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Characterizing Neuro-PASC outcome with the mobile Neuro-COVID recovery care companion application

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Abstract

Background Long COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), affects 14 million people in the US. Neurologic manifestations of PASC (Neuro-PASC) are particularly debilitating. However, the evolution of these symptoms and factors associated with recovery are poorly understood. This study aimed to characterize Neuro-PASC symptom evolution using a mobile phone application and assess user experience.

Methods The Neuro-COVID Recovery Care Companion (NCRCC) mobile application consists of questionnaires integrated within Northwestern Medicine's online MyChart platform which interfaces with the electronic medical record. Neuro-PASC patients completed daily surveys of twelve Neuro-PASC symptoms and their perceived percent recovery compared to their pre-COVID baseline. Patients also completed Patient-Reported Outcomes Measurement Information System (PROMIS) quality-of-life (QoL) surveys and NIH toolbox cognitive assessments at baseline and at 3-month follow up. Participants were retrospectively classified as "Improvers" or "Non-Improvers" based on the slope and range of their percent subjective recovery.

Results Data from 63 participants presenting an average of 12.7 months after symptom onset were analyzed, including 27 (42.9%) Improvers and 36 (57.1%) Non-Improvers. Fewer women were Improvers (50% vs 75.7%; $p=0.04$). Multiple correspondence analysis showed that patients presenting with a constellation of anosmia, dysgeusia, and a lack of insomnia ($p=0.023$) were less likely Improvers. Improvers had more fluctuations in their subjective recovery than Non-Improvers with greater mean variance (7.01 vs 3.79; $p=0.0004$) and positive recovery slope (5.84 vs 0; $p<0.0001$). There were no differences in QoL and cognition at initial assessment, but Improvers showed a trend toward increased processing speed and decreased sleep disturbance after 3 months. Both groups found the NCRCC application easy-to-use, useful, and satisfactory.

Conclusions Our findings reveal previously unrecognized fluctuations in subjective recovery of Neuro-PASC, and that women and patients presenting with anosmia and dysgeusia are less likely to improve one year from COVID-19 onset. We found broad alterations in QoL in both groups suggesting that strategies to reduce sleep disturbance and

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improve cognition may contribute to subjective improvement. Our results suggest similar mobile applications may benefit patients with other ill-defined chronic diseases, by equipping and empowering them on their often windy road to recovery.

Keywords Application, Neurology, Post-Acute Sequelae of SARS-CoV-2 Infection (PASC), Long COVID, COVID-19, Symptom tracker

Background

Since the beginning of the COVID-19 pandemic, the WHO has reported over 778 million cases worldwide [1]. Many of these patients developed Long-COVID, or post-acute sequelae of SARS-CoV-2 infection (PASC), a debilitating condition characterized by persistent and highly variable symptoms across one or more organ systems [2–4]. While SARS-CoV-2 vaccines have prevented severe COVID-19 pneumonia and death, they only caused a modest decrease in the incidence of PASC [5], which remains a severe health problem with important economic implications. As of September 2024, 5.3% of all US adults had PASC [6], and it is estimated that over 400 million people suffer from PASC worldwide, with an annual economic impact of $1 trillion globally [7].

The neurologic manifestations of PASC (Neuro-PASC) are a major indication for referral to Post-COVID clinics [8]. Symptoms may persist years after acute COVID-19 and are often debilitating as they impact quality of life and cognition [9–13].

Two major concerns of Neuro-PASC patients evaluated in our clinic are whether they will improve, and the anticipated timeline of recovery. Although patients have reported variations in their symptoms [14], few studies have explored the fluctuations of PASC symptoms [15–17] and fewer still have focused on Neuro-PASC [18].

PASC symptoms may improve with time [18, 19], and prior studies have shown relationships between comorbidities, such as obesity, cardiovascular conditions, and female sex with increased time until PASC recovery [20–22]. However, it remains unclear what factors might predict a better or worse outcome for Neuro-PASC patients.

Given the lack of data regarding Neuro-PASC recovery and the large unmet clinical need, our first aim was to characterize the evolution of Neuro-PASC symptoms. Using a patient-centered approach, we developed the Neuro-COVID Recovery Care Companion (NCRCC) smart phone application, which enabled us to capture fluctuations in Neuro-PASC symptom frequency and identify features associated with improvement in Neuro-PASC. As a second aim, we sought to characterize patients' experience with the NCRCC app to determine its utility for future studies.

Methods

Patients

We enrolled 128 patients who presented to the Neuro-COVID-19 Clinic at Northwestern Memorial Hospital in Chicago, Illinois, between July 2022 and May 2024.

Patients were enrolled in the NCRCC application and consented for the study if they had documented history of SARS-CoV-2 infection and clinical manifestations of Neuro-PASC lasting greater than 6 weeks from COVID-19 symptom onset, had access to a mobile device, and were willing to use the NCRCC application for at least 3 months. Our inclusion of patients presenting 6 weeks after symptom onset was stricter than the CDC or NIH definitions of Neuro-PASC, as those agencies' definitions only required symptoms lasting more than 4 weeks. This study was conducted prior to the release of the National Academies of Science, Engineering, and Medicine (NASEM) definition of Neuro-PASC requiring that symptoms last more than 3 months [4, 23]. In our previous work, we found no differences between our patients presenting ≥ 6 weeks after symptom onset as compared to the > 3 months needed for the WHO or CDC Neuro-PASC definitions [24]. This study received prior approval from the Northwestern University institutional review board (STU00212583).

Procedures

Enrolled patients completed an initial visit and a final visit 3 months later. At each visit, we assessed patients' reported quality of life in cognition, fatigue, sleep disturbance, anxiety, and depression using the validated Patient Reported Outcome Measurement Information System (PROMIS) [25, 26]. Patients also completed an in-person cognitive function evaluation with the National Institutes of Health (NIH) toolbox. NIH toolbox v.2.1 includes assessments of processing speed (pattern comparison processing speed test); attention (inhibitory control and attention test); executive function (dimensional change card sort test); and working memory (list sorting working test) [27–30]. Both PROMIS and NIH Toolbox results are expressed as T-scores, with a score of 50 representing the normative mean/median of the US reference population with a standard deviation of 10. NIH toolbox results are controlled for age, sex, education, race, and ethnicity. Lower cognition T-scores indicate poorer performance, while higher fatigue, sleep disturbance, anxiety, and depression T-scores indicate greater severity.

Finally, patients were also asked about their subjective impression of their percent recovery compared to their pre-COVID-19 baseline, as overarching measurement of their improvement.

To digitally extend the care team and ensure patient confidentiality, the NCRCC was configured from the Epic MyChart Care Companion suite of tools. Patient-entered flowsheets and questionnaires were delivered via frequency-controlled tasks, grouped together by a template which further determined sequence of task delivery and duration of program. Analytics built with Epic Reporting Workbench (RW) complemented the core NCRCC. Combined with an Epic Our Practice Advisory and additional technical configuration, an analytics-driven workflow automated program enrollment. Finally, for care team transparency and analysis, patients were grouped into various adherent and non-adherent analytics via RW.

Patients were enrolled in the NCRCC application and completed a single enrollment questionnaire. Patients then were asked to report their subjective impression of percent recovery compared to their pre-COVID-19 baseline and to complete a daily symptom questionnaire for three months (Fig. 1B). The questionnaire tracked the presence or absence of 12 Neuro-PASC symptoms most

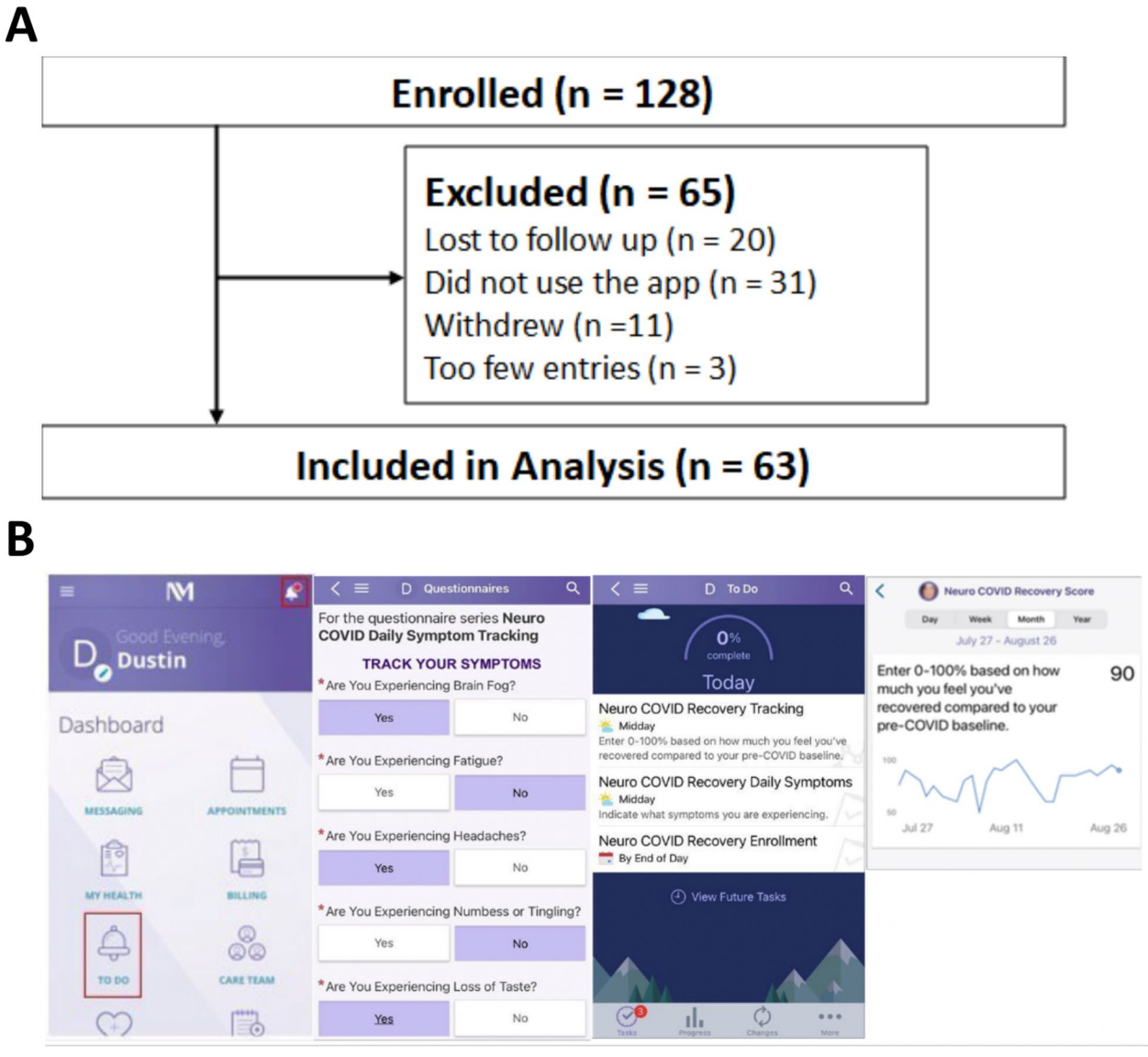


Fig. 1 Flow chart of patient recruitment and Neuro-COVID Recovery Care Companion (NCRCC) Application Design
A Of 128 patients enrolled in the study, 65 were excluded as they were either lost to follow up (LTFU) ($n=20$), did not use the application ($n=31$), had insufficient number of entries for analysis ($n=3$), or withdrew from the study ($n=11$). Sixty-three patients were included in the final analysis. **B** Screen shots of the NCRCC incorporated into the MyNM smartphone application. After the initial enrollment task (here shown for a mock participant), patients can complete symptom questionnaires and percent recovery scores daily, and they can view their recovery scores on a graph over time. A sample of Neuro-COVID recovery score of an actual patient data is shown

commonly seen in our clinic [11, 24, 31, 32]. Patients' usage of the application was tracked through our electronic medical record (EMR).

Patients completed a validated mHealth app user experience questionnaire (MAUQ) [33] at their final 3-month visit, using a 5-point Likert scale to evaluate the NCRCC application for ease-of-use, interface and satisfaction, and usefulness.

Statistical analysis

Data were run through a normality test to determine normality of the distribution, and were then summarized as number of patients (frequency), mean (standard deviation), for normally distributed variables, and median (interquartile range [IQR]) for non-normally distributed variables. Group differences were assessed using unpaired t-tests for normally distributed variables, and Fisher's exact test, Mann–Whitney test, and Kruskal–Wallis tests for non-normally distributed variables. To determine if results of PROMIS and NIH Toolbox domains differed from initial to final visit, patient group T-scores at baseline were compared to patient group T-scores at the final visit using Mann–Whitney tests. We used the Wilcoxon signed ranks test with pairwise Holm-Bonferroni adjustment to determine if the monthly frequency of reported symptoms differed across the three months of application usage. To evaluate the association of patient characteristics with their reported percent recovery, we included those patients with ≥ 4 recordings of the percent (%) recovery score in the NCRCC application in a 3-month period. All data received from these participants were analyzed. Patients were then categorized as "Improvers" or "Non-Improvers". Patients with a statistically significant positive percent recovery slope, determined by linear regression, as well as ≥ 10-point increase from first percent recovery measurement after 3 months were termed "Improvers". Participants were termed "Non-Improvers" if their percent recovery slope was not significantly positive (including statistically negative or zero slopes), and provided they had a < 10-point increase, no change, or decrease in their percent recovery score from first measurement after 3 months.

To capture fluctuations in recovery over the course of the study, variance in percent recovery scores were calculated per individual and is summarized as median variance for the Improvers and Non-Improvers groups. Two-sided $p \leq 0.05$ was considered significant and the above analyses were performed in GraphPad Prism version 9.0.0. Study data were collected and managed using Redcap electronic data capture tools.

To summarize and visualize the multidimensional symptom profiles of the subject cohort and the relationships between the Neuro-PASC symptoms, we performed multiple correspondence analysis (MCA) using those symptoms reported as present in 15% or more patients. MCA results are presented graphically as patient and symptom point clouds in two-dimensional space, defined by the first and second principal component dimensions (the two orthogonal axes with the largest portion of the data inertia, or amount of variation, explained by the component). Three-dimensional graphs were not used to present the MCA analysis because the third principal component dimension neither defined a global constellation of symptom presence nor differed between Improver and Non-Improver groups. In the MCA graphs, points further from the origin have greater influence on the component axes, patients plotted in similar locations in space have similar symptom profiles, and symptom categories with similar profiles of patients are grouped together. MCA was performed using the FactoMineR package in R (R version 4.2.1, Vienna, Austria).

Results

Enrollment

We enrolled a total of 128 patients in the study. Sixty-five patients were excluded for the following reasons: 20 were lost to follow up (unable to contact and/or missed their final appointment), 31 did not use the application, 11 withdrew, and 3 had an insufficient number of data entries for analysis. In total, 63 patients were included in the final analysis.

Percent recovery compared to pre-COVID-19 baseline

We invited Neuro-COVID-19 clinic patients to record their subjective impression of their recovery compared to a 100% pre-COVID-19 baseline daily within the NCRCC application. Individual patient trajectories over a 3 month-period are shown in Fig. 2. Patients were classified retrospectively as "Improvers" or "Non-Improvers," as described in the methods. Most Improvers presented to Neuro-COVID-19 clinic between 3–18 months from symptom onset, whereas Non-Improvers were more evenly distributed up to 35 months from symptom onset. Improvers had greater median variance among their recovery score measures over time compared to Non-Improvers (7.01 vs 3.79; $p = 0.0004$, Fig. 3a), indicating that perceived recovery is associated with greater magnitude of fluctuations over time. As expected, Improvers had a greater, more positive median slope in percent recovery over time than Non-Improvers (5.84 vs 0.00; $p < 0.0001$, Fig. 3b).

Patient demographics & comorbidities

Of all participants, the average age was 45.6 years, with a trend toward older patients in the Improvers group compared to the Non-Improvers group (49.5 vs 42.9 years; $p = 0.06$). Conversely, there was a higher frequency of

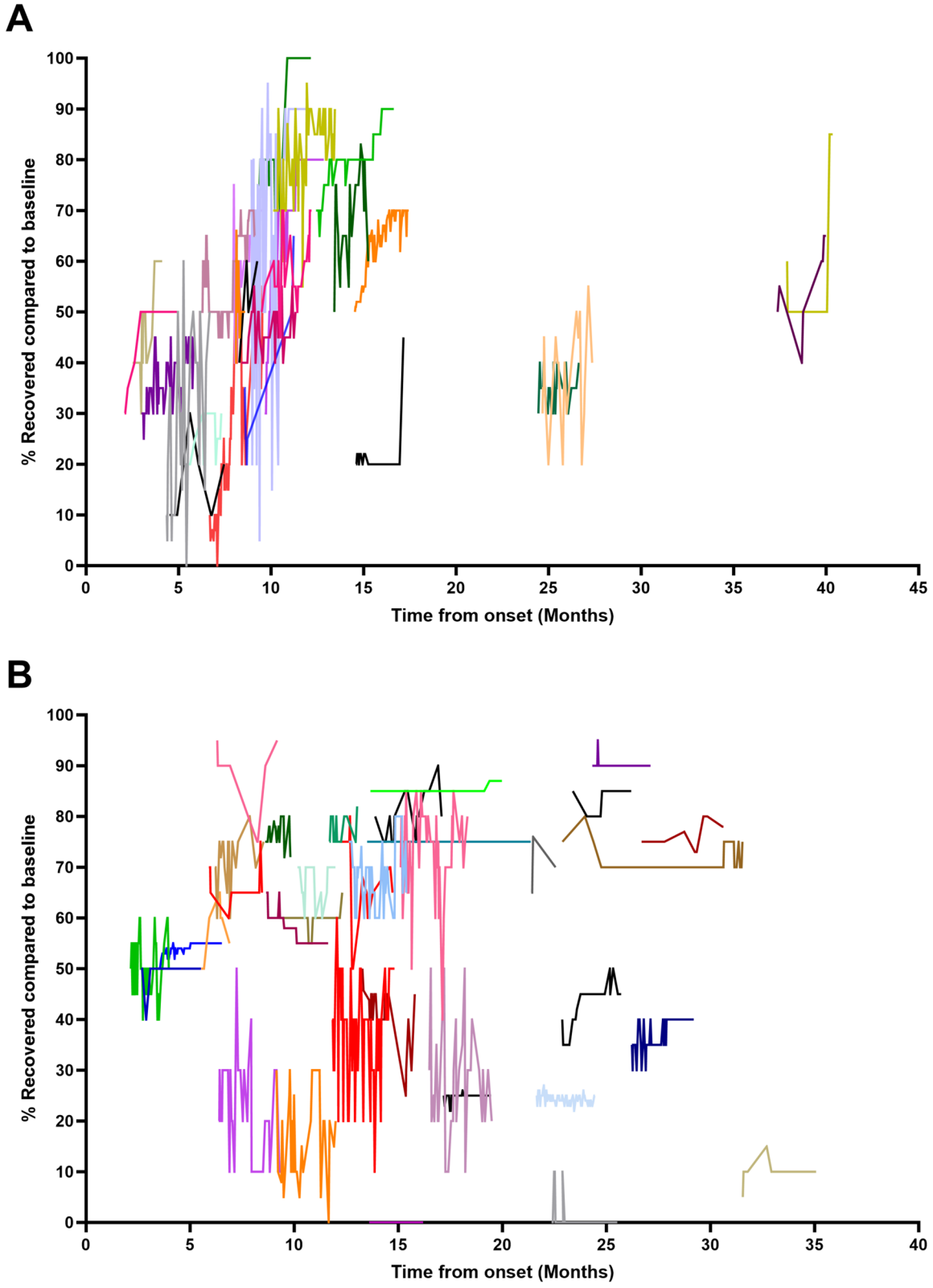


Fig. 2 (See legend on next page.)

(See figure on previous page.)

Fig. 2 Subjective recovery compared to pre-COVID baseline
Patients were divided into Improvers and Non-Improvers. Subjective impression of recovery compared to pre-COVID-19 baseline for Improvers (**A**) and Non-Improvers (**B**). Patients were asked to gauge their recovery daily during a 3-month period and enter it into the application, assuming a pre-COVID-19 baseline of 100%. Each participant is represented by a single line. Patients were designated as Improvers if they had a ≥ 10% improvement in subjective impression of recovery and a statistically significant positive slope (A) or as Non-Improvers if they had < 10% improvement in subjective impression of recovery and a nonsignificant positive slope or a negative slope

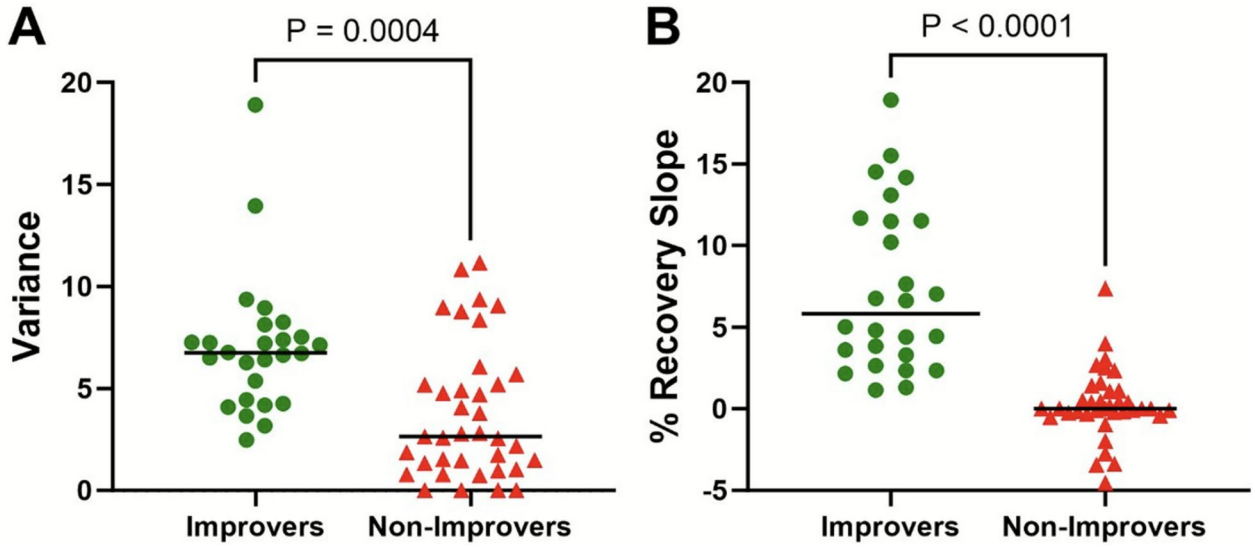


Fig. 3 Comparison of variance and slope of subjective recovery between Improvers and Non-Improvers
Variance (**A**) and Slope (**B**) of subjective impression of recovery compared to pre-COVID-19 baseline over a 3-month period. The variance and the slope of recovery for Improvers was greater than for Non-Improvers. Note that Non-Improvers could have numerically positive but not statistically significant slopes determined by linear regression of their percent recovery to time data

females in the Non-Improvers than in the Improvers group (75.7 vs 50%, $p = 0.04$).

Altogether, 74.6% of participants were White, 4.8% were Black, and 87.6% were not Hispanic, without significant differences between the two groups. Of all patients, 93.7% had never been hospitalized at the time of their acute COVID-19 presentation, without significant difference between Improvers and Non-Improvers. (Table 1). No significant demographic differences were identified between participants who completed the study and those who dropped out (data not shown).

The most prevalent comorbidities overall were depression/anxiety, headache, hypertension, autoimmune disorders, non-type 2 diabetes mellitus endocrine disorders and insomnia. Only non-type 2 diabetes mellitus endocrine disorders were more frequent in Improvers than in Non-Improvers (23.1% vs 2.7%, $p = 0.02$) (Table 2).

Frequency of neurologic symptoms and signs attributed to PASC

Patients were evaluated in our clinic an average of 12.7 months after COVID-19 symptom onset, with Improvers tending to be evaluated sooner than Non-Improvers (10.8 vs 14 mo.; $p = 0.06$). The median number of neurologic symptoms attributed to PASC was 5 and 68.3% reported more than four neurological symptoms. Overall, the most common symptoms were nonspecific cognitive complaints termed "brain fog" (95.2%), headache (69.8%), dizziness (61.9%), myalgia (61.9%), numbness/tingling (54%), tinnitus (46%), blurred vision (42.9%), anosmia (25.4%), and dysgeusia (15.9%), with only anosmia being less frequent in Improvers compared to Non-Improvers (11.1% vs 35.1%, $p = 0.04$).

The most common non-neurologic symptoms included fatigue (95.2%), depression/anxiety (87.3%), insomnia (58.7%), pain other than chest (57.1%), shortness of breath (50.8%), chest pain, 39.7%, gastrointestinal symptoms (nausea, vomiting, diarrhea; 39.7%), with no differences between the two groups (Table 3).

Multiple correspondence analysis

Seventeen symptoms were present in 15% or more of patients at their first visit and were therefore included in the MCAs, as graphically displayed in Fig. 4. Dimension 1 explained 17.5% of the variance while dimension 2 explained 13.3% of the variance; dimension 3 explained an additional 11.0% of the variance but the remaining dimensions explained 8.6% or less of the variance. Five

Table 1 Demographics of improving vs. non-improving Neuro-PASC patients

	Overall	Improvers	Non-Improvers	*p*
n	63	26	37	
Age, years (mean (1 SD))	45.6 (13.6)	49.5 (13.6)	42.9 (13)	0.06
Gender				**0.04**
Female, n (%)	41 (65.1)	13 (50)	28 (75.7)	
Male, n (%)	22 (34.9)	13 (50)	9 (24.3)	
Race, n (%)				0.13
White	47 (74.6)	22 (84.6)	25 (67.6)	
Black or African American	3 (4.8)	0 (0)	3 (8.1)	
Asian	1 (1.6)	0 (0)	1 (2.7)	
Native Hawaiian or Other Pacific Islander	1 (1.6)	0 (0)	1 (2.7)	
Multiracial	1 (1.6)	0 (0)	1 (2.7)	
Other	3 (4.8)	1 (3.8)	2 (5.4)	
Not Specified	7 (11.1)	3 (11.5)	4 (10.8)	
Ethnicity, n (%)				1.00
Not Hispanic or Latino	55 (87.3)	22 (84.6)	33 (89.2)	
Hispanic or Latino	4 (6.3)	2 (7.7)	2 (5.4)	
Not Specified	4 (6.3)	2 (7.7)	2 (5.4)	
Hospitalization Status, n (%)				0.67
Hospitalized	4 (6.3)	1 (3.8)	3 (8.1)	
Non-hospitalized	59 (93.7)	25 (96.2)	34 (91.9)	

P-values that are significant $p < 0.05$ are highlighted in bold

Table 2 Comorbidities of improving vs. non-improving Neuro-PASC patients at initial visit

	Overall	Improvers	Non-Improvers	*p*
n	63	26	37	
Any pre-existing Comorbidity, n (%)				
Depression/anxiety	29 (46)	11 (42.3)	18 (48.6)	0.62
Headache	15 (23.8)	6 (23.1)	9 (24.3)	0.91
Hypertension	13 (20.6)	5 (19.2)	8 (21.6)	0.82
Autoimmune disease	9 (14.3)	6 (23.1)	3 (8.1)	0.14
Other endocrine disorders	7 (11.1)	6 (23.1)	1 (2.7)	**0.02**
Insomnia	7 (11.1)	3 (11.5)	4 (10.8)	1.00
Dyslipidemia	6 (9.5)	5 (19.2)	1 (2.7)	0.07
Type 2 Diabetes	5 (7.9)	3 (11.5)	2 (5.4)	0.64
Lung disease	3 (4.8)	2 (7.7)	1 (2.7)	0.56
Neuropsychiatric disease	2 (3.2)	0 (0)	2 (5.4)	0.5
Cardiovascular disease	2 (3.2)	2 (7.7)	0 (0)	0.17
Traumatic brain injury	2 (3.2)	0 (0)	2 (5.4)	0.5
Cancer	1 (1.6)	0 (0)	1 (2.7)	1
Gastrointestinal disease	1 (1.6)	0 (0)	1 (2.7)	1
Peripheral vascular disease	1 (1.6)	0 (0)	1 (2.7)	1
Cerebrovascular disease	1 (1.6)	1 (3.8)	0 (0)	0.41
Other	37 (58.7)	16 (61.5)	21 (56.8)	0.70

P-values that are significant $p < 0.05$ are highlighted in bold

symptoms had correlation coefficient squared values (r2) with dimension 1 that reached 0.25: blurred vision (0.40), dysautonomia (0.35), fatigue (0.32), neuropathy (0.29), shortness of breath (0.28) with all other symptoms having r2 values between 0.00 and 0.24. For dimension 2, only three symptoms had r2 values exceeding 0.25: anosmia (0.65), dysgeusia (0.61), and insomnia (0.40) with all other symptoms having r2 values below 0.1. For dimension 3, only three symptoms had r^2 values exceeding 0.25: depression/anxiety (0.39), headache (0.37), and brain fog (0.29) with all other symptoms having r^2 values between 0.00 and 0.22. MCA results are displayed in Figs. 4 A-B. Dimension 1 globally separates "yes" from "no" symptom categories (except for dysgeusia, which has only a minor contribution to dimension 1) such that "no" symptom categories have larger dimension 1 values and are towards the right of the graph. Dimension 1 values did not differ significantly for Improver versus Non-Improver groups ($p = 0.52$), suggesting that the groups had a similar frequency of "yes" symptom responses in their global symptom profile. The presence or absence of anosmia and dysgeusia are the predominant contributors to dimension 2, with a lesser contribution from insomnia. In contrast to dimension 1, the Non-Improver group had significantly larger dimension 2 values ($p = 0.023$), suggesting a constellation of symptoms more characterized by dysgeusia, anosmia, and, to a lesser degree, an absence of insomnia. Dimension 3 values did not differ between Improver and Non-Improver groups ($p = 0.90$) and both "yes" and "no" symptom categories were present on either side of the dimension 3 axis. Since Dimension 3 neither globally separates "yes" from "no" symptom categories nor differed between groups, it was not added to Figs. 4A-B. However, MCA graphs of dimension 1 versus dimension 3 and dimension 2 versus dimension 3 are included in Supplemental Figure 2.

Neuro-PASC symptom frequency

We analyzed the frequency of 12 Neuro-PASC symptoms in Improvers vs Non-Improvers using patient-reported data from the NCRCC application. The results are displayed in Fig. 5. The most common symptoms reported in both groups were brain fog and fatigue. While the frequency of some symptoms, notably brain fog and fatigue,

Table 3 Neurologic symptoms and signs attributed to PASC in improving vs. non-improving Neuro-PASC patients

	Overall	Improvers	Non-Improvers	*p*
n	63	26	37	
Time from symptom onset to clinic visit (months, mean [1 SD])	12.7 (8.4)	10.8 (8.42)	14 (8.3)	0.06
No. of neurological manifestation/symptoms attributed to COVID-19 (median, [IQR])	5 (3–7)	5 (3–5)	5 (3–7)	0.14
Neurologic symptoms, n (%)				
≥ 4	43 (68.3)	18 (69.2)	25 (67.6)	0.89
Brain fog	60 (95.2)	24 (92.3)	36 (97.3)	0.56
Headache	44 (69.8)	17 (65.4)	27 (73)	0.52
Dizziness	39 (61.9)	14 (53.8)	25 (67.6)	0.27
Myalgia	39 (61.9)	12 (46.2)	27 (73)	1
Numbness/tingling	34 (54)	14 (53.8)	20 (54.1)	0.99
Tinnitus	29 (46)	15 (57.7)	14 (37.8)	0.12
Blurred Vision	27 (42.9)	11 (42.3)	16 (43.2)	0.94
Anosmia	16 (25.4)	3 (11.5)	13 (35.1)	**0.04**
Dysgeusia	10 (15.9)	2 (7.7)	8 (21.6)	0.10
Seizure	2 (3.2)	1 (3.8)	1 (2.7)	1
Focal motor deficit	1 (1.6)	0 (0)	1 (2.7)	1
Other symptom n (%)				
Fatigue	60 (95.2)	24 (92.3)	36 (97.3)	0.56
Depression/anxiety	55 (87.3)	23 (88.5)	32 (86.5)	1
Insomnia	37 (58.7)	16 (61.5)	21 (56.8)	0.70
Pain other than chest	36 (57.1)	13 (50)	23 (62.2)	0.34
Shortness of breath	32 (50.8)	13 (50)	19 (51.4)	0.92
Chest Pain	25 (39.7)	9 (34.6)	16 (43.2)	0.49
GI symptoms	25 (39.7)	8 (30.8)	17 (45.9)	0.23

P-values that are significant $p < 0.05$ are highlighted in bold

decreased in Improvers over time, there was no statistically significant difference in the monthly frequency of any of the individual symptoms over a 3-month period in either group. Overall symptom burden was not significantly increased in Non-Improvers compared to improvers (45.5% vs. 37.4%, $p = 0.34$).

Quality of life measures and standardized cognitive tests

We analyzed the impact of PASC over a 3-month period on subjective quality of life of Improvers and Non-Improvers with the subjective PROMIS measures, and evaluated their cognition with the NIH toolbox tests, both reported as T scores. The results of the initial and 3-month visit are displayed in Fig. 6. At their initial visit, there were no significant differences between either group for subjective QoL measures (Fig. 6A). However, at the 3-month visit the Improvers reported less sleep disturbance than the Non-Improvers which neared significance (T score 51.2 vs 56.8; $p = 0.06$, Fig. 6B). Similarly, there were no significant differences at initial visit in any of the objective cognitive measures (Fig. 6C) between the two groups. However, at the final visit, there was a trend for Improvers to have higher processing speed compared to Non-Improvers (T-score 67 vs 55.5, $p = 0.06$) (Fig. 6D). There were no differences in percent change in either the PROMIS domains or the NIH Toolbox measures between initial and final visits between the two groups (Supplemental Fig. 1).

User experience with the NCRCC mobile application

Participants completed a validated MAUQ questionnaire [33] at their final 3-month visit, evaluating the application in 3 different domains (ease-of-use, interface & satisfaction, and usefulness) using a 5-point Likert scale. Participants agreed the application was easy to use and satisfactory. Participants somewhat agree that the application was useful. Median ratings did not vary between Improvers and Non-Improvers (Supplemental Table 1).

Discussion

This study aims to fill a key gap in our current knowledge regarding the evolution of Neuro-PASC, a significant unmet clinical need given the unknown natural history of Neuro-PASC to date.

Our data defines characteristics that may be associated with Neuro-PASC patients' recovery trajectory. We and others have shown that women are more often affected by Neuro-PASC than men [11, 34, 35] and accordingly, close to two thirds of our study participants were women. Importantly, our findings indicate that women are also less likely to improve. This is consistent with a study of 97 Neuro-PASC patients a median of 9 months from symptom onset, which found that women are more likely to have persistent executive dysfunction and neurologic symptoms than men [36]. One explanation is that PASC is an autoimmune condition triggered by SARS-CoV-2 infection, associated with autoantibodies and autoreactive T-cells [37–41]. As women are more likely to be affected by autoimmune conditions than men [42–44], it is plausible that women may experience more prolonged suffering from Neuro-PASC.

Interestingly, MCA analysis suggested that the cluster of anosmia, dysgeusia, and a lack of insomnia at initial presentation to the clinic was associated with a lack of self-reported improvement at 3 months. Indeed, anosmia has been shown to persist for up to 1 year in one third of patients [45]. Severe alteration of smell has also been associated with protracted recovery of olfaction [46, 47]. This can be explained by the pathophysiology of anosmia in Neuro-PASC, thought to be due to disruptions of the supporting sustentacular and microvillar cells of

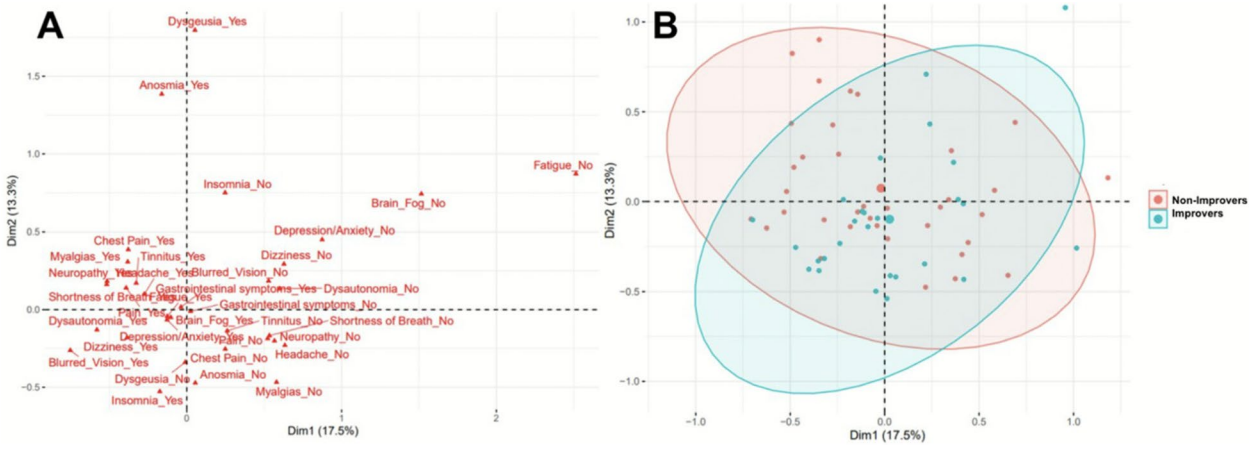


Fig. 4 Multiple Correspondence Analysis of Neuro-PASC symptoms

A Cohort symptoms point cloud. **B** Cohort patient point cloud with Improvers and Non-Improvers group concentration ellipses. Larger-sized points represent the mean values of each respective group's distribution. Increasing distance between the origin and a given symptom category indicates a greater contribution of that category to the pole of the corresponding dimension. Symptom categories with similar profiles of patients are grouped together. Dimension 1 globally separates "yes" from "no" symptom categories (except for dysgeusia, which has only a minor contribution to dimension 1) such that "no" symptom categories with larger dimension 1 values are towards the right of the graph. The Improver and Non-Improver group have similar dimension 1 values ($p = 0.52$), suggesting the groups had a similar frequency of "yes" symptom responses in their global symptom profile. The presence or absence of anosmia and dysgeusia are the predominant contributors to dimension 2, with a lesser contribution from insomnia. In contrast to dimension 1, the Non-Improver group had significantly larger dimension 2 values ($p = 0.023$) than the Improver group, suggesting a constellation of symptoms more characterized by dysgeusia and anosmia and, to a lesser degree, an absence of insomnia

the olfactory mucosa, which remain inflamed long after resolution of COVID-19 [48, 49]. Although persistent alterations in taste and smell may not seem as detrimental to patients' recovery when compared to brain fog and fatigue, they have a profound effect on patient's quality of life [50]. In fact, a retrospective study of patients with post-COVID olfactory impairment found that poor olfactory quality of life was significantly associated with a positive PHQ-2 screen ($p < 0.001$), and therefore with Major Depressive Disorder (MDD) [51]. Quality of life is known to be decreased in hyposmic and parosmic patients vs. normosmic patients [50, 52–54]. This may be due to the unpleasant sensation of foul odors triggered by normally pleasant-smelling items like coffee, perfume, and chocolate [53].

This information suggests that the study participants who presented with anosmia and associated dysgeusia may have been less likely to report improvement due to significant impacts on their quality of life and the lengthy time often required to recover from olfactory deficits. Our finding that a constellation of anosmia, dysgeusia, and lack of insomnia is more characteristic of Non-Improvers highlight the importance of recognizing and acknowledging Neuro-PASC patients' experiences with these symptoms.

Additionally, it is notable that insomnia is a component of Improvers' baseline symptom cluster, and conversely that the absence of insomnia contributes to Non-Improvers' baseline symptom cluster. Insomnia is among the most common long-COVID symptoms [11, 55], and Neuro-PASC patients have delayed sleep latency and poorer sleep efficiency compared to people without Neuro-PASC [56].The presence of insomnia in our improving participants at baseline, coupled with the trend in lessened sleep disturbance in Improvers vs. Non-Improvers at follow up visit, suggests that treating insomnia when present in Neuro-PASC patients could be a key factor in their recovery.

Interestingly, our results showed only a trend toward higher symptom burden in Non-Improvers compared to Improvers, suggesting the symptom burden disparity between these two groups is not a key factor differentiating between the two groups. Rather, variance in self-perceived recovery emerged as a more salient feature differentiating Improvers and Non-Improvers. Variations in Improvers' recovery trajectory were significantly increased compared to Non-Improvers. This is analogous to the pattern seen in post-concussion syndrome [57].

Previous studies assessing long-term Neuro-PASC symptoms with periodic patient evaluations (month to year-long increments) indicate some improvement in persistence and severity of neurological symptoms one year after infection, but most studies do not capture the fluctuations and experience of Neuro-PASC patients [18, 58]. This is the first study to characterize these fluctuations using a mobile application in the Neuro-PASC patient population. Similarly, current mobile applications developed for Neuro-PASC patients in the literature do not address Neuro-PASC symptom tracking or allow the patient to gauge their recovery in real time [59–62]. The

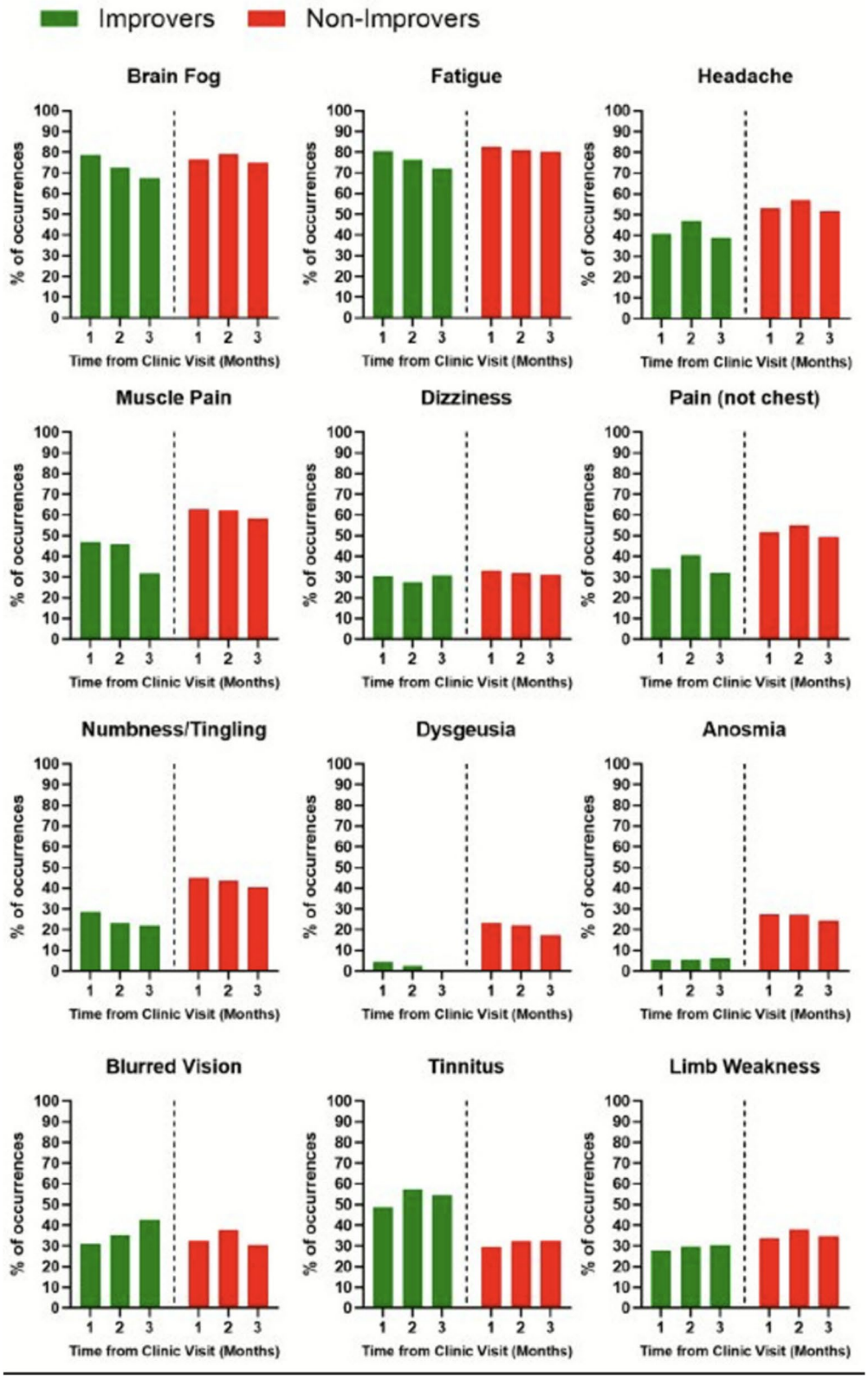
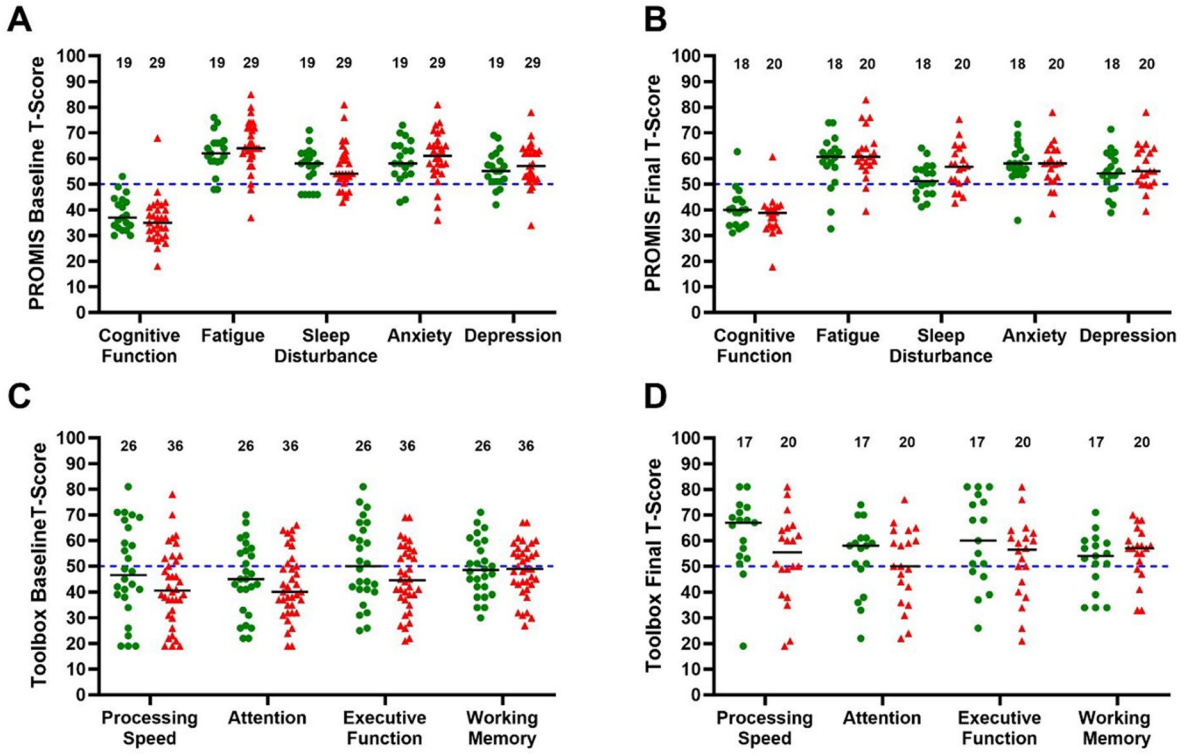


Fig. 5 Relative frequency of Neuro-PASC symptoms logged in the Neuro-COVID Recovery Care Companion Application
Patients were asked to report their Neuro-PASC symptoms over a 3-month period in the NCRCC application. Relative frequency of Neuro-PASC symptoms reported as percentages in 1-month periods in Improvers and Non-Improvers



Assessment Domain	Overall Initial	Improver	Non-Improver	*p*	Overall Final	Improver	Non-Improver	*p*
PROMIS Quality of Life (median (IQR))								
Cognitive Function	36.5 (32-42)	37 (33-44)	35 (29.5-40.5)	0.12	39.1 (34.1-41.6)	40 (34.1-44)	38.9 (33.6-41.1)	0.36
Fatigue	64 (59-71.8)	62 (59-66)	64 (60.5-72)	0.25	60.6 (56.9-64.5)	60.7 (55.1-64.5)	60.6 (57.1-65.4)	0.54
Sleep Disturbance	55.7 (50.8-61.8)	58 (46-62)	54 (51.2-61)	0.69	54.3 (46.8-58.3)	51.2 (46.3-56.1)	56.8 (50.8-63.6)	0.06
Anxiety	60.5 (54.3-65)	58 (54-65)	61 (55.5-66)	0.52	58 (53.5-63.3)	58 (55.1-63.8)	58 (51.6-63.3)	0.60
Depression	57 (52-62)	55.1 (51-61)	57 (52-62.6)	0.33	55 (49.9-62.2)	54.3 (48.4-61.4)	55 (50.1-63.4)	0.54
NIH Toolbox (median (IQR))								
Processing Speed	42.5 (33.8-56.5)	46.5 (37-65.8)	40.5 (31.5-52.8)	0.17	60 (49.5-68.5)	67 (53.5-72)	55.5 (41.5-64.8)	0.06
Attention	43 (32.8-54.3)	45 (32.5-56.3)	40 (32.8-50.8)	0.37	57 (40-61)	58 (43.5-61)	50 (37.5-63)	0.54
Executive Function	45 (38.8-58.3)	50 (40.8-64.8)	44.5 (37.3-55.8)	0.14	57 (45-68)	60 (47-76.5)	56.5 (41-62.5)	0.26
Working Memory	49 (42-57)	48.5 (41.3-59.3)	49 (43-56.5)	0.91	57 (48-60)	54 (42.5-59.5)	57 (49.8-62.3)	0.40

Fig. 6 Quality of life (A & B) and cognitive results (C & D) in Improvers and Non-Improvers at initial and final visit 3 months later
There were no significant differences in initial subjective quality of life domains (6A) and NIH toolbox cognitive tests results (6C) between the two groups. However, Non-Improvers exhibit a trend toward impaired sleep disturbance (6B) and processing speed (6D) after 3 months compared to Improvers

patient's perceived recovery is an important metric to follow going forward, and the NCRCC is the first reported mobile application enabling it.

Our study has limitations. Only 49% of participants who enrolled completed the study. This is slightly greater than other symptom tracking applications for Type 1 Diabetes Mellitus, cancer and MDD, which report attrition rates of 20–49% [63–65]. Additionally, one study of an application for patients with depression reports that 15/18 patients tracked their symptoms < 8% of the days they were evaluated [66]. Our result is not unexpected as Neuro-PASC patients suffer from fatigue and cognitive difficulties, which correlates with an increased study dropout rate [67]. Participants cited exhaustion secondary to Neuro-PASC-related fatigue, difficulty looking at screens, and experiencing a plateau in their recovery score as reasons for their discontinued or reduced engagement with the NCRCC application. Additionally, several patients enrolled at the beginning of the study experienced technical difficulties using the application. These concerns were addressed quickly to minimize loss to follow up, however they may have contributed to the loss of patient follow-up observed early in the study. Other possibilities for decreased engagement with the application include that patients who improve may eventually feel they no longer need to track their experiences, or that patients' frustration caused by their lack of recovery may lead them to abandon the application.

The frequency of NCRCC application use was variable among participants and could not be standardized in this study. To address this concern, symptoms were reported as percentages of overall entries. A third limitation is that patients entered the study at various timepoints from symptoms onset. Further studies extending beyond 3 months are needed to truly understand the evolution of this syndrome. Additionally, given the small sample size (63 participants), larger prospective studies are needed to confirm our findings.

Given the use of self-reported measures in this study, results may be susceptible to recall bias, response bias, and inconsistent interpretation across participants. To address possible differences in question interpretation, the explicit meaning of "percent recovery compared to pre-COVID baseline" was clearly explained during the first visit. Finally, the use of the NCRCC mobile application avoids any recall bias related to symptom tracking, as participants were asked to report their symptoms and subjective impression of percent recovery daily in real time.

Conclusions

This study is the first to define factors associated with recovery from Neuro-PASC, and to characterize the fluctuations involved in the process. This knowledge will allow practitioners to provide Neuro-PASC patients with evidence-based expectations for recovery. Based on our findings, clinicians should consider focusing their efforts on treating Neuro-PASC patients' insomnia.

Neuro-PASC symptoms are known to persist up to 2 years [9, 10]. Further research is needed to decipher Neuro-PASC recovery patterns over time, with frequent observations to accurately characterize patients' lived experience.

This study is also the first-of-its-kind to describe the use of a mobile phone application to evaluate Neuro-PASC recovery. This is a notable milestone, as the larger public has shown interest in using digital technologies to advance scientific knowledge of COVID-19 impacts [68]. Additionally we demonstrate that a user-friendly mobile health application may be successfully integrated into an EMR, providing a platform from which population-scale studies can be conducted to further elucidate the natural history of Neuro-PASC. We hope the NCRCC may serve as a model for similar applications to define recovery from other chronic conditions, equipping and empowering patients on the long and often windy road to recovery.

Abbreviations

PASC	Post-Acute Sequelae of SARS-COV-2 Infection
Neuro-PASC	Neurologic manifestations of Post-Acute Sequelae of SARS-CoV-2 infection
NCRCC	Neuro-COVID Recovery Care Companion
QoL	Quality of life
CDC	Centers for Disease Control and Prevention
NIH	National Institutes of Health
NASEM	National Academies of Sciences, Engineering, and Medicine
PROMIS	Patient Reported Outcome Measurement Information System
MAUQ	Mobile health app user experience questionnaire
IQR	Interquartile range
MCA	Multiple correspondence analysis
MDD	Major Depressive Disorder

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Supplementary Material 3.

Supplementary Material 4.

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Authors' contributions

GL, SB, CJD, DB, DK, IK, contributed to the conception and design of the study. GL, SB, JI, SM, TS, AV, MJ, JM, ML, SB, EL, BH, IK, contributed to acquisition and analysis of data. GL, SB, JI, CJD, MJ, ML, APB, AB, EL, IK contributed to drafting the text or contributed to preparing the figures.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study received prior approval from the Northwestern University institutional review board (STU00212583) in accordance with US federal regulations including 45 CFR 46.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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