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Neurocognitive Profiles in Patients With Persisting Cognitive Symptoms Associated With COVID-19

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Abstract

Objective: A subset of individuals with coronavirus disease 2019 (COVID-19) appears to develop persisting cognitive and medical symptoms. Research in the acute stages of illness, generally utilizing cognitive screening measures or case reports, suggests presence of deficits in attention and executive function. This observational study investigated cognitive functioning among individuals with persistent cognitive complaints about 5.5 months after COVID-19 infection.
Methods: Patients with polymerase chain reaction confirmed COVID-19 and persistent cognitive complaints underwent comprehensive in-person neuropsychological evaluations. Patients with prior neurological disorders were excluded. When diagnosed, 40% required hospitalization, 15% were in an intensive care unit, 10% needed mechanical ventilation, and 10% experienced delirium.
Results: This sample was predominately women (90%), White non-Hispanic (70%), with average education of 15 years. Mild cognitive deficits were seen on tests involving attention and processing speed or executive function. Seventy percent of patients were diagnosed with a mood disorder prior to COVID-19 infection. At the time of testing, 35%–40% endorsed moderate to severe mood symptoms and 85% noted significant fatigue as measured by the Fatigue Severity Scale.
Conclusions: The pattern of cognitive deficits, although mild, is consistent with prior research at the acute stage of the illness. These findings suggest that psychological factors and other persisting symptoms (e.g., sleep, fatigue) may play a significant role in subjective cognitive complaints in patients with persisting complaints post COVID-19 who did not require intensive treatment. These patients would likely benefit from resources to manage persisting or new mood symptoms and compensatory strategies for the cognitive inefficiencies they experience.

Keywords: COVID-19; Long COVID; Cognition; Neuropsychology; Brain fog

Introduction

Since the first cases were initially reported in December 2019, Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2; also known as coronavirus disease 2019 [COVID-19]) has affected life worldwide. As of this writing, over 250 million infections and over 5 million deaths related to the virus have been reported.

Common symptoms include shortness of breath, fatigue, headache, and loss of sense of taste or smell, although presentation varies. Likewise, the disease course also appears variable, as some individuals may be asymptomatic, whereas others experience severe illness that may progress to death. Factors underlying a more severe or protracted disease course are uncertain, but may relate to preexisting health conditions (e.g., pulmonary disease, cardiac conditions), male sex (Viveiros et al., 2021), and a recent

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work that has estimated that up to 80% of patients with COVID-19 may show persistent symptoms beyond the period of acute infection (Lopez-Leon et al., 2021).

Although not consistent, some individuals have had neurological manifestations that have been attributed to COVID-19, including stroke or persistent cognitive impairment (Arenivas, Carter, Harik, & Hays, 2020; Collantes, Espiritu, Sy, Anlacan, & Jamora, 2021; Mao et al., 2020; Taquet, Geddes, Husain, Luciano, & Harrison, 2021). To this point, little information exists regarding cognitive function in survivors of COVID-19. Recent research has documented cognitive functioning using brief screening measures, such as the Montreal Cognitive Assessment (MoCA) or Mini Mental Status Examination (MMSE). One such study reported a higher rate of decline on MoCA among individuals who were seropositive for COVID-19 when compared with individuals who were seronegative (Del Brutto et al., 2021). A second study examined performance on MoCA and the Frontal Assessment Battery (FAB) among 13 inpatients diagnosed with severe COVID-19 who were in the post-critical acute phase of the illness (Beaud et al., 2021). The authors described two cognitive profiles that emerged from their data: normal cognitive function, with relative weaknesses in executive functions, and more globally impaired performance on MoCA, with relatively preserved orientation and language. Alemanno et al. (2021) identified cognitive impairment in 80% of inpatients infected with COVID-19 using MoCA and MMSE, whereas Ortelli et al. (2021) reported significantly lower scores on MoCA, as well as brief measures of cognitive control and executive function, among patients with COVID-19 relative to healthy controls. Using the Modified Telephone Interview for Cognitive Status, Woo et al. (2020) found that patients recovering from COVID-19 scored significantly lower than healthy controls, particularly on measures of short-term memory, attention, and concentration/language. Jaywant et al. (2021) used the Brief Memory and Executive Test to examine cognitive function in 57 medically stable inpatients recovering from COVID-19. Attention and executive functions were the most common areas of deficit identified. Miskowiak et al. (2021) examined performance on the Screen for Cognitive Impairment in Psychiatry and the Trail Making Test in 29 individuals who had recovered from COVID-19. They found that the majority of patients (59%–65%) had cognitive impairment 3–4 months following hospital discharge. Altogether, available data suggest that COVID-19 infection can be associated with cognitive dysfunction, even months after the acute illness.

Although research using brief cognitive screening tools has been more common, studies utilizing more thorough cognitive evaluations of COVID-19 survivors have been rare. A recent study reported results of a full neuropsychological battery administered over the telephone to three inpatients who had severe COVID-19 symptoms and underwent intensive care unit (ICU) stays (Whiteside et al., 2021). Findings suggested impairments in memory encoding and verbal fluency, as well as new-onset psychiatric symptoms (i.e., depression, anxiety). Using a brief, iPad-based cognitive battery focused on attention and processing speed, Zhou et al. (2020) found evidence of slower reaction times and poorer vigilance among individuals who had recovered from COVID-19 in China, which were hypothesized to be related to inflammatory processes. A study from Spain examined neuropsychological performance in 35 patients with COVID-19, which revealed impaired scores in memory, attention/working memory, verbal fluency, and mental flexibility (Almeria, Cejudo, Sotoca, Deus, & Krupinski, 2020); however, patients over age 60 were excluded from the analyses. Additionally, results from a large web-based study ($N = 81{,}337$) found cognitive deficits among individuals who reported confirmed or suspected COVID-19 infection, even in those who were no longer symptomatic and after controlling for many confounding variables (Hampshire et al., 2021). Findings provide evidence of persistent cognitive changes in survivors of COVID-19. Despite these efforts, however, there are little data describing the cognitive profile of individuals who have been infected with COVID-19 in the more chronic stages of recovery. Such data would be informative in identifying risk factors for cognitive impairment following COVID-19 infection as well as the cognitive domains that are most commonly affected.

The goal of this study was to document cognitive function among individuals recovering from COVID-19 who were subsequently seen for comprehensive in-person neuropsychology evaluations in an academic medical center setting. We examined neuropsychological performance in patients with new-onset cognitive complaints following COVID-19 diagnosis with no prior cognitive concerns. We additionally aimed to identify factors that were associated with outcomes, including preexisting health conditions and severity of COVID-19 illness.

Methods

Study design and setting

This observational study included patients with a history of COVID-19 who were seen for outpatient neuropsychological evaluation at an academic medical center between September 2020 and April 2021. Referral sources included Neurology ($n = 2$), Memory Disorders Clinic ($n = 5$), and a multidisciplinary clinic for patients with post-acute sequelae of COVID-19 ($n = 13$).

Patients

Inclusion criteria for this study were adults over age 18 years who were diagnosed with COVID-19 from a polymerase chain reaction (PCR) test. All patients underwent neuropsychological evaluation for subjective cognitive concerns. Exclusion criteria were major preexisting neurological conditions that can affect cognitive functioning (e.g., Parkinson's disease, traumatic brain injury, multiple sclerosis, brain tumor, stroke, epilepsy, and autoimmune disorders), and suboptimal task engagement based on formal and embedded performance validity tests (Slick 1997).

Additional variables of interest

Other relevant variables were collected that were thought to potentially contribute to cognitive outcomes include age, sex, duration of hospitalization, duration of ICU stay, use of supplemental oxygen, use of mechanical ventilation, presence of acute delirium, and historical psychiatric diagnoses. Relevant past medical histories were also collected, including history of sleep apnea, chronic respiratory conditions, diabetes, hypertension, hyperlipidemia, and coronary artery disease. Neuroimaging is also a variable of interest; however, as patients were assessed for clinical purposes, few underwent neuroimaging and thus, this variable was excluded from further analyses. Finally, patients were administered self-report measures to assess for depression (Beck Depression Inventory-Second Edition; Beck, Steer, & Brown, 1996), anxiety (Beck Anxiety Inventory; Beck & Steer, 1993), and fatigue (Fatigue Severity Scale [FSS]; Krupp, LaRocca, Muir-Nash, & Steinberg, 1989).

Neuropsychological testing

Participants were administered a standardized neuropsychological battery. Memory measures included Wechsler Memory Scale- IV (WMS-IV) Logical Memory (Pearson 2009; Wechsler, 2009), Rey Auditory Verbal Learning Test (Rey, 1964), and Brief Visuospatial Memory Test-Revised (Benedict, 1997). Language tests included the Reading subtest from the Wide Range Achievement Test-IV (Wilkinson & Robertson, 2006), Boston Naming Test-Second edition (Delis, Kaplan, & Kramer, 2001; Kaplan, Goodglass, & Weintraub, 2001), and lexical and semantic verbal fluencies (Goodglass & Kaplan, 1972; Spreen & Benton, 1977). Visuospatial testing included Judgment of Line Orientation (Benton, Hamsher, Varney, & Spreen, 1983). Attention and executive functioning measures included Digit Span, Matrix Reasoning, and Similarities subtests from the Wechsler Adult Intelligence Scale-IV (WAIS-IV; Wechsler, 2008), DKEFS Color-Word Interference (Delis et al., 2001), Trail Making Test (Reitan & Wolfson, 1985), Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and Conners Continuous Performance Test-3 (Conners, 2014). Processing speed was measured through Coding and Symbol Search subtests from the WAIS-IV (Wechsler, 2008) and the Symbol Digit Modalities Test (Smith, 1982); however, other tests mentioned earlier (e.g., Trail Making Test) also include a processing speed component.

Data analysis. Neuropsychological data were converted from raw scores to standardized scores (e.g., T-scores) based on published normative data. Scores that were 1.5 *SD* or more below the mean were considered "impaired" for the current purposes.

Results

Patient descriptives

Demographic information for the sample is included in Table 1. The initial sample included 40 patients. Twelve patients were excluded due to preexisting neurological/medical conditions (i.e., s/p left ventricular assist device placement, deep brain stimulation device placement, autoimmune disorder, multiple sclerosis, Parkinson's disease, epilepsy, and amnestic mild cognitive impairment). Five patients were excluded due to lack of PCR-confirmed COVID diagnosis. Three were excluded for suboptimal task engagement based on performance validity testing (i.e., failed two standalone task engagement measures). This final sample included 20 patients.

Patients were an average age of 45 years and the majority were women (90%), White Non-Hispanic (70%), with an average of 15 years of formal education. Ninety percent of patients were employed—nine patients were healthcare workers and three others worked in the medical field (lab analyst, claims examiner, and medical sales). All patients were right hand dominant. On average, patients had a positive test 168 days before their neuropsychological evaluation, although there was significant variability ($SD = 69.3$ days, range 79 to 320 days). Neuropsychological evaluations took place between September 2020 and

Table 1. Patient descriptors ($n = 20$)

Age (years)	M = 44.75 (*SD* = 10.8); Range 25–65
Sex	90% women
Race/Ethnicity	70% White Non-Hispanic
Education (years)	M = 15.2 (*SD* = 2.6); Range 10–19
Handedness	100% Right-Handed
LOT between COVID-19 positive test and NP Evaluation (days)	168.2 (*SD* = 69.3); Range 79–320

Note: LOT: length of time, NP: neuropsychological, COVID-19 positive test: PCR confirmed COVID-19

Table 2. Prior medical and psychiatric comorbidities

Diagnosis	% of Patients
Depression	50%
Anxiety	45%
Hypertension	40%
Obesity	25%
Migraine Headache or Chronic Headache	25%
Hyperlipidemia/Hypercholesterolemia	25%
Diabetes	20%
Asthma	20%
Other Mental Health Diagnosis	15%
Obstructive Sleep Apnea	10%
Degenerative Disc Disease	10%
Hashimoto Disease/Hypothyroidism	10%
Remote Concussion	10%
Lung Mass	5%
Chronic Kidney Disease	5%
Vitamin B12 Deficiency	5%
Rheumatoid Arthritis	5%
Anemia	5%
Lipid Metabolism	5%
Fatty Liver Disease	5%
Constipation	5%
Pulmonary Embolism	5%
Vertigo	5%

April 2021. Three patients had at least one dose of the COVID vaccine before neuropsychological testing. Thirteen patients were not vaccinated at the time of evaluation. Vaccine status is unknown in remaining four patients.

Prior medical and mental health comorbidities

According to medical chart review, 85% of patients had a previous medical and/or mental health diagnosis before testing positive for COVID-19, with most common diagnoses of depression (50%), anxiety (45%), hypertension (40%), obesity (25%), migraine headache or chronic headache (25%), and hyperlipidemia/hypercholesterolemia (25%). Notably, 70% of patients were diagnosed with depression or anxiety disorders prior to COVID-19 infection (some had both), which suggests only 30% of patients did not have a mental health diagnosis prior to COVID-19 infection. For a complete list of all prior medical and psychiatric comorbidities, please see Table 2.

Persistent symptoms following COVID-19 infection

As part of their broader medical workup, patients were asked about commonly reported COVID-19-related symptoms during their initial visit with a medical health professional. Among the sample of patients referred to neuropsychology, the two most commonly reported persistent symptoms included cognitive symptoms, specifically memory deficits (95%) and lack of concentration/brain fog (85%). Other common symptoms included fatigue (75%), exertional intolerance (65%), exhaustion/prolonged fatigue (60%), and shortness of breath or dyspnea on exertion (60%). One patient developed seizures after COVID-19 illness. A complete list of symptoms endorsed by patients can be seen in Table 3.

Table 3. COVID-19-related symptoms at the time of neuropsychological evaluation

Symptom	Endorsed by % of patients
Memory Deficits	95%
Lack Concentration/Brain Fog	85%
Fatigue	75%
Exertional Intolerance	65%
Exhaustion/Prolonged Fatigue	60%
Shortness of Breath or Dyspnea on Exertion	60%
Joint Pain/Body Aches	50%
Headaches	50%
Chest Discomfort/Pain	45%
Cough	40%
Palpitations	40%
Difficulty Sleeping	35%
Dizziness	35%
Diarrhea or Nausea	15%
Altered Taste/Smell	10%
Syncope	10%
Heart Failure Symptoms	10%
Fever	5%

Table 4. Hospitalization status and other relevant data

	% Patients	Mean and Range	Data Unknown
Hospitalized	40%	M = 11.1 days; Range 4–33	
Required Supplemental O2	20%	M = 21.5 days; Range 6–56	1 NA
ICU Stay	15%	M = 10 days; Range 4–16	
Required Mechanical Ventilation	10%	M = 11.5 days; Range 7–16	1 NA for LOT
History of Delirium During Illness	10%		

Note: ICU- Intensive Care Unit; LOT- length of time; NA- not available

Hospitalization data

Among the sample, slightly less than half (40%) of patients were hospitalized during the course of their illness and the length of hospitalization ranged from 4 to 33 days. A smaller percentage of patients (20%) received supplemental oxygen. Fifteen percent of patients were hospitalized in an ICU and 10% required mechanical ventilation. Additionally, 10% of patients experienced an episode of delirium during their illness. For additional information please see Table 4.

Neuropsychological findings

As mentioned previously, neuropsychological test scores were considered to be "impaired" if they fell at least 1.5 *SD* below the mean. The percentage of patients with impairment were calculated for each test and grouped according to cognitive domain (i.e., language, visuospatial function, attention and processing speed, executive function, and memory). Twenty percent of patients or more showed impairment on the following tests: Trail Making Test A, Continuous Performance Test (Hit RT, Hit RT ISI Change, and Hit RT Block Change), Wisconsin Card Sorting Test Trials to First Category, and Brief Visuospatial Memory Test-Revised Recognition Discrimination. Table 5 provides a complete list of tests, according to cognitive domain, with percentage of impairment for the sample. Additionally, 40% of patients endorsed moderate to severe symptoms of anxiety (Beck Anxiety Inventory) and 35% endorsed moderate to severe symptoms of depression (Beck Depression Inventory-II) at the time of their evaluation. Among the patients who completed the FSS, 85% endorsed a significant level of fatigue. Fifty percent of the patients who did not require hospitalization ($n = 12$) and 63% of hospitalized patients ($n = 8$) demonstrated cognitive impairments (1.5 *SD* below the mean) on four or more measures described in Table 5. Of note, the patient with the greatest number of impaired cognitive scores was thought to experience new-onset seizures and was subsequently started on anti-epileptics.

Table 5. Impairment on neuropsychological tests by domain

Language	Mean and SD	% Impaired
WRAT-IV Reading Subtest	100.4 (12.7) SS	5%
Boston Naming Test	42.2 (9.0) T	16% ($n = 19$)
Animal Naming	46.7 (8.9) T	16% ($n = 19$)
Visuospatial		
JOLO	50.9 (33.2) %ile	16% ($n = 17$)
Attention and Processing Speed		
WAIS-IV Digit Span Total	9.4 (2.9) ss	5%
Trail Making Test A	47.0 (14.2) T	20%
WAIS-IV: Coding	10.6 (2.3) ss	5%
WAIS-IV: Symbol Search	11.0 (2.4) ss	6% ($n = 18$)
DKEFS: Color Naming	9.1 (3.1) ss	11% ($n = 19$)
DKEFS: Word Reading	9.3 (3.3) ss	16% ($n = 19$)
CPT-3 Omissions	50.4 (7.6) T	7% ($n = 14$)
CPT-3 Comissions	47.2 (7.6) T	0% ($n = 14$)
CPT-3 Hit RT	55.9 (13.2) T	21% ($n = 14$)
CPT-3 Hit RT ISI Change	62.2 (10.7) T	36% ($n = 14$)
CPT-3 Hit RT Block Change	53.9 (10.1) T	21% ($n = 14$)
Executive Function		
Phonemic Verbal Fluency	45.6 (10.5) T	16% ($n = 19$)
Trail Making Test B	48.0 (6.8) T	5%
WAIS-IV: Matrix Reasoning	10.4 (2.6) ss	5% ($n = 19$)
WAIS-IV: Similarities	10.6 (2.2) ss	0% ($n = 18$)
DKEFS- Inhibition	9.4 (2.9) ss	11% ($n = 19$)
DKEFS- Inhibition/Switching	10.3 (2.1) ss	0% ($n = 18$)
WCST Total Errors	91.5 (11.5) SS	11% ($n = 19$)
WCST Perseverative Errors	92.0 (12.3) SS	16% ($n = 19$)
WCST Conceptual Responses	91.8 (11.2) SS	11% ($n = 19$)
WCST Categories Completed	5.3 categories (1.3)	11% ($n = 19$)
WCST Trials to First Category	9.7 (6.3) %ile	53% ($n = 19$)
WCST Set Loss Errors	13.9 (4.5) %ile	16% ($n = 19$)
Memory		
WMS-IV: Logical Memory Immediate	9.2 (3.1) ss	15%
WMS-IV: Logical Memory Delay	8.6 (3.3) ss	10%
WMS-IV: Logical Memory Recognition	44.0 (27.1) %ile	0%
BVMT-R Total Recall	47.3 (10.6) T	10%
BVMT-R Learning	52.4 (12.2) T	15%
BVMT-R Delayed Recall	51.8 (11.4) T	10%
BVMT-R Recognition Discrimination	13.4 (6.1) %ile	20%
RAVLT Total Recall	102.2 (16.7) SS	10%
RAVLT List B	98.2 (16.1) SS	5%
RAVLT Trial 6	103.2 (18.0) SS	5%
RAVLT Trial 7	99.3 (17.3) SS	10%
RAVLT Recognition	107.1 (13.0) SS	5%
Mood and Other Self-Report Inventories		
BDI-II	19.6 (14.0) (raw score)	20% mild, 10% moderate, 25% severe
BAI	17.0 (13.2) (raw score)	30% mild, 20% moderate, 20% severe
Fatigue Severity Scale	48.9 (16.8) (raw score)	85% significant ($n = 13$)

Note: Measures with less than $n = 20$ are notated in parentheses for each measure.
SS = Standard Score, T = T-score, ss = scaled score, %ile = percentile; % percentage
Impairment measured as 1.5 SD below the mean (Standard Score ≤ 77.5; T-score ≤ 35 or ≥ 65 (for select measures); scaled score ≤ 5.5; percentile $\leq 7^{th}$
Bolded values indicate 20% or more patients evidenced impairment on measure
WRAT: Wide Range Achievement Test-IV; JOLO: Judgment of Line Orientation; WAIS-IV: Wechsler Adult Intelligence Scale- Fourth Edition; DKEFS: Delis-Kaplan Executive Function System; CPT-3: Conners Continuous Performance Test- Third Edition; WCST: Wisconsin Card Sorting Test- Computer Version; WMS-IV: Wechsler Memory Scale- Fourth Edition; BVMT-R: Brief Visuospatial Memory Test-Revised; RAVLT: Rey Auditory Verbal Learning Test; BDI-II: Beck Depression Inventory- Second Edition; BAI: Beck Anxiety Inventory; FSS: Fatigue Severity Scale

Discussion

This is among the first studies to describe neuropsychological findings for in-person and comprehensive cognitive evaluations in patients with PCR confirmed COVID-19 at the more chronic stage of recovery (approximately 5.5 months post onset of COVID-19 diagnosis). Primary findings include deficits in attention and processing speed, and aspects of executive function. Additionally, this cohort demonstrates a high prevalence of prior psychiatric history as well as worsening of mood symptoms post-COVID-19 illness.

Studies have described presence of adverse neurological and psychiatric outcomes after COVID-19 (Taquet et al., 2021; Wild et al., 2021). Research quantifying cognitive dysfunction post COVID-19 has been largely based on virtual assessments or brief cognitive screeners and primarily focused on the acute stage of illness (Alemanno et al., 2021; Del Brutto et al., 2021; Jaywant et al., 2021; Ortelli et al., 2021;Whiteside et al., 2021 ; Wild et al., 2021). The majority of patients in this study were cognitively intact on neuropsychological testing approximately five and a half month post-onset of COVID-19 diagnosis. Cognitive deficits, when present, were largely seen on tests involving attention and processing speed, or aspects of executive function, which is a nonspecific pattern. Deficits in these cognitive domains is consistent with prior case studies in patients during the acute stage of illness (Hampshire et al., 2021; Jaywant et al., 2021; Whiteside et al., 2021). This suggests that patients may continue to experience cognitive deficits at more chronic stages, albeit reduced in severity. However, the etiology of the deficits is unclear. Although almost half of the patients were hospitalized, only three were in the ICU and required mechanical ventilation. Patients requiring higher levels of acute care did not demonstrate greater deficits on cognitive measures, which is contrary to some findings (Whiteside et al., 2021; Wild et al., 2021), but consistent with others (Woo et al., 2020). A review of literature related to acute respiratory distress syndrome (ARDS) suggests presence of cognitive deficits up to 5 years after the acute illness with preexisting neurological dysfunction, delirium, and psychological comorbidities as risk factors (Herridge et al., 2016; Mart & Ware, 2020). Generally, ARDS suggests presence of hypoxemia even in patients who did not require hospitalization but may have required supplemental oxygen. Patients in this study were not diagnosed with ARDS. Future studies should investigate the relationship between ARDS in patients with COVID-19 and its impact on cognition.

One possible explanation for the cognitive findings is that other factors may be contributing to cognitive impairment during later stages of recovery. Whiteside et al. (2021) describe a model where cognitive complaints in cognitively intact patients may be a consequence of secondary factors not directly related to COVID-19, such as mood disorders, sleep dysfunction, and fatigue. The majority of this study sample fits that description.

One of the most striking findings in this study is that over 70% of patients in this sample had previously been diagnosed with depression or anxiety prior to COVID-19 infection. Furthermore, most patients reported worsening mood symptoms post COVID-19. In fact, only six patients (30%) did not have prior psychiatric history and reported no current symptoms. This high prevalence of prior psychiatric history is consistent with previous findings in the literature on COVID-19 (Taquet et al., 2021). In comparison, Wild et al. (2021) demonstrate no relationship between mental health and cognitive deficits in their study. Although potential mechanisms behind these contrary findings are unclear, they may be an important avenue for future research as it is possible that a certain subset of patients with persisting symptoms post COVID-19 experiences greater psychological distress. More importantly, this study highlights the importance of assessing and addressing psychiatric and psychological symptoms in patients even at the acute stage as it can affect cognitive function.

A majority of the patients described here were seen at a specialty neuropsychology clinic designed for individuals with persistent symptoms after COVID-19, referred to as “long COVID” in the literature (Lopez-Leon et al., 2021). Patients typically endorsed a wide range of persisting symptoms at least 28 days after acute infection, even among those who did not require hospitalization. The most frequently endorsed complaints of memory loss, brain fog, fatigue, and exertional tolerance noted by patients in this study is consistent with what has been discussed as predominant persisting symptoms post-COVID-19 in the literature. In this study, the level of fatigue as measured by FSS did not appear to mitigate severity of cognitive deficits. Assessment of fatigue on cognition has been well studied in populations of multiple sclerosis and post-concussive syndrome/mild traumatic brain injury. Fatigue is recognized as a common complaint in patients but the direct impact on cognition is unclear and investigations into the neuropathology of this relationship are in their infancy (Golan et al., 2018). Little is known about pathophysiology of fatigue in patients with COVID-19, which warrants further investigations.

Limitations

One limitation of this study was the relatively small sample size ($n = 20$) and lack of a control group, which limits power to detect significant results and affects generalizability of the findings. However, ours is one of the first studies of this type reporting results of full neuropsychological evaluations in individuals who have had COVID-19, and future work should focus on obtaining larger sample sizes in this population.

Secondly, a majority of patients in this study experienced mild symptoms of COVID-19. It is possible that patients with more severe forms of illness and other complications (such as presence of delirium) may experience greater cognitive deficits. This is highlighted by one patient in this study who developed new onset left-temporal lobe seizures post-COVID-19. In this paper, we excluded patients diagnosed with neurological disorders prior to developing COVID-19. Focusing on those patients and comparing their cognitive trajectory with patients without preexisting conditions may further elucidate cognitive recovery profiles post COVID-19. There are also concerns about changes in sleep patterns post-COVID-19 that were not evaluated in this study. About half of the patients in this study were prescribed sleep medicine for new-onset sleep disruption, which suggests that sleep may have played a role in the cognitive presentation.

This sample also had a higher level of education than the general population and primarily consisted of women, non-Hispanic white participants, many of whom had preexisting psychiatric diagnoses (e.g., depression, anxiety). Cognition can be affected during the perimenopausal stage, which may play a role in this sample. The factors contributing to the characteristics of this participant sample can only be hypothesized but may relate to access to medical care and/or help-seeking behaviors. Almost half of the patients described here work in healthcare professions, specifically nursing. Women make up more than 85% of workers in this nursing per CDC (Day & Christnacht, 2019). Research suggests sex differences in Covid-19 where men are more likely to develop severe illness with higher rates of mortality than women (Viveiros et al., 2021). These authors propose multiple mechanisms for this sex difference including differences in hormonal signaling pathways and hypothesize that women have a heightened immune response. Future research should focus on the impact of sex differences on cognitive recovery post COVID-19. Altogether, these factors limit generalizability of the findings to dissimilar patients, and we cannot exclude the possibility that some of these factors were driving the results that were obtained. As research in this area progresses, future work should aim to capture larger groups of participants with characteristics that are more representative of the general population.

Conclusions

It is well established that a subset of patients with a history of COVID-19 experience persisting medical and cognitive symptoms. This study illustrates that patients with prior psychiatric history may experience greater levels of cognitive dysfunction. Cognitive deficits, when present, appear mild and isolated to domains of attention and processing speed, and executive function in a sample where the majority of patients did not require intensive treatment. This finding may be a consequence of other factors developed as a result of COVID-19 (worsening mood, sleep disruption, fatigue, etc.) rather than a direct result of COVID-19 infection. However, this hypothesis needs to be further investigated. In our clinical experience, patients appear receptive to psychoeducation about the impact of factors such as mood, pain, sleep, and fatigue on cognition. Quantitative studies are warranted to determine the impact of COVID-19 on cognition and investigate the role of mood, pain, sleep, and fatigue in the patients' cognitive recovery.

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Conflict of interest

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