Neurologic Manifestations of Long COVID Disproportionately Affect Young and Middle-Age Adults

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Objective: To investigate neurologic manifestations of post-acute sequelae of SARS-CoV-2 infection (Neuro-PASC) in post-hospitalization Neuro-PASC (PNP) and non-hospitalized Neuro-PASC (NNP) patients across the adult lifespan.
Methods: Cross-sectional study of the first consecutive 200 PNP and 1,100 NNP patients evaluated at a Neuro-coronavirus disease 2019 (COVID-19) clinic between May 2020 and March 2023. Patients were divided into younger (18–44 years), middle-age (45–64 years), and older (65+ years) age groups.
Results: Younger and middle-age individuals accounted for 142 of 200 (71%) of PNP and 995 of 1100 (90.5%) of NNP patients. Significant age-related differences in the frequencies of comorbidities and abnormal neurologic findings demonstrated higher prevalence in older patients. Conversely, 10 months from COVID-19 onset, we found significant age-related differences in Neuro-PASC symptoms indicating lower prevalence, and therefore, symptom burden, in older individuals. Moreover, there were significant age-related differences in subjective impression of fatigue (median [interquartile range (IQR)] patient-reported outcomes measurement information system [PROMIS] score: younger 64 [57–69], middle-age 63 [57–68], older 60.5 [50.8–68.3]; $p = 0.04$) and sleep disturbance (median [IQR] PROMIS score: younger 57 [51–63], middle-age 56 [53–63], older 54 [46.8–58]; $p = 0.002$) in the NNP group, commensurate with higher impairment in quality of life (QoL) among younger patients. Finally, there were significant age-related differences in objective executive function (median [IQR] National Institutes of Health [NIH] toolbox score: younger 48 [35–63], middle-age 49 [38–63], older 54.5 [45–66.3]; $p = 0.01$), and working memory (median [IQR] NIH toolbox score: younger 47 [40–53], middle-age 50 [44–57], older 48 [43–58]; $p = 0.0002$) in NNP patients, with the worst performance coming from the younger group.
Interpretation: Younger and middle-age individuals are disproportionally affected by Neuro-PASC regardless of acute COVID-19 severity. Although older people more frequently have abnormal neurologic findings and comorbidities, younger and middle-age patients suffer from a higher burden of Neuro-PASC symptoms and cognitive dysfunction contributing to decreased QoL. Neuro-PASC principally affects adults in their prime, contributing to profound public health and socioeconomic impacts warranting dedicated resources for prevention, diagnosis and interventions.

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As of October 2024, more than 776 million total cases and over 7 million deaths have been reported since the beginning of the global coronavirus disease 2019 (COVID-19) pandemic. This includes more than 103 million total cases with over 1.2 million deaths in the United States (US) alone.[1] For many COVID-19 survivors, post-COVID

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symptoms last long after the initial recovery from acute infection. A recent systematic review and meta-analysis of approximately 200 worldwide studies comprising over 700,000 patients estimated that 45% of COVID-19 survivors still experienced residual and persistent symptoms at ≥1 month after the onset of infection.[2] Symptoms generally appear to improve over time, but may persist for years in some individuals, with 15% of patients continuing to experience symptoms 12 months after the initial infection.[3] This syndrome has been called "post COVID-19 condition", "post-acute sequelae of SARS-CoV-2 infection (PASC)", and most commonly, "long COVID."[4,5] This condition affects people across all sectors of age, gender, race and ethnicity, educational background, socioeconomic status, pre-existing health status, and severity of acute COVID-19.[6,7]

The symptoms attributed to PASC are widespread and multi-systemic, involving constitutional, respiratory, cardiovascular, musculoskeletal, neurologic, psychiatric, and gastrointestinal systems.[8] The neurologic manifestations of PASC, also known as "Neuro-PASC," may be particularly debilitating and contribute to a significant proportion of the morbidity and disability faced by PASC patients. We have previously characterized the symptoms, comorbidities, neurologic exam findings, subjective quality of life (QoL), and objective cognitive performance of our prospective outpatient cohort, which revealed important differences between post-hospitalization Neuro-PASC (PNP) and non-hospitalized Neuro-PASC (NNP) patients.[9]

Prior studies have enumerated the morbidity, decreased QoL, and health care burden associated with PASC.[10–13] Greater understanding of the risk factors involved in the development and severity of PASC is needed to facilitate the formation of sustainable prevention and mitigation strategies. Female sex has consistently shown to be associated with development of PASC.[14–17] The evidence of an association of age with PASC remains a matter of debate, with different studies showing increased frequency with younger age, older age, or no age association.[7,10,12,15] To date, there have been no prospective studies detailing the impact of Neuro-PASC in adults by different age groups.

The aim of this study is to characterize the neurologic manifestations of PASC across the adult lifespan. Because older individuals are at higher risk of neurologic manifestations during acute COVID-19,[18,19] we hypothesized that they may also be more severely affected by Neuro-PASC. We sought to characterize neurologic symptoms, neurologic exam findings, QoL, and cognitive performance among patients with Neuro-PASC in younger, middle-age, and older adults. Such knowledge would help to facilitate risk stratification and prioritize resource allocation for prevention, treatment, rehabilitation, and long-term care in patients experiencing morbidity and disability from Neuro-PASC.

Subjects/Materials and Methods

Patients

We prospectively evaluated all patients seen at the Neuro-COVID-19 clinic of Northwestern Memorial Hospital, in Chicago, Illinois, and undertook a cross-sectional study of the first 1,300 (200 PNP and 1,100 NNP) patients who tested positive for SARS CoV-2, between May 2020 and March 2023. The first 600 patients were previously reported for comparisons of PNP and NNP groups, but not for age-related analyses.[9] Patients were able to schedule their initial appointment via either physician- or self-referral. We accepted patients complaining of any neurologic symptoms associated with SARS-CoV-2 infection for evaluation. Our only exclusion criteria were absence of any neurologic symptoms.

Patients were included in the study if they had: (1) a history of clinical manifestations of COVID-19 consistent with those described by the Centers for Disease Control and Prevention (CDC); (2) positive confirmation of associated infection by SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test collected via nasopharyngeal swab, and/or by subsequent positive serum SARS-CoV-2 total antibody (before COVID-19 vaccinations) or nucleocapsid antibody (before or after COVID-19 vaccinations); and (3) persistent neurological symptoms lasting ≥6 weeks from onset of COVID-19. Our criteria for long COVID or Neuro-PASC were defined before that of the CDC, which includes a symptom duration of ≥4 weeks from onset of COVID-19; and the World Health Organization (WHO), which is defined as "the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation." The study received prior approval by the Northwestern University institutional review board (STU00212583).

Procedures

All patients were evaluated by a board-certified attending neurologist, at times assisted by a neuroimmunology fellow, physician assistant, nurse practitioner, or neurology resident. Patients were seen either in-person or by video-based telehealth visit; the latter included patients from 37 US states. Medical records, including dates of positive SARS-CoV-2 testing, were obtained, reviewed, and recorded ahead of scheduled office visits. All appointments were allotted 1 hour, and recording of medical history was standardized via a "Neuro-COVID Consult" history and physical note template on the electronic medical record at Northwestern Memorial Hospital. Before their visit, patients filled out questionnaires based on the validated patient-reported outcomes measurement information system (PROMIS), leading to reported

measures for QoL domains including cognition, fatigue, sleep disturbance, anxiety, and depression.[20,21] PROMIS measures are reported as T-scores, with lower scores indicating greater severity of dysfunction for cognition, and higher scores indicating greater severity of fatigue, sleep disturbance, anxiety, and depression. Patients were also asked to report their subjective impression of Neuro-PASC symptom recovery at the time of the clinic visit as a percentage relative to a pre-COVID-19 baseline of 100%.

Parts of the neurologic exam (full cranial nerve exam, muscle strength and tone, reflexes, and sensation) were limited during telehealth visits, but full neurologic exams were performed during in-person visits. A more detailed assessment of cognitive function was performed using the National Institute of Health (NIH) Toolbox (version 2.1) for patients who were amenable and able to come to the clinic in-person, either during or within a week after the initial visit.[22–25] The NIH toolbox includes assessments of processing speed (pattern comparison processing speed test), attention (Flanker inhibitory control and attention test), executive function (dimensional change card-sorting test), and working memory (list-sorting working memory test). The results are expressed as T-scores, with a score of 50 representing the normative US reference population with a standard deviation of 10. NIH Toolbox results are additionally standardized across age, sex, education, race, and ethnicity.

Statistical Analysis

Data were 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 Fisher's exact and Chi squared tests for categorical data such as comparisons of sex, race/ethnicity, frequency of signs and symptoms, visit types, and pre-existing comorbidities. Between group differences in continuous variables were assessed using one-way analysis of variance for normally distributed variables and Kruskal-Wallis test for non-normally distributed variables. Relationships between variables were assessed with Pearson's correlation. Patient group T-scores for PROMIS and NIH Toolbox domains are compared to the demographic-matched, normative US population median of 50, using 1-sample Wilcoxon signed-rank tests. Two-sided $p \leq 0.05$ was considered statistically significant. 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 PNP and NNP cohorts and the relationships between the Neuro-PASC symptoms, we performed multiple correspondence analysis (MCA) using those symptoms reported as present in ≥20% of patients. MCA results are presented graphically as patient and symptom point clouds in 2-dimensional space, defined by the first and second principal component dimensions (the 2 orthogonal axes with the largest portion of the data inertia, or amount of variation, explained by the component). 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). We used the post hoc Holm-Bonferroni method to identify statistically significant pair-wise comparison.

Results

Patient Demographics

A total of 1,300 patients were included in the study, including 200 PNP and 1,100 NNP patients with evidence of prior positive SARS-CoV-2 test by RT-PCR, rapid antigen, or serology. Patients were divided into younger (18–44 years), middle-age (45–64 years), and older (65+ years) groups. Middle-age patients constituted the largest PNP group, whereas younger patients predominated in the NNP group. Altogether, younger and middle-age individuals accounted for 142 of 200 (71%) of PNP and 995 of 1100 (90.5%) of NNP patients. The mean age of PNP patients was 55.6 years (35.2, 54.4, and 71.9 years for younger, middle-age, and older groups, respectively), compared to 46.2 years for NNP patients (34.7, 53.9, and 72.6 years for younger, middle-age, and older groups, respectively). There was a difference in age-related sex distribution in NNP patients only (female: younger 64.4%, middle-age 72.2%, older 59%; $p = 0.006$), with the middle-age group having the highest proportion of females (72.2%) versus males (27.8%). The race distribution was consistent with our previous study among PNP and NNP patients, without differences between the age groups, whereas the difference in ethnicity among NNP patients (Hispanic or Latino: younger 12.5%, middle-age, 10.2%, older 4.8%; $p = 0.002$) was driven by the lower frequency of Hispanics in the older group. There were significant differences in the visit types in both PNP (in-person: younger 45%, middle-age, 55.9%, older 69%; $p = 0.03$) and NNP patients (in-person: younger 53.9%, middle-age, 57.6%, older 38.1%; $p = 0.002$). The older PNP group most frequently had in-person visits, whereas the older NNP group most frequently had telehealth visits. Demographics and clinic visit types for PNP and NNP patients are reported in Table 1.

Pre-Existing Comorbidities

As previously noted, the frequencies of different comorbidities significantly vary between PNP and NNP groups.[9] In this study, we further characterized comorbidities among PNP and NNP patients over the adult lifespan. There were significant age-related differences in the frequencies of pre-existing hypertension, dyslipidemia and cancer among both PNP and NNP patients, and type 2 diabetes in NNP patients, driven by a higher prevalence with increasing age group. Conversely, significant

TABLE 1. Demographics in post-hospitalization and non-hospitalized Neuro-PASC patients across the adult lifespan

	Overall PNP	PNP 18–44 yr	PNP 45–64 yr	PNP 65+ yr	*p*	Overall NNP	NNP 18–44 yr	NNP 45–64 yr	NNP 65+ yr	*p*
n (%)	200	40 (20)	102 (51)	58 (29)	**<0.0001**	1,100	542 (49.3)	453 (41.2)	105 (9.5)	**<0.0001**
Age, yr, mean (1 SD)	55.6 (14)	35.2 (7.3)	54.4 (4.9)	71.9 (6.2)		46.2 (14)	34.7 (7.1)	53.9 (5.5)	72.6 (6.11)	
Gender, n (%)					0.2					**0.006**
Male	89 (44.5)	19 (47.5)	39 (38.2)	31 (53.4)		362 (32.9)	193 (35.6)	126 (27.8)	43 (40.9)	
Female	111 (55.5)	21 (52.5)	63 (61.7)	27 (46.6)		738 (67.1)	349 (64.4)	327 (72.2)	62 (59)	
Race, n (%)					0.3					0.26
White	121 (60.5)	27 (67.5)	54 (52.9)	41 (70.7)		823 (74.8)	396 (73.1)	337 (74.4)	90 (85.7)	
Black or African American	41 (20.5)	6 (15)	24 (23.5)	11 (18.9)		87 (7.9)	38 (7)	43 (9.5)	6 (5.7)	
Asian	7 (3.5)	1 (2.5)	5 (4.9)	1 (1.7)		42 (3.8)	26 (4.8)	15 (3.3)	1 (1)	
American Indian/ Alaskan Native	3 (1.5)	0 (0)	2 (1.9)	1 (1.7)		3 (0.3)	0 (0)	3 (0.6)	0 (0)	
Native Hawaiian/ other Pacific Islander	1 (0.5)	0 (0)	1 (0.9)	0 (0)		2 (0.2)	2 (0.4)	0 (0)	0 (0)	
Other	16 (8)	2 (5)	12 (11.7)	2 (3.4)		73 (6.5)	42 (7.7)	26 (5.7)	5 (4.8)	
Multiracial	5 (2.5)	1 (2.5)	3 (2.9)	1 (1.7)		13 (1.2)	6 (1.1)	6 (1.3)	1 (1)	
Not specified	6 (3)	3 (7.5)	1 (0.9)	2 (3.4)		57 (5.2)	30 (5.5)	25 (5.5)	2 (1.9)	
Ethnicity, n (%)					0.45					**0.002**
Not Hispanic or Latino	161 (80.5)	30 (75)	80 (78.4)	51 (87.9)		920 (83.6)	442 (81.5)	381 (84.1)	97 (92.4)	
Hispanic or Latino	33 (16.5)	8 (20)	19 (18.6)	6 (10.3)		119 (10.9)	68 (12.5)	46 (10.2)	5 (4.8)	
Not specified	6 (3)	2 (5)	3 (2.9)	1 (1.7)		61 (5.5)	32 (5.9)	26 (5.7)	3 (2.9)	
Visit type, n (%)					**0.03**					**0.002**
In-person	115 (57.5)	18 (45)	57 (55.9)	40 (69)		593 (53.9)	292 (53.9)	261 (57.6)	40 (38.1)	
Televisit	85 (42.5)	22 (55)	45 (44.1)	18 (31)		507 (46.1)	250 (46.1)	192 (42.4)	65 (61.9)	
SARS-CoV-2 positive, n (%)	200 (100)	40 (100)	102 (100)	58 (100)		1,100 (100)	542 (100)	453 (100)	105 (100)	

Abbreviations: NNP = non-hospitalized neurologic post-acute sequelae of SARS-CoV-2 infection; PNP = post-hospitalization neurologic post-acute sequelae of SARS-CoV-2 infection; SD = standard deviation. *p* values that are statistically significant $p < 0.05$ are highlighted in bold.

differences in the frequency of pre-existing headaches in PNP patients reflected a higher prevalence with decreasing age group. Finally, significant differences in the frequencies of pre-existing autoimmune disease, endocrine disorders other than type 2 diabetes, cardiovascular and peripheral vascular diseases, and chronic kidney disease were found in NNP patients only, driven by a higher prevalence with increasing age group. Pre-existing

TABLE 2. Comorbidities in post-hospitalization and non-hospitalized Neuro-PASC patients across the adult lifespan

	Overall PNP	PNP 18–44 yr	PNP 45–64 yr	PNP 65+ yr	*p*	Overall NNP	NNP 18–44 yr	NNP 45–64 yr	NNP 65+ yr	*p*
n	200	40	102	58	**<0.0001**	1,100	542	453	105	**<0.0001**
Pre-existing comorbidity n (%)										
Hypertension	71 (35.5)	5 (12.5)	34 (33.3)	32 (55.2)	**<0.0001**	175 (15.9)	28 (5.2)	98 (21.6)	49 (46.7)	**<0.0001**
Type 2 diabetes	48 (24)	4 (10)	29 (28.4)	15 (25.9)	0.06	51 (4.6)	7 (1.3)	34 (7.5)	10 (9.5)	**<0.0001**
Dyslipidemia	38 (19)	3 (7.5)	16 (15.7)	19 (32.8)	**0.008**	141 (12.8)	20 (3.7)	77 (17)	44 (41.9)	**<0.0001**
Depression/anxiety	34 (17)	9 (22.5)	17 (16.7)	8 (13.8)	0.54	266 (24.2)	143 (26.4)	103 (22.7)	20 (19)	0.18
Lung disease	30 (15)	4 (10)	16 (15.7)	10 (17.2)	0.65	188 (17.1)	83 (15.3)	89 (19.6)	16 (15.2)	0.17
Autoimmune disease	25 (12.5)	4 (10)	13 (12.7)	8 (13.8)	0.92	134 (12.2)	46 (8.5)	68 (15)	20 (19)	**0.0005**
Cancer	22 (11)	0 (0)	8 (7.8)	14 (24.1)	**0.0003**	61 (5.5)	10 (1.8)	32 (7.1)	19 (18.1)	**<0.0001**
Other endocrine disorders	21 (10.5)	3 (7.5)	10 (9.8)	8 (13.7)	0.13	72 (6.5)	26 (5)	35 (7.7)	11 (10.5)	0.05
Gastrointestinal disease	18 (9)	4 (10)	10 (9.8)	4 (6.9)	0.85	85 (7.7)	40 (7.4)	31 (6.8)	14 (13.3)	0.07
Headache	13 (6.5)	4 (10)	9 (8.8)	0 (0)	**0.02**	150 (13.6)	72 (13.3)	64 (14.1)	14 (13.3)	0.92
Insomnia	8 (4)	4 (10)	3 (2.9)	1 (1.7)	0.12	82 (7.5)	34 (6.3)	40 (8.8)	8 (7.6)	0.31
Cardiovascular disease	8 (4)	0 (0)	3 (2.9)	5 (8.6)	0.09	33 (3)	7 (1.9)	15 (3.3)	11 (10.5)	**<0.0001**
Chronic kidney disease	8 (4)	0 (0)	4 (3.9)	4 (6.9)	0.14	14 (1.3)	2 (0.4)	6 (1.3)	6 (5.7)	**0.0006**
Peripheral vascular disease	5 (2.5)	0 (0)	3 (2.9)	2 (3.4)	0.71	8 (0.7)	1 (0.2)	4 (0.9)	3 (2.9)	**0.02**
Dysautonomia	5 (2.5)	1 (2.5)	3 (2.9)	1 (1.7)	0.2	18 (1.6)	12 (2.2)	4 (0.9)	2 (1.9)	0.22
Cerebrovascular disease	5 (2.5)	0 (0)	2 (1.9)	3 (5.2)	0.34	9 (0.8)	2 (0.4)	5 (1.1)	2 (1.9)	0.13
Neuropsychiatric disease	3 (1.5)	0 (0)	3 (2.9)	0 (0)	0.44	53 (4.8)	27 (5)	22 (4.8)	4 (3.8)	0.96
Traumatic brain injury	3 (1.5)	0 (0)	2 (1.9)	1 (1.7)	1	49 (4.5)	26 (4.8)	20 (4.4)	3 (2.9)	0.79
Neuromuscular disease	1 (0.5)	1 (2.5)	0 (0)	0 (0)	0.2	3 (0.3)	0 (0)	2 (0.4)	1 (1)	0.07
Organ transplant	1 (0.5)	0 (0)	1 (0.98)	0 (0)	1	1 (0.09)	0 (0)	0 (0)	1 (1)	0.09
Other	57 (28.5)	9 (22.5)	28 (27.5)	20 (34.5)	0.43	300 (27.3)	120 (22.1)	119 (26.3)	61 (58.1)	**<0.0001**

Abbreviations: NNP = non-hospitalized neurologic post-acute sequelae of SARS-CoV-2 infection; PNP = post-hospitalization neurologic post-acute sequelae of SARS-CoV-2 infection. *p* values that are statistically significant $p < 0.05$ are highlighted in bold.

comorbidities in PNP and NNP patients are shown in Table 2.

Neurologic Manifestations of Long COVID

There was a significant difference in the time from Neuro-PASC symptom onset to initial clinic visit among the different age groups in NNP patients only (mean ± SD: younger 9.48 ± 6.18, middle-age 10.24 ± 7.01, older 11.61 ± 7.41 months; $p = 0.04$), reflecting a shorter delay in seeking care among younger patients. PNP and NNP patients reported similar subjective impression of recovery compared to a pre-COVID-19 baseline, and there were no significant differences between the age groups. Overall, PNP and NNP patients had a median of 5 neurologic manifestations or symptoms attributed to PASC, with significant age-related differences in PNP patients (median [IQR] number of symptoms: younger 6 [4–8], middle-age 5 [3–7], older 4 [2–6]; $p = 0.001$) and borderline

significance in NNP patients (median [IQR] number of symptoms: younger 5 [3–7], middle-age 5 [3–7], older 4 [3–6]; $p = 0.05$), reflecting a lower number of neurologic symptoms in older patients. Significant age-related differences in the frequencies of neurologic symptoms among age groups were observed for headache in PNP and NNP patients, numbness/tingling, dysgeusia and anosmia in NNP patients, and blurred vision in PNP patients, all reflecting lower prevalence in the older group. This was also the case for non-neurologic symptoms of depression/anxiety in NNP patients, insomnia in PNP patients, as well as chest pain and dysautonomia (self-reported variation of heart rate, blood pressure and/or temperature) in PNP and NNP patients, all driven by lower frequencies in the older age group. These data indicate a lower burden of neurologic and non-neurologic symptoms in older individuals with Neuro-PASC.

Interestingly, the opposite trend was observed on the neurologic exam, with significant age-related differences seen for an abnormal exam in PNP patients, sensory and motor dysfunction in NNP patients, and gait dysfunction in both PNP and NNP patients, driven by a higher prevalence of these findings in the older group. These findings demonstrate an overall increase in abnormal neurologic exam findings among older patients with Neuro-PASC. Neurologic signs and symptoms and other symptoms attributed to PASC in PNP and NNP patients are reported in Table 3A and 3B.

QoL and Cognitive Measures

Subjective QoL measures based on the PROMIS questionnaire were expressed as median scores and are displayed in Figure 1. Higher subjective impairment is reflected by lower scores for cognitive function and higher scores for fatigue, sleep disturbance, anxiety, and depression. We have previously reported decreased QoL measures for all tested domains in both PNP and NNP patients.[9] In the present study, we additionally found significant age-related differences in subjective impression of fatigue (median [IQR] PROMIS score: younger 64 [57–69], middle-age 63 [57–68], older 60.5 [50.8–68.3]; $p = 0.04$) and sleep disturbance (median [IQR] PROMIS score: younger 57 [51–63], middle-age 56 [53–63], older 54 [46.8–58]; $p = 0.002$) in NNP patients, reflecting higher subjective impairment in QoL among the younger group. Those differences in T-scores also translate in difference in categorization: among the NNP group, sleep disturbance T scores of 57 (young) or 56 (middle-age) correspond to "mild dysfunction" (range 56–60), whereas a T-score of 54 (old) remains within normal limits (range 10–55). Similarly, a fatigue T-score of 61 to 70 is considered "moderate," which is the case for young and middle-age group, compared to "mild" for older people in both PNP and NNP groups. There were no significant age-related differences in QoL in PNP.

Objective cognitive performance measures based on the NIH Toolbox assessment were expressed as median scores and are displayed in Figure 1. Worse cognitive impairment is reflected by lower median T-scores for all domains, including processing speed, attention, executive function, and working memory. We have previously reported decreased performance in processing speed, attention, and working memory for PNP patients and in attention only for NNP patients compared to a normative US population. In this study, we additionally found borderline age-related differences in executive function among PNP patients (median [IQR]: younger 36 [29.5–61], middle-age 44 [35–58], older 49.5 [41–56.5]; $p = 0.05$) and significant differences in NNP patients (median [IQR] NIH toolbox score: younger 48 [35–63], middle-age 49 [38–63], older 54.5 [45–66.3]; $p = 0.01$), reflecting worse objective cognitive performance in the younger group. Finally, there were also significant age-related differences in working memory among NNP patients, with the worst performance coming from the younger group (median [IQR] NIH toolbox score: younger 47 [40–53], middle-age 50 [44–57], older 48 [43–58]; $p = 0.0002$). These results suggest that older individuals suffer less disruptions to their QoL and cognitive performance, whereas younger patients experience greater QoL and cognitive impairments, because of Neuro-PASC.

MCA

Seventeen symptoms were reported as present in ≥20% of patients and were, therefore, included in the MCAs, graphically displayed in Figure 2. Interpretation of the MCA graphs in PNP and NNP patients is described in the caption for Figure 2. For the PNP cohort, dimension 1 explained 23.1% of the variance, whereas dimension 2 explained 9.7% of the variance; each of the remaining 15 dimensions explained ≤7.8% of the variance. Six symptoms had correlation coefficient squared values (r^2) with PNP dimension 1 that reached 0.25: dizziness (0.38), myalgias (0.37), pain (0.36), chest pain (0.32), fatigue (0.27), and shortness of breath (0.25), with all other symptoms having r^2 values between 0.13 and 0.22. For PNP dimension 2, only two symptoms had r^2 values exceeding 0.25: anosmia (0.66) and dysgeusia (0.59), with all other symptoms having r^2 values below 0.08. MCA results for PNP patients are displayed in Figure 2A, B.

For the NNP cohort, dimension 1 explained 20.0% of the variance, whereas dimension 2 explained 10.3% of the variance; each of the remaining 15 dimensions explained <8.0% of the variance. Six symptoms had r^2

TABLE 3A. Neurologic symptoms and signs attributed to PASC in post-hospitalization Neuro-PASC (PNP) patients across the adult lifespan

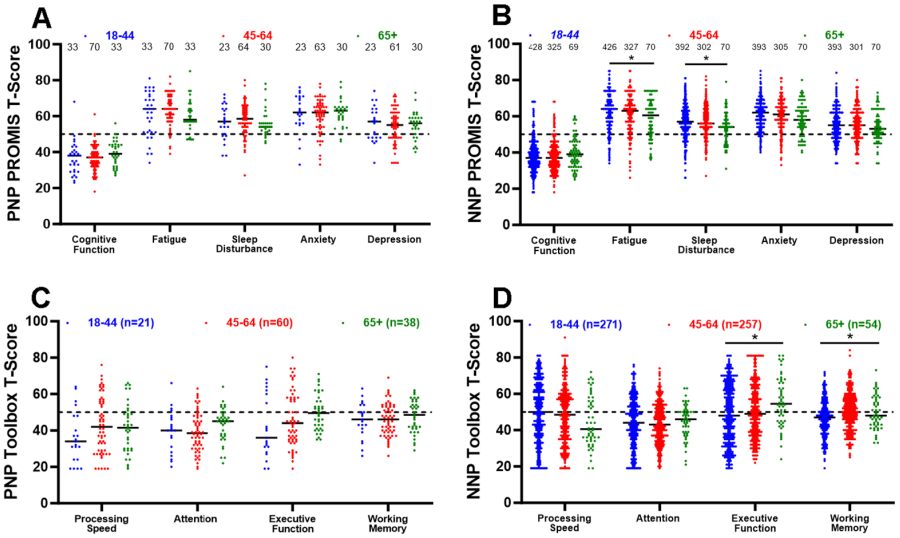
	Overall PNP	PNP 18–44 years	PNP 45–64 years	PNP 65+ years	p
Time from symptom onset to clinic visit (month, mean (1 SD))	9.6 (6.3)	7.6 (5.4)	10.2 (6.3)	10 (6.8)	0.07
Subjective recovery to pre-COVID baseline (mean % (1 SD))	55.6 (25.3)	54.3 (27.8)	57 (23.4)	53.8 (26.9)	0.74
No. of Neuro-PASC symptoms / manifestations (median [IQR])	5 [3–7]	6 [4–8]	5 [3–7]	4 [2–6]	**0.001**
Neurologic symptoms n (%)					
≥4	138 (69)	30 (75)	75 (73.5)	33 (56.9)	0.06
Brain fog	173 (86.5)	34 (85)	91 (89.2)	48 (82.8)	0.49
Headache	113 (56.5)	32 (80)	60 (58.5)	21 (36.2)	**<0.0001**
Numbness/tingling	113 (56.5)	23 (57.5)	63 (61.8)	27 (46.6)	0.18
Dizziness	111 (55.5)	25 (62.5)	60 (58.8)	26 (44.8)	0.14
Myalgia	106 (53)	27 (67.5)	54 (52.9)	25 (43.1)	0.06
Pain other than chest	93 (46.5)	19 (47.5)	53 (52)	21 (36.2)	0.16
Dysgeusia	87 (43.5)	21 (52.5)	45 (44.1)	21 (36.2)	0.27
Anosmia	84 (42)	18 (45)	44 (43.1)	22 (37.9)	0.75
Tinnitus	67 (33.5)	15 (37.5)	38 (37.3)	14 (24.1)	0.2
Blurred vision	60 (30)	14 (35)	36 (35.3)	10 (17.2)	**0.04**
Ischemic Stroke	5 (2.5)	0 (0)	1 (1)	4 (6.9)	0.05
Seizure	4 (2)	3 (7.5)	1 (1)	0 (0)	**0.03**
Movement disorder	2 (1)	2 (5)	0 (0)	0 (0)	**0.04**
Meningitis	2 (1)	1 (2.5)	1 (1)	0 (0)	0.44
Encephalitis	1 (0.5)	0 (0)	1 (1)	0 (0)	1
Focal sensory deficit	1 (0.5)	1 (2.5)	0 (0)	0 (0)	0.2
Focal motor deficit	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Hemorrhagic stroke	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Other symptom *n* (%)					
Fatigue	172 (86)	32 (80)	89 (87.3)	51 (87.9)	0.5
Shortness of breath	140 (70)	30 (75)	76 (74.5)	34 (58.6)	0.09
Depression/Anxiety	137 (68.5)	28 (70)	68 (66.7)	41 (43.1)	0.9
Insomnia	123 (61.5)	29 (72.5)	69 (67.6)	25 (43.1)	**0.003**
Chest pain	80 (40)	20 (50)	46 (45.1)	14 (24.1)	**0.01**
Dysautonomia	67 (33.5)	20 (50)	37 (36.3)	10 (17.2)	**0.002**
GI symptoms	46 (23)	14 (35)	23 (22.5)	9 (15.5)	0.08
Sign n tested/total (%)	190/200 (95)	37/40 (92.5)	96/102 (94.1)	57/58 (98.3)	0.98
Abnormal exam	110 (55)	15 (40.5)	53 (55.2)	42 (73.7)	**0.002**
Memory deficit	68 (34)	12 (32.4)	29 (30.2)	27 (47.4)	0.06
Attention deficit	33 (16.5)	9 (24.3)	15 (15.6)	9 (15.8)	0.52
Sensory dysfunction	32 (16.8)	4 (10.8)	16 (16.7)	12 (21.1)	0.43
Gait dysfunction	31 (16.3)	2 (5.4)	11 (11.5)	18 (31.6)	**0.0007**
Motor dysfunction	22 (11.6)	5 (13.5)	8 (8.3)	9 (15.8)	0.35
Cranial nerve dysf.	7 (3.7)	0 (0)	2 (2.1)	5 (8.8)	**0.04**
Cerebellar dysf.	4 (2.1)	0 (0)	2 (2.1)	2 (3.5)	0.51
Movement disorder	4 (2.1)	3 (8.1)	1 (1)	0 (0)	**0.02**

Abbreviations: COVID = coronavirus disease; dysf = dysfunction; IQR = interquartile range; Neuro-PASC = neurologic post-acute sequelae of SARS-CoV-2 infection; PNP = post-hospitalization neurologic post-acute sequelae of SARS-CoV-2 infection; SD = standard deviation. *p* values that are statistically significant $p < 0.05$ are highlighted in bold.

TABLE 3B. Neurologic symptoms and signs attributed to PASC in non-hospitalized Neuro-PASC (NNP) patients across the adult lifespan

	Overall NNP	NNP 18–44 years	NNP 45–64 years	NNP 65+ years	p
Time from symptom onset to clinic visit (month, mean (1 SD))	10 (6.7)	9.48 (6.18)	10.24 (7.01)	11.61 (7.41)	**0.04**
Subjective recovery to pre-COVID baseline (mean % (1 SD))	57.7 (24.5)	57.9 (24)	57.9 (24.2)	55.9 (28.5)	0.98
No. of Neuro-PASC symptoms / manifestations (median [IQR])	5 [3–7]	5 [3–7]	5 [3–7]	4 [3–6]	0.05
Neurologic symptoms n (%)					
≥4	797 (72.4)	395 (72.9)	338 (74.6)	64 (61)	**0.02**
Brain fog	923 (83.9)	466 (86)	376 (83)	81 (77.1)	0.06
Headache	780 (70.9)	408 (75.3)	315 (69.5)	57 (54.3)	**<0.0001**
Numbness/tingling	456 (41.5)	212 (39.1)	207 (45.7)	37 (35.2)	**0.04**
Dizziness	592 (53.8)	290 (53.5)	247 (54.5)	55 (52.4)	0.91
Myalgia	585 (53.2)	283 (52.2)	250 (55.2)	52 (49.5)	0.47
Pain other than chest	481 (43.7)	227 (41.9)	215 (47.5)	39 (37.1)	0.08
Dysgeusia	535 (48.6)	263 (48.5)	234 (51.7)	38 (36.2)	**0.02**
Anosmia	566 (51.5)	279 (51.5)	247 (54.5)	40 (38.1)	**0.01**
Tinnitus	365 (33.2)	178 (32.8)	157 (34.7)	30 (28.6)	0.48
Blurred vision	346 (31.5)	169 (31.2)	151 (33.3)	26 (24.8)	0.23
Ischemic Stroke	15 (1.4)	3 (0.6)	7 (1.5)	5 (4.8)	**0.005**
Seizure	21 (1.9)	12 (2.2)	9 (2)	0 (0)	0.37
Movement disorder	6 (0.5)	5 (0.9)	0 (0)	1 (1)	0.07
Meningitis	0 (0)	0 (0)	0 (0)	0 (0)	N/A
Encephalitis	1 (0.1)	0 (0)	0 (0)	1 (1)	0.1
Focal sensory deficit	3 (0.3)	0 (0)	3 (0.7)	0 (0)	0.14
Focal motor deficit	2 (0.2)	2 (0.4)	0 (0)	0 (0)	0.6
Hemorrhagic stroke	1 (0.1)	1 (0.2)	0 (0)	0 (0)	1
Other symptom *n* (%)					
Fatigue	963 (87.5)	479 (88.4)	388 (85.7)	96 (91.4)	0.19
Shortness of breath	511 (46.5)	244 (45)	221 (48.8)	46 (43.8)	0.42
Depression/anxiety	763 (69.4)	387 (71.4)	318 (70.2)	58 (55.2)	**0.004**
Insomnia	627 (57)	299 (55.2)	275 (60.7)	53 (50.5)	0.08
Chest pain	334 (30.4)	181 (33.4)	133 (29.4)	20 (19)	**0.01**
Dysautonomia	398 (36.2)	210 (38.7)	167 (36.9)	21 (20)	**0.001**
GI symptoms	299 (27.2)	156 (28.8)	119 (26.3)	24 (22.9)	0.39
Sign n tested/total (%)	1019/1100 (92.6)	507/542 (93.5)	415/453 (91.6)	97/105 (92.4)	0.51
Abnormal exam	406 (39.8)	190 (37.5)	168 (40.5)	48 (49.5)	0.08
Memory deficit	263 (25.8)	127 (25)	106 (25.5)	30 (30.9)	0.47
Attention deficit	116 (11.4)	54 (10.7)	52 (12.5)	10 (10.3)	0.63
Sensory dysfunction	74 (7.3)	23 (4.5)	35 (8.4)	16 (16.5)	**<0.0001**
Gait dysfunction	47 (4.6)	15 (3)	18 (4.3)	14 (14.4)	**<0.0001**
Motor dysfunction	29 (2.8)	12 (2.4)	9 (2.2)	8 (8.2)	**0.003**
Cranial nerve dysf.	22 (2.2)	7 (1.4)	12 (2.9)	3 (3.1)	0.23
Cerebellar dysf.	6 (0.6)	1 (0.2)	4 (1)	1 (1)	0.27
Movement disorder	15 (1.5)	5 (1)	6 (1.4)	4 (4.1)	0.06

Abbreviations: COVID = coronavirus disease; dysf = dysfunction; IQR = interquartile range; Neuro-PASC = neurologic post-acute sequelae of SARS-CoV-2 infection; NNP = non-hospitalized neurologic post-acute sequelae of SARS-CoV-2 infection; SD = standard deviation. *p* values that are statistically significant $p < 0.05$ are highlighted in bold.



Assessment Domain	Overall PNP	PNP 18-44 y	PNP 45-64 y	PNP 65+ y	*p*	Overall NNP	NNP 18-44 y	NNP 45-64 y	NNP 65+ y	*p*
PROMIS Quality of Life (median (IQR))										
Cognitive Function	37 (32-43)	38 (29.25-40.75)	37 (32-40)	39 (32-44)	0.23	37 (32-42)	37 (33-42)	37 (32-42)	39 (33.5-46)	0.2
Fatigue	63 (57-69)	64 (51-71.5)	64 (59-71)	58 (56.5-64.8)	0.08	64 (55.5-69)	64 (57-69)	63 (57-68)	60.5 (50.8-68.3)	**0.04**
Sleep Disturbance	56 (52-63.3)	57 (49-64)	59 (52-65.5)	54 (52-56)	0.22	56 (52-62.3)	57 (51-63)	56 (53-63)	54 (46.8-58)	**0.002**
Anxiety	62 (56-66.5)	62 (56-71)	62 (54-66)	63 (58-65)	0.8	61 (56-65)	62 (56-67)	61 (56-65)	58 (53-65)	0.09
Depression	56 (48-61)	57 (48-64)	55 (48-62)	56 (50-59)	0.8	55 (49-62)	55 (49-62)	55 (49-62)	53 (49-60)	0.37
NIH Toolbox (median (IQR))										
Processing Speed	40 (29-54)	34 (24-48)	42 (29-56)	41.5 (29.8-49.5)	0.24	49 (36-60)	50 (37-63)	48.5 (32.3-59)	40.5 (34-56.5)	0.09
Attention	40.5 (32.75-48)	40 (29.5-47.5)	38.5 (30.5-47.8)	45 (37-49.3)	0.11	44 (36-53)	44 (35-54)	43 (35-52)	46 (38.8-50.3)	0.55
Executive Function	45 (35.8-58)	36 (29.5-61)	44 (35-58)	49.5 (41-56.5)	0.05	49 (37-63)	48 (35-63)	49 (38-63)	54.5 (45-66.3)	**0.01**
Working Memory	47 (39.8-54)	46 (40-54)	46 (39-53)	48.5 (41-56)	0.55	48 (41-56)	47 (40-53)	50 (44-57)	48 (43-58)	**0.0002**

FIGURE 1: Quality of life and cognitive results in post-hospitalization (PNP) and non-hospitalized (NNP) neurologic post-acute sequelae of SARS-CoV-2 infection (Neuro-PASC) patients, ages 18–44, 45–64, and 65+ years. Patient-reported outcomes measurement information system (PROMIS) T-scores for PNP (A), and NNP (B) patients show significant differences in NNP patients in the quality of life (QoL) domains of fatigue and sleep disturbance. National Institutes of Health (NIH) Toolbox T-scores for PNP (C), and NNP (D) patients reveal borderline age-related differences in executive function in the PNP group and significant age-related differences in the NNP group for executive function and working memory.

values with NNP dimension 1 that reached 0.25: myalgias (0.31), dizziness (0.29), blurred vision (0.27), shortness of breath (0.27), pain (0.26), and neuropathy (0.25), with all other symptoms having r^2 values between 0.07 and 0.22. For NNP dimension 2, only two symptoms had r^2 values exceeding 0.25: anosmia (0.80) and dysgeusia (0.79), with all other symptoms having r^2 values below 0.03. MCA results for NNP patients are displayed in Figure 2C, D.

For both PNP (median [IQR]: younger −0.206 [−0.547, 0.315], middle-age −0.102 [−0.414, 0.339], older 0.196 [−0.093, 0.495]), and NNP (median [IQR]: younger −0.015 [−0.313, 0.336], middle-age −0.007 [−0.361, 0.280], older 0.156 [−0.193, 0.482]) cohorts, the older age group had significantly larger dimension 1 values than younger or middle-age patients (post hoc Holm-Bonferroni method, $p < 0.002$ for each pairwise comparison with older age), suggesting that older patients had a global symptom profile with more frequent "no" symptom responses than either middle-age or younger patients. For both PNP and NNP patients, dimension 1 values were not significantly different between younger and middle-age groups and dimension 2 values were not significantly different between any of the age groups.

In view of the different definitions of PASC between the CDC/NIH and WHO, we have also analyzed the PASC symptoms in the 90.1% of our study participants who came to the clinic >3 months from symptom onset, and therefore correspond to the WHO definition of PASC. The data shows similar findings than with our entire study population (Fig S1). Finally, MCA of PASC symptoms of patients evaluated in-person with those seen in televisit showed overlapping ellipses, demonstrating that these two groups were largely identical (Fig S2).

Recovery to Pre-COVID Baseline as a Function of Time from COVID-19 Onset

We aimed to determine whether there was an age-related difference in the subjective impression of recovery in our patient population. Overall, there was no significant relationship between the length of time from COVID-19

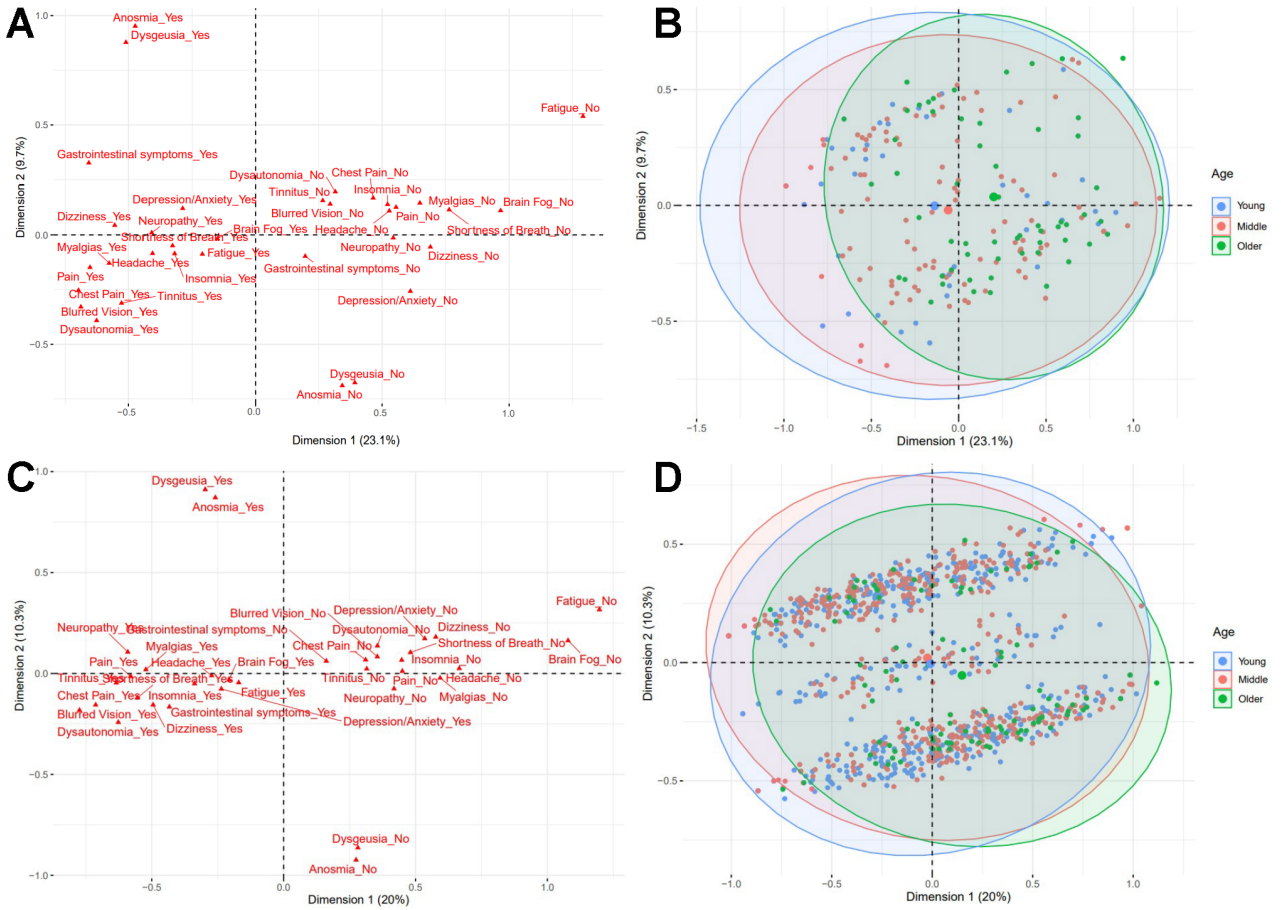


FIGURE 2: Multiple correspondence analysis of neurologic post-acute sequelae of SARS-CoV-2 infection (Neuro-PASC) symptoms across the adult lifespan. (A) Post-hospitalization Neuro-PASC (PNP) cohort symptom point cloud. (B) PNP cohort patient point cloud with age group concentration ellipses. (C) Non-hospitalized Neuro-PASC (NNP) cohort symptom point cloud. (D) NNP cohort patient point cloud with age group concentration ellipses. Larger-sized points represent the mean values of each respective age 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. For both PNP and NNP patients, dimension 1 globally separates "yes" from "no" symptom categories such that "no" symptom categories with larger dimension 1 values are toward the right of the graph. For both PNP and NNP, the presence or absence of anosmia and dysgeusia are the predominant contributors to dimension 2. The predominance of anosmia and dysgeusia in dimension 2, relative to other symptoms, results in a visually stratified patient symptom cloud (particularly for the NNP cohort) such that presence of anosmia and dysgeusia with larger dimension 2 values are toward the top of the graph. For both PNP (median [interquartile range]: younger −0.206 [−0.547, 0.315], middle-age −0.102 [−0.414, 0.339], older 0.196 [−0.093, 0.495]), and NNP (median [interquartile range]: younger −0.015 [−0.313, 0.336], middle-age −0.007 [−0.361, 0.280], older 0.156 [−0.193, 0.482]) cohorts, the older age group had significantly larger values located on the right distal part of dimension 1 than younger or middle-age patient (post hoc Holm-Bonferroni method, $p < 0.002$ for each pairwise comparison with older age) suggesting that older patients had a milder global symptom profile with more frequent "no" symptom responses.

onset and the subjective impression of recovery reported at the time of the initial clinic visit. This was seen among all PNP and NNP age groups (Fig 3).

Discussion

We and others have previously shown that it is crucial to evaluate PNP and NNP patients separately. PNP patients are a decade older, have a higher burden of comorbidities and neurologic findings, and a broader pattern of cognitive dysfunction than NNP patients.[9,26–28] This present study aims to fill a key gap in our current knowledge regarding the impact of age on Neuro-PASC symptoms among both PNP and NNP patients.

Although older age is a risk factor for severe COVID-19 pneumonia requiring hospitalization, the older PNP group comprised less than a third of all PNP patients in our study. Furthermore, the older NNP group contained less than 10% of all NNP patients. These

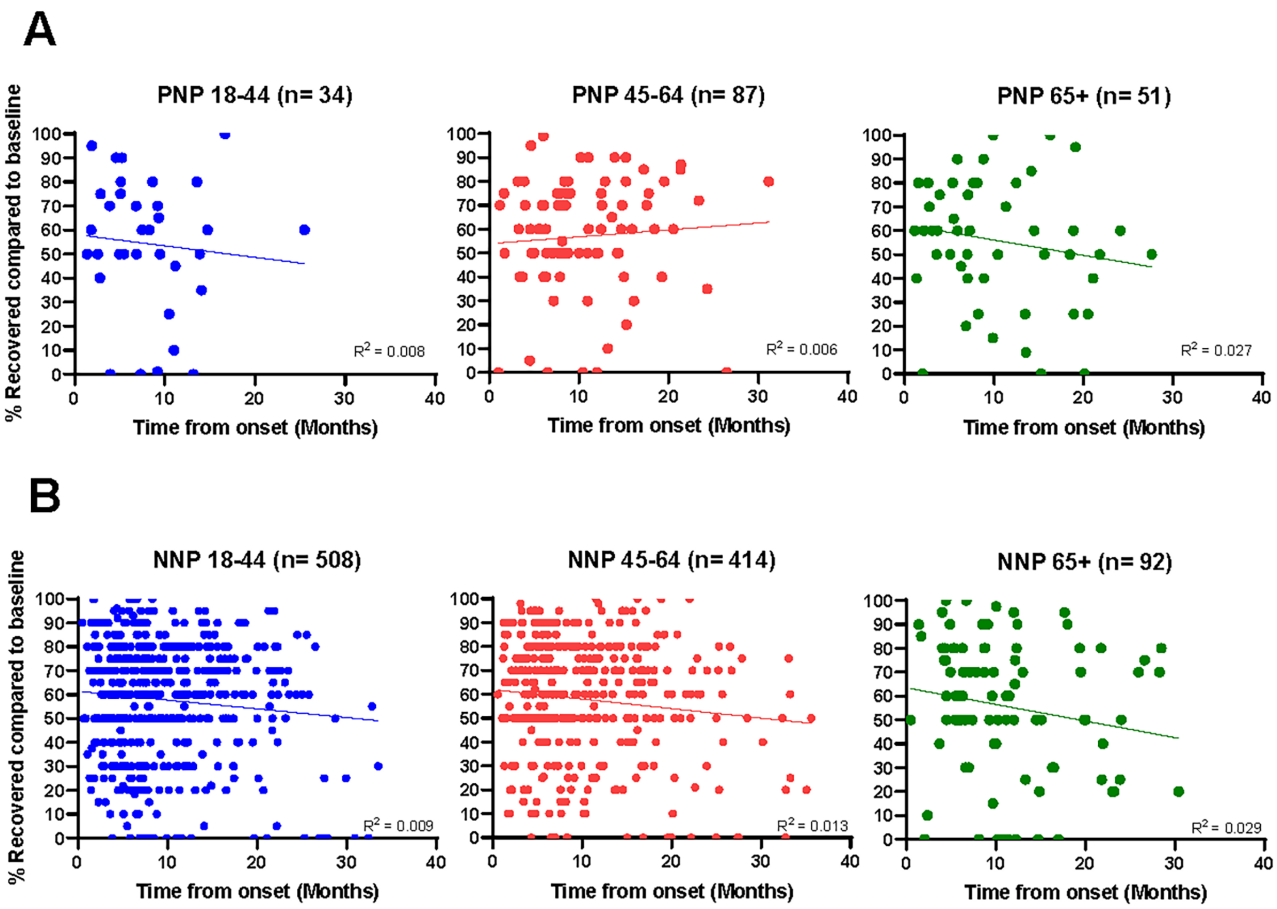


FIGURE 3: Recovery to pre-coronavirus disease (COVID) baseline in post-hospitalization neurologic post-acute sequelae of SARS-CoV-2 infection (Neuro-PASC) (PNP) and non-hospitalized Neuro-PASC (NNP), ages 18–44, 45–64, and 65+ years. Subjective impression of recovery reported at time of clinic visit, compared to pre-COVID-19 baseline of 100%, for all PNP and NNP patients, further stratified by age groups. R^2 values demonstrate no significant relationship between time from COVID-19 onset and percent recovery in PNP and NNP regardless of age group.

results indicate that the majority of Neuro-PASC patients represent the younger and middle-age segments of the adult US population. As expected, the highest burden of pre-existing comorbidities was found in older PNP and NNP patients, who also more frequently had an abnormal neurologic exam. Surprisingly, older PNP and NNP patients had lower frequencies of most neurologic and non-neurologic symptoms attributed to PASC. These results indicate that despite carrying a higher burden of comorbidities and objective neurologic dysfunction, older adults are less frequently affected by Neuro-PASC symptoms than younger age groups, regardless of their hospitalization status during acute COVID-19.

The higher PASC-related symptom burden affecting the younger age groups in our study further translated to worse subjective impression of QoL in domains of fatigue and sleep disturbance in younger and middle-age NNP patients, who also had worse results on tests of executive function than the older group. These results suggest that younger and middle-age adults are more severely affected by subjective alterations of their QoL and by objective cognitive dysfunction attributed to Neuro-PASC than older adults. The singular age-related differences in PASC symptoms were also demonstrated with MCA, which showed that in both PNP and NNP patients, older individuals had a milder phenotype compared to the younger and middle-age groups.

Previous studies have investigated age as a risk factor associated with the development of long COVID.[29] In a retrospective cohort including 388 patients with Neuro-PASC and 149 patients with neurologic sequelae due to influenza, Neuro-PASC was associated with older age.[30] However, in another longitudinal observational cohort including >150,000 COVID-19 patients, people were found to be at higher risk of all neurologic outcomes at 12 months after SARS-CoV-2 infection, regardless of age, compared to uninfected controls.[11] The latter study did show a stronger risk of memory and cognitive disorders, sensory disorders, and other neurologic disorders in younger adults with PASC, whereas older adults had higher risk

of mental health disorders, musculoskeletal disorders, and episodic disorders.

An important confounder for age-related associations in many long PASC studies is the lack of separation of post-hospitalization and non-hospitalized individuals during analyses.[31,32] Because post-hospitalization patients are a decade older than non-hospitalized patients, the predominance of one group over the other in any given population may skew the results if both groups are analyzed together. Furthermore, because PNP and NNP patients differ not only in their demographics, but also in their comorbidities, neurologic symptoms and signs as well as pattern of cognitive dysfunction, admixture of those two groups will hamper any attempt to develop a PASC case definition.[32,33] Another aspect to consider is whether studies report subjective symptoms only, or also objective findings from the neurologic exam. Interestingly, reported sensory Neuro-PASC symptoms of high frequency are consistent with that of a large online survey,[34] but contrast with a lower frequency of corresponding abnormalities on the sensory neurologic exam in our study, reflecting a discrepancy between subjective and objective Neuro-PASC manifestations. Finally, age-related associations with PASC may be biased by the study population. This explains why symptoms of peripheral neuropathy seem more frequent in a study from the Veterans Administration database (mean age of COVID-19 patients = 61.4 year, 89% male, 30.9% of type II diabetes)[11] than in our younger patient population.

Our findings are consistent with data from an ongoing Long COVID Household Pulse Survey, carried out by the National Center for Health Statistics, which provides easily accessible and up-to-date information on PASC trends on the CDC website.[35] As of September 16, 2024, 61.6% of all US adults report that they have had COVID-19. Of these, 29.8% report that they had PASC and 8.7% are still currently experiencing PASC. Most significantly 24.3% of all US adults who currently have PASC report having significant activity limitations because of this condition. Moreover, stratification by age group shows that the frequency of PASC increases from the second to fourth decades and decreases steadily thereafter from the fifth to eight decades. This data is consistent with the higher utilization of the Neuro-COVID-19 clinic by younger and middle-age compared to older adults.

The importance of neurologic complications of COVID-19 have been highlighted recently by the Global Burden of Disease Study, which demonstrated that neurologic disorders are the leading cause of overall disease burden in the world, accounting for at least 443 million disability-adjusted life years (DALYs) and affecting 3.4 billion people (43% of the global population). Of the 37 neurologic conditions in the study, neurologic complications because of COVID-19 were ranked 20th and accounted for 2.48 million global DALYs in 2021.[6] In addition, we have shown that Neuro-PASC is the leading cause of consultation at our multispecialty Comprehensive COVID Center, accounting for 49% of all outpatient clinic visits, ahead of pulmonology (25%), cardiology (12%), and nine other specialty clinics.[8] Together, these data indicate that neurologic manifestations are also the leading contributor of disease burden and disability among all people suffering from PASC.

Our study also has far-reaching implications for public health. Because younger and middle-age people are the most frequently and severely affected by Neuro-PASC, whether this could potentially translate into a higher or earlier incidence of subsequent cognitive impairment and neurodegenerative diseases in this population is a matter of serious concern for our clinic patients. A study of electronic medical records of 35,362 COVID-19 outpatients in Denmark showed an increased relative risk (RR) of 3.5 for Alzheimer's disease and 2.6 for Parkinson's disease compared to outpatients who did not have COVID-19.[36] A meta-analysis of 12 studies including 2.6 million post-COVID-19 cases and 30.4 million controls showed a significant association between SARS-CoV-2 infection and increased risk of new-onset Alzheimer's disease (HR = 1.50), dementia (HR = 1.66), and Parkinson's disease (HR = 1.44) among COVID-19 survivors.[37] Potential mechanisms triggering or accelerating neurodegeneration may include persistent inflammation, immune dysregulation, mitochondrial dysfunction, and/or endotheliopathy.[38,39] These mechanisms may be enhanced in younger people who display a more robust inflammatory response unique to COVID-19,[40] whereas they may be less prominent in older individuals secondary to immunosenescence.[41] However, the full impact of PASC in the development of neurodegenerative diseases may not be known for decades, as the current population of younger and middle-age adults affected by Neuro-PASC reaches old age.[42,43]

Our study has the following limitations. First, our definition of PASC differed from the CDC/NIH and WHO definitions regarding duration of symptoms (6 weeks in our study, compared to 4 weeks for CDC/NIH and 3 months for WHO). However, our definition had already been established before that of either of these organizations, and >90% of our patients fit the WHO definition. Moreover, all participants fit the CDC/NIH criteria. Next, outside of the MCA, our statistical analyses did not adjust for multiple covariates. This is because of

the exploratory nature of this first-of-its-kind study aiming at guiding further investigations, because those adjustments may increase the type II error for those associations that are not null.[44,45] Like all studies researching diseases in the health care setting, the patients included in this report are those who chose to seek care at our Neuro-COVID-19 clinic. This selection bias also applies to other research settings including online questionnaires and may be influenced by multiple factors including geographic location, technological access, and socioeconomic status. To facilitate access to care, we did not require physician referral and opened the clinic to patients either in-person or by telehealth visits. Therefore, our study population coming from 37 states is representative of those who seek care at post-COVID clinics in the entire United States. We have found no evidence that this self-referral bias leads to a younger age-based skew in our Neuro-COVID-19 clinic patients. The average age of our NNP group is 46 years old, which is similar to the average age (45 years) of the entire patient population of the Comprehensive COVID Center at Northwestern Medicine that comprises 12 specialty clinics.[8] It is also identical to the average age (46 years) in a newly published study from the RECOVER cohort with 8,746 PASC patients, including 91% who were non-hospitalized, recruited from 83 sites from 33 US states plus Washington DC and Puerto Rico.[46] Although we used a uniform template for all our patients, those who came via telehealth visits had a limited neurologic examination compared to those evaluated in person. Principal component analyses performed in our previous study demonstrated that these two groups were largely identical.[9] We could not test a control group of individuals without COVID-19 for cognitive and QoL measures because of the limitations on human subjects' research during the pandemic. Therefore, we used PROMIS and NIH toolbox measures that have been extensively validated for neurologic research and include normative data from large US populations. Although the NIH Toolbox test was performed in-person under direct supervision, patients answered computer-adaptive PROMIS questionnaires ahead of the clinic visit. PROMIS questionnaires have been designed to be answered independently and do not require investigator supervision. A recent study tested PROMIS cognition screeners for the Medicare annual wellness visit and used them either before or at the time of the visit interchangeably.[47] Finally, we were not able to determine possible age-related effects of different SARS-CoV-2 variants on Neuro-PASC, because there was no method to retrospectively confirm the exact viral strain for each patient, given this testing was not routinely performed within our institution.

Conclusions

Together, these data refute our initial hypothesis that the burden of Neuro-PASC will be greater for older adults. Our study demonstrates the opposite finding that younger and middle-age patients with Neuro-PASC are more severely affected than older patients, regardless of the severity of their acute COVID-19 and hospitalization status. We showed that younger and middle-age patients suffer from a higher burden of neurologic symptoms, fatigue, sleep disturbance, and cognitive dysfunction contributing to decreased QoL, compared to older patients with Neuro-PASC. However, older Neuro-PASC patients more frequently have abnormal findings on their neurologic exam, likely corresponding with a higher burden of pre-existing comorbidities. This is the first cross-sectional study to report an association of neurologic manifestations of PASC with young and middle age. Longitudinal studies are needed to truly capture the duration and fluctuation of Neuro-PASC over time.

These findings have immense public health impact given that Neuro-PASC significantly contributes to the leading global burden of disability and disease caused by neurologic disorders. The impact of this condition causing disproportionate morbidity and disability in younger adults in their prime, who provide much of the workforce, productivity, and innovation in our society, may lead to critical issues of increased health care system burden, mental health crisis, socio-cultural deterioration, and economic recession.

Continued identification and risk stratification for factors contributing to the development and severity of PASC is vital to minimizing and improving the disease and disability burden of this condition, which remains a significant global public health threat. Resources and efforts for prevention, detection/diagnosis, treatment/palliation, and rehabilitation should be increasingly focused on groups disproportionately affected by this condition.

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Author Contributions

N.C., S.M., T.C., A.V., A.B., E.L., and I.K. contributed to the conception and design of the study; N.C., S.M., T.C., A.V., G.P.G., M.J., J.M., M.L., B.H., A.P.B, A.B.,

E.L., and I.K contributed to the acquisition and analysis of the data; N.C., M.J., M.L., B.H., A.B., E.L., and I.K. contributed to drafting the text or contributed to preparing the figures.

Potential Conflict of Interest

Nothing to report.

Data Availability

Deidentified data will be deposited in the COVID-19 Neuro Databank after publication.

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