigue, sleep disturbance, and ability to participate in social roles and activities. In an analysis of neuro-PASC treatment, we found that roughly a third of participants started at least one new medication for COVID-19-associated neuropsychiatric symptoms. A wide variety of medications were used and most of these were started for fatigue.

Although we observed both a decrease in the average total MFIS and a decrease in percentage of participants meeting the instrument-specific cut-off for fatigue from baseline to 1-year, fatigue was the still most commonly experienced symptom at 1 year, with over half of participants (52.5%) reporting persistent fatigue. When analyzing intra-participant changes, we found that there was clinically relevant improvement in MFIS score (− 4.45 points) at 1 year, but the result did not reach nominal statistical significance. Thus, although there is a promising trend towards improvement in the severity of fatigue over the year, the prevalence of fatigue remains high and is an important target for future research and treatment. In our analysis of treatments targeting fatigue, amantadine was the most prescribed medication for fatigue in our patients. Amantadine is a commonly used medication for MS-related fatigue and relatively accessible without controlled substance restrictions. The mechanism underlying fatigue in long COVID is still being evaluated, but it has been hypothesized to be related to an aberrant

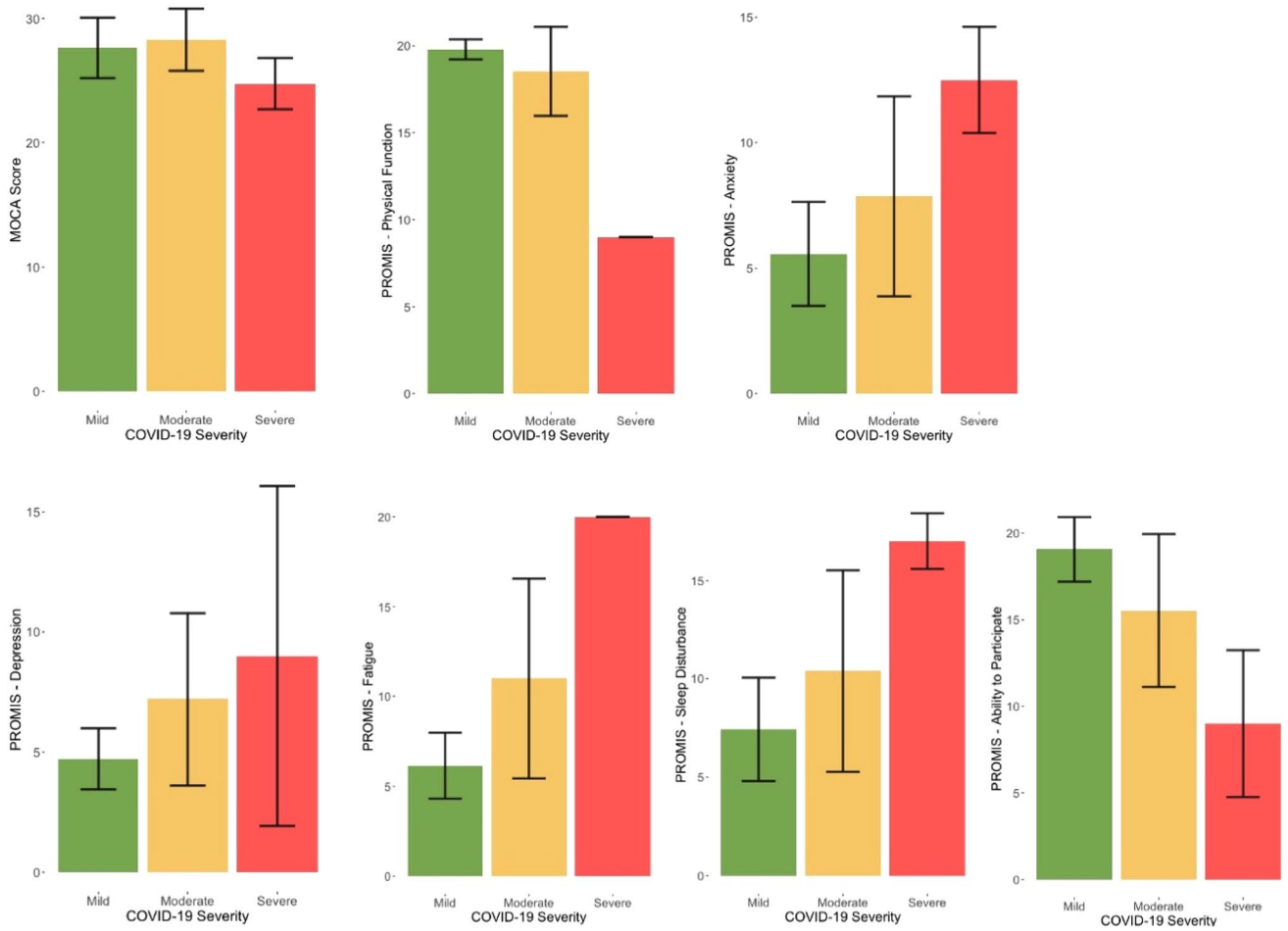


**Fig. 1** Comparison of initial COVID-19 infection severity and 1-year outcomes. Error bars denote means and standard errors

immune response to the virus and may have similarities to autoimmune CNS diseases [15]. Specific causal mechanisms proposed for MS-related fatigue include proinflammatory cytokines (including interferon-γ and TNF-α), alterations in the hypothalamic–pituitary–adrenal axis, loss of axons, and differential patterns of brain activation (including cingulate gyri and left primary sensory cortex) [16]. Alternatively, the fatigue may also be driven or exacerbated by increased respiratory effort from chronic pulmonary complications [17]. The prevalence of fatigue in PASC favors its selection as a primary symptom target for clinical trials. Two different studies seeking to treat Post-Viral or Post-COVID-19 Fatigue Syndrome are taking different approaches, one using Ruconest, a recombinant C1 esterase inhibitor indicated for the treatment of acute angioedema attacks, and the other using low-dose naltrexone (LDN) [18, 19]. Ruconest is a strong inhibitor of the complement system, kallikrein–kinin system, and the contact activation system, and is hypothesized to potentially correct immune dysfunction resulting from COVID-19 infection [20]. LDN has been demonstrated to exhibit immunomodulatory activity involving inhibition of B- and T-lymphocytes, antagonism of opioid growth factor receptor, and modulation of antigen-presenting cells such as microglia and macrophages; use of LDN has been shown to have some benefits in symptom control in conditions including multiple sclerosis and chronic fatigue syndrome [21, 22].

The approximate 50% decrease in the percentage of total participants meeting the best cut-off for a probable diagnosis of PTSD at 1 year compared to baseline illustrates that while acute COVID-19 infection and onset of PASC were initially viewed as a traumatic event, the impact of the events improve over time. However, the finding that a proportion of patients may still be categorized as meeting the best cut-off for a probable diagnosis of PTSD over a year after infection underscores the critical and lasting impact that COVID-19. For comparison, it has been estimated that approximately 20–30% of ICU survivors experience clinically relevant PTSD symptoms during their first year post-discharge [23]. This underscores the importance of evaluating the psychosocial impacts of COVID-19 infection in patients even long after their recovery from the acute infection. While there was an improvement in overall MoCA score and decrease

**Table 5** Treatment started for COVID-19-related neuropsychiatric symptoms

| Indication | Number of participants (*n*) | Medications |
|---|---|---|
| Anxiety | 4 | Clonazepam, sertraline, duloxetine, psychologist/therapy, fluvoxamine, diazepam, escitalopram, hydroxyzine, gabapentin[a], alprazolam |
| Depression | 5 | Bupropion (2), fluoxetine, escitalopram, duloxetine, psychologist/therapy |
| Trouble concentrating | 5 | Adderall (2), vyvanse (2), modafinil |
| Fatigue | 13 | Amantadine (7), acetyl-L-carnitine (4), modafinil (2), adderall, glutathione, amitriptyline, taxifolin |
| Insomnia | 8 | Zolpidem (4), melatonin (3), alprazolam (2), amitriptyline, doxepin, trazadone |
| PTSD | 2 | Sertraline, psychologist/therapy |
| Other | | 14 |
| Migraine | 8 | Amitriptyline (2), ondansetron (2), galcanezumab (2), sumatriptan (2), memantine (2), venlafaxine (2), butalbital/acetaminophen/caffeine, nortriptyline, erenumab, topiramate, rizatriptan, meloxicam (for headaches, not specified as migraine) |
| Neuropathy | 4 | Duloxetine (3), gabapentin (2) |
| Mood disorder NOS | 1 | Lithium |
| Myoclonus | 1 | Clonazepam |

Multiple patients were trialed on numerous medications for a single indication. The number in parentheses next to a given drug reflects the number of patients who were prescribed that drug

*NOS* not otherwise specified

[a]Authors acknowledge that this is not a typical drug prescribed for anxiety, but was indicated in the patient's chart for anxiety by the treating physician

in the percentage of participants meeting the score cut-off for mild cognitive impairment at the 1-year period, 20% of total participants still are characterized as mildly cognitively impaired at 1 year. Although MoCA score is only a screening tool, these findings illustrate the persistence of cognitive deficits in neuro-PASC. This finding is supported by anecdotal and self-reported statements by the participants. During follow-up study visits, many of these individuals reported an inability or difficulty to work at their old job, complete common activities of daily living (e.g., remember appointments and grocery lists and focus long enough to complete basic tasks), and interact with friends and family, which all have severe impacts on quality of life. These difficulties are likely multi-factorial, stemming from potential neurocognitive changes due to PTSD symptoms, other mood changes, and impacts from fatigue.

In addition to recognizing persistent long-term symptoms experienced in neuro-PASC, we found a wide spectrum of medications and supplements prescribed by physicians to treat neuropsychiatric symptoms in neuro-PASC patients. This highlights the need for evaluation of more standardized treatment guidelines for neuro-PASC. Additionally, approximately 40% patients of those who started new medication were tried on multiple medications for a single indication, suggesting that the current approach is more trial and error. Currently, treatment for neuro-PASC is focused on targeting individual symptoms as they arise, rather than treating the potential underlying mechanism or cause of neuro-PASC, which is still under investigation. Although we are only providing a descriptive look at medications used and not examining the efficacy of various treatments due to observational design and small sample size, we have highlighted current practice and this descriptive data may help inform clinicians treating similar patients and contribute to the ongoing larger effort to create efficacious treatment guidelines for neuro-PASC.

Emerging data identify immunological dysregulation and prolonged inflammation as underlying causes of many long-COVID symptoms, including neuro-PASC.[24, 25]. Current efforts in treating neuro-PASC include immunomodulatory therapies. For example, methylprednisolone and intravenous immunoglobulin (IVIG) are being explored as treatment for symptoms of long COVID with ongoing neurologic symptoms such as dizziness, trouble walking, or problems with strength [26]. Additionally, the efficacy and safety of temelimab, a recombinant humanized IgG4 monoclonal antibody that blocks the HERV-W protein, is currently being trialed as a treatment for PASC neuropsychiatric symptoms [27]. HERV activity has been hypothesized to influence PASC development; in addition to general activation in inflammation, in bronchial alveolar lavage samples of COVID-19 patients, upregulated expression of numerous HERV families were found [28, 29]. The HERV-W protein has also been correlated with the pathology of autoimmune disorders including type 1 diabetes and multiple sclerosis [30]. Specifically, MS-associated retrovirus (MSRV) and ERVWE1 are two members of the HERV-W family that have been identified as potential MS co-factors [31]. Activation of HERV-W/

MSRV by Epstein–Barr virus (EBV) has been hypothesized as a mechanism underlying the association between EBV infections and autoimmune diseases such as MS [31, 32]. Results from the CHANGE-MS phase 2b trial of temelimab has demonstrated radiological indicators of potential anti-neurodegenerative effects in MS [33]. Other clinical trials for neuro-PASC include the use of vortioxetine, an antidepressant with established pro-cognitive properties, to potentially treat cognitive deficits developing during and/or after COVID-19 infection [34]. Vortioxetine is a receptor antagonist at the 5-HT receptor subtypes 3, 7, and 1D, a receptor agonist and partial agonist at the 5-HT 1A and 1B subtypes, respectively, and a serotonin transporter (SERT) inhibitor [35].

Limitations of this study include the modest sample size. During the peak of the pandemic, providers made strong efforts to advise and protect patients, including those with neurologic conditions that rendered them high risk for poor infection outcomes. In part because of these efforts and the cautiousness of high-risk patients, there was a lower rate of COVID-19 infections among chronic neurological disease patients compared to the overall population [36]. This may have contributed to the small sample size of cohort 1 individuals with prior neurological conditions. Although conclusions regarding differences in intra-group and intra-participant changes are limited by modest sample size, descriptive patterns and symptom evolution over time are important findings that may inform future studies. Furthermore, we acknowledge that there may be response bias such that participants who return for their 1-year follow-up may be the ones more likely to still be experiencing significant symptoms or conversely those with increased disability may not have been able to attend later visits. Additionally, there may be a potential recruitment bias, since participants were recruited at subspecialty referral centers where they are more likely to experience symptoms and seek medical care.

Strengths of this study include the longitudinal design and length of follow-up time, the extensive testing metrics and validated surveys used, and the capture of specific treatment modalities used to treat neuro-PASC. The longitudinal design allowed the demonstration of prolonged persistence of neuropsychiatric symptoms in PASC. Our findings are consistent with those of Rass et al. who examined neurological outcomes including fatigue, concentration difficulties, forgetfulness, hyposmia, headache, limb weakness, and myalgia [37]. They found that 1 year after COVID-19 infection, 59% of participants reported at least one neurological symptom and objective neurological examination revealed abnormalities in 64% of individuals.[37]. Additionally, our study includes a reference group of individuals who had pre-existing neurologic conditions prior to COVID-19 infection. This reference group allows us to observe whether there appears to be a difference in recovery trajectory between individuals with previous neurologic conditions and those without a prior neurological disease as well as compare the neuropsychiatric effects of COVID-19 to those with chronic neurologic illness. Furthermore, we have identified specific treatments strategies employed by our physicians to treat COVID-19-related neuropsychiatric symptoms.

Overall, our data highlight the persistent and severe nature of neuropsychiatric and cognitive symptoms after COVID-19 infection. These symptoms should be regarded as outcomes evaluated in future clinical trials targeting neuro-PASC. Multi-center studies with larger data sets may help with causal inference for the correlation between disease exposure and objective measures of cognition. In addition to strengthening this correlation, targeted treatments for neuro-PASC should continue to be trialed to provide meaningful improvements to patients' symptoms and quality of life.

## Conclusion

In conclusion, the high prevalence and severity of neuropsychiatric symptoms in PASC are an issue in need of treatment guidelines. Our data highlight that the treatment of neuro-PASC is symptomatic and highly variable. The underlying etiology of neuro-PASC is emerging as complex and will likely require a multi-modal treatment protocol, involving different targets to ameliorate symptoms and treat the underlying pathophysiology. Establishing effective therapies to treat PASC will not only improve quality of life for those directly impacted but will also have important implications for understanding the pathophysiology of neuro-PASC and future post-infectious neuroinflammatory disorders.

**Author contributions** All authors contributed to the study conception and design. Data collection and analysis were performed by EL, JY, LP, and JA. The first draft of the manuscript was written by EL and all authors commented on previous versions of the manuscript. AG was responsible for project concept co-development and referrals. RE contributed to referrals and general collaboration. JG is the PI of this project and is responsible for the project conception, study design, data collection, analysis plan, and drafting. All authors read and approved the final manuscript.

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**Data availability** Anonymized data and datasets not published within this article will be made available by request from any qualified investigator.

## Declarations

**Conflicts of interest** Emilie Liu, Jennifer Yang, Lucas Patel, Jasmine Arora, Amanda Gooding, and Ronald Ellis report no disclosures relevant to the manuscript. Unrelated to the current work, Jennifer Graves has received grant or clinical trial funding from the NMSS, UCSD, Octave, Biogen, EMD-Serono and ABM. She serves on a steering committee for a clinical trial with Novartis and served on advisory boards for TG therapeutics, Genentech and Bayer.

**Ethics statement** All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Consent to participate** Written informed consent was obtained from every participant.

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