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Original Research Article

# Neuropsychological, Medical, and Psychiatric Findings After Recovery From Acute COVID-19: A Cross-sectional Study

Stephen J. Ferrando, M.D., Rhea Dornbush, Ph.D., M.P.H., Sean Lynch, M.D., Sivan Shahar, B.A., Lidia Klepacz, M.D., Carol L. Karmen, M.D., Donald Chen, M.D., Stephen A. Lobo, M.D., Dania Lerman, M.S.W.

**Background:** *Persistent cognitive, medical and psychiatric complaints have been extensively described after recovery from acute SARS-CoV-2 infection.* **Objective:** *To describe neuropsychological, medical, psychiatric, and functional correlates of cognitive complaints experienced after recovery from acute COVID-19 infection.* **Methods:** *Sixty participants underwent neuropsychological, psychiatric, medical, functional, and quality-of-life assessments 6–8 months after acute COVID-19. Those seeking care for cognitive complaints in a post-COVID-19 clinical program for post-acute symptoms of COVID-19 (clinical group, N = 32) were compared with those recruited from the community who were not seeking care (nonclinical, N = 28). A subset of participants underwent serological testing for proinflammatory cytokines C-reactive protein, interleukin-6, and tumor necrosis factor-α to explore correlations with neuropsychological, psychiatric, and medical variables.* **Results:** *For the entire sample, 16 (27%) had extremely low test scores (less than second percentile on at least 1 neuropsychological test). The clinical group with cognitive complaints scored lower than age-adjusted population norms in tests of attention, processing speed, memory, and executive function and scored significantly more in the extremely low range than the nonclinical group (38% vs. 14%,* $P < 0.04$*). The clinical group also reported higher levels of depression, anxiety, fatigue, posttraumatic stress disorder, and functional difficulties and lower quality of life. In logistic regression analysis, scoring in the extremely low range was predicted by acute COVID-19 symptoms, current depression score, number of medical comorbidities, and subjective cognitive complaints in the areas of memory, language, and executive functions. Interleukin-6 correlated with acute COVID symptoms, number of medical comorbidities, fatigue, and inversely with measures of executive function. C-reactive protein correlated with current COVID symptoms and depression score but inversely with quality of life.* **Conclusion:** *Results suggest the existence of extremely low neuropsychological test performance experienced by some individuals months after acute COVID-19 infection, affecting multiple neurocognitive domains. This extremely low neuropsychological test performance is associated with worse acute COVID-19 symptoms, depression, medical comorbidities, functional complaints, and subjective cognitive complaints. Exploratory correlations with proinflammatory cytokines support further research into inflammatory mechanisms and viable treatments.*

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**Key words:** COVID-19, post-acute symptoms of COVID-19 (PASC), neuropsychological testing, cognitive complaints, neuropsychiatry.

Received October 11, 2021; revised January 7, 2022; accepted January 15, 2022. From the Department of Psychiatry (S.J.F., R.D., S.L., L.K.), Westchester Medical Center Health System, Valhalla, NY; New York Medical College (S.J.F., R.D., S.L., S.S., lL.K., C.L.K., D.C., S.A.L.), Valhalla, NY; and Department of Medicine (C.L.K., D.C., S.A.L.), Westchester Medical Center Health System, Valhalla, NY. Send correspondence and reprint requests to Stephen J. Ferrando, MD, Director, Professor and Chairman, Department of Psychiatry, Westchester Medical Center Health System, New York Medical College, 100 Woods Road, Valhalla, New York 10595; e-mail: Stephen.Ferrando@wmchealth.org

## INTRODUCTION

Severe acute respiratory syndrome coronavirus 2, the virus that causes COVID-19, has multiple neuropsychiatric manifestations in the acute stages, particularly among severely ill hospitalized patients. These include headache, fatigue, encephalopathy, encephalitis, delirium, depression, anxiety, and psychosis.[1–4] Respiratory, cardiac, gastrointestinal, neuropsychiatric, and other symptoms may persist months after infection, giving rise to the terms "long COVID" or "post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection".[5]

The neuropsychiatric symptoms of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection include subjective cognitive complaints (colloquially described as "brain fog" by many patients) such as diminished focus and mental clarity, forgetfulness, mental fatigue, and difficulty making decisions and multitasking. These complaints often co-occur with fatigue, sleep disorders, depression, and anxiety, among others.[6] Cognitive complaints have been studied in multiple other clinical entities, including other infectious disease states,[7–9] postural orthostatic tachycardia syndrome,[10] patients receiving chemotherapy,[11] those with chronic fatigue syndrome,[12] and neurological conditions such as multiple sclerosis,[13] among others. The specific neuropsychological (NP) characteristics of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 infection, including course, risk factors, and prognosis, have yet to be fully elucidated, leading to calls for large-scale, longitudinal studies.[5,6]

Neuropsychiatric symptoms of COVID-19 may occur through direct effects of the virus on the central nervous system and/or through other mechanisms, such as anoxia, inflammation ("cytokine storm"), or an autoimmune response.[14] The virus may access the brain by attaching to Angiotensin-Converting Enzyme-2 (ACE-2) receptors in the nasopharynx, traversing the olfactory nerve to the piriform cortex.[15–17] ACE-2 exists on blood vessel epithelial cells, the blood-brain barrier, and in multiple brain structures, including neurons and glial cells, all of which may influence neurotransmission.[18,19] While there are isolated reports of severe acute respiratory syndrome coronavirus 2 detected in CSF, clinical series have generally not found viral particles in CSF, even among patients with neurological complications.[15,20] However, a transgenic mouse model detected widespread microglial activation, macrophage, and T-cell-dominated inflammatory response with microglial apoptosis, suggesting an inflammatory mechanism.[21]

Few studies have included NP screens or formal testing. In a comprehensive review of 12 studies on cognitive impairment after recent COVID-19 infection (time frame 0–6 months), Daroische et al. (2021) described global cognitive impairment in 15–80% of study participants, with impairment in memory, attention, executive function and verbal fluency documented in a small number of studies.[22] Most of these studies were conducted in the acute or subacute setting of COVID-19 requiring hospitalization, used brief bedside assessments, either the Montreal Cognitive Assessment or the Folstein Mini-Mental State Examination, and few used formal NP testing.[22] In a longer term follow-up study, Pilotto et al. (2020) found that 16% of hospitalized COVID-19 patients screened positive for cognitive impairment via the Montreal Cognitive Assessment at 6-month follow-up, which was significantly correlated with COVID-19 illness severity.[23] Of 120 health-care workers recovered from mild-moderate COVID-19 illness assessed with a NP test battery 4 months after diagnosis, Mattioli et al. (2021) found no difference in general cognitive function or performance in specific cognitive domains compared with a COVID-negative comparison group.[24] In contrast, 24 nonhospitalized COVID-19 patients tested in a specialized COVID-19 neurology clinic 5–6 months after infection scored in the impaired range on measures of attention and working memory relative to population-based norms.[25]

With this background, this cross-sectional study aimed to investigate longer term neuropsychiatric sequelae of COVID-19 by assessing individuals recovered from an acute COVID-19 illness with NP, psychiatric, medical, and sociodemographic instruments. Study questions included,

1. How frequent is NP test impairment, as defined by extremely low NP test scores, in individuals recovered from acute COVID-19 infection?
2. Do individuals seeking care for cognitive complaints have higher rates of NP impairment and psychiatric and medical symptoms than those not seeking care?
3. Are there clinical predictors of extremely low NP test scores that identify potential risk factors?
4. Do elevations in proinflammatory cytokines interleukin-6 (IL-6), tumor necrosis factor-alpha

(TNF-α), or C-reactive protein (CRP) correlate with NP or other post-COVID-19 symptoms?

## METHODS

Data for this study were obtained from the baseline assessment of 60 participants enrolled in an ongoing longitudinal investigation of NP, medical, and psychiatric sequelae of COVID-19. Participants were recruited from the Westchester County, New York, USA, community via social media, flyers, and word of mouth. In addition, a sample of patients seeking care for post-acute cognitive complaints were referred from the Westchester Medical Center Health System (WMCHealth) Post-COVID-19 Recovery Program. Interested persons were screened via telephone to determine eligibility, based on the following criteria: (1) age at least 20 years; (2) a documented positive COVID-19 nasopharyngeal test or positive antibody test before vaccination; (3) recovered from acute COVID-19 infection as per Centers for Disease Control and Prevention recommendations (10–20 days after symptom onset and 24 hours without fever); (4) completed minimum eighth grade education; (5) fluent in English; and (6) capable of signing informed consent. Persons with a prior diagnosis of a major neurocognitive disorder, traumatic brain injury with loss of consciousness, uncorrected visual/hearing deficits, intellectual disability, or unstable psychiatric symptoms were excluded.

At the baseline visit, eligible participants were explained the risks and benefits and signed informed consent. The study was approved by the New York Medical College Institutional Review Board as well as the Westchester Medical Center Health System Clinical Research Institute.

Participants met with study assessors (S.L., S.S.), who were trained to perform and score the assessment battery and were supervised by the study principal investigator (S.J.F.) and co-principal investigator (R.D.), the latter is a board-certified neuropsychologist. Participants were compensated with $40 for their time.

### Study Measurements and Instruments

Sociodemographic measures included age, gender, race, relationship status, years of education, and current employment.

Medical measures included self-reported medical history, including a detailed history of COVID-19 illness with symptoms, treatment, and hospitalization, time since diagnosis, and number of medical comorbidities. COVID-19 symptom severity at the time of acute infection as well as at the time of the study appointment was determined by a score on an instrument adapted from published Centers for Disease Control and Prevention COVID-19 symptoms, assessing severity (absent, mild, moderate, severe) on 11 COVID-19 symptoms, which is scored from 0 to 33.[26] Participants were also administered the Lawton-Brody Instrumental Activities of Daily Living Scale (IADL), which measures increasing difficulty with practical aspects of everyday functioning on a scale of 0–8,[27] and the 11-item Chalder Fatigue Scale, which measures the severity of both mental and physical fatigue and is scored from 0 to 33. A cutoff score of >21 is considered clinically significant fatigue.[28] Serological samples were obtained from a subset of participants and assayed for CRP, IL-6, and TNF-α, as elevated levels of these specific proinflammatory markers have been associated with neurocognitive and psychiatric disorders.[29] Assays were performed by the Mayo Clinic Laboratories, and standardized reference ranges were used (normal = CRP ≤ 8.0 mg/L; IL-6 ≤ 1.8 pg/ml; TNF-α ≤ 2.8 pg/ml).

Psychiatric measures included pre-COVID-19 psychiatric and substance use disorder history, current psychiatric medication use, and self-report questionnaires to assess current psychiatric symptoms and disorders. Self-report questionnaires included the Patient Health Questionnaire-9 (PHQ-9), which queries Diagnostic and Statistical Manual for Mental Disorders-5 Edition major depression criteria and has a maximum score of 27[30]; the Endicott Quality of Life Enjoyment and Satisfaction Scale (Endicott QLESQ), which queries overall life satisfaction in 14 areas and has a raw score range of 0–70[31]; the Posttraumatic Stress Disorder Checklist for DSM-5, which has a maximum score of 80[32]; and the Generalized Anxiety Disorder-7 questionnaire, which is scored from 0 to 21.[33] Scores on the questionnaires were categorized based on cutoff values in the medical literature. For PHQ-9, a score of ≥11 may indicate clinically significant depressive symptoms[30]; for Generalized Anxiety Disorder-7, a score ≥10 indicates clinically significant anxiety symptoms[33]; for Posttraumatic Stress Disorder

Checklist for DSM-5, a score of ≥33 indicates clinically significant PTSD symptoms.[32]

The NP battery consisted of measures assessing specific cognitive domains that have been implicated in other infectious and clinical disease states.[7–11] The battery included the Test of Premorbid Function, to obtain an estimate of premorbid (i.e., pre-COVID-19) intellectual function.[34] Participants also completed the Patient Assessment of Own Function (PAOF), which queries subjective cognitive complaints yielding an average score of 0–5 for memory, language and communication, handedness, sensory perception, and cognitive/intellectual functioning.[35] For the study, the PAOF subscales most associated with everyday cognitive functioning, including memory, language, and cognitive/intellectual/executive functioning, served as measures of subjective cognitive complaints. Participants were administered NP tests assessing attention; auditory/verbal and visual immediate and delayed memory; visuospatial and constructional abilities; psychomotor speed; language; and executive function. The battery included the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) Form A (total and 5 subscale scores), the Trail Making Test Parts A and B, verbal fluency (letter and category), and the Stroop Color-Word Test, yielding 11 test scores per participant.[36–39]

NP test scores were converted to standardized t-scores and analyzed in two ways: (1) as continuous measures and (2) to categorize scores as unimpaired or extremely low. For the first, to assess participants' performance relative to a standardized comparison group without COVID-19, scores on each NP test were converted to t-scores according to their respective manuals and compared with age- and education-adjusted (where available) population-based norms. Thus, performance of the entire group and the subgroups of interest could be compared with that of a non-COVID-19 comparison population. For the second, we applied accepted clinical practice for assessing extremely low NP test performance, defined as ≥2 standard deviations below (less than or equal to second percentile) the age- and education-adjusted norms on *one or more* of the 11 tests.[34,36,40]

Analyses were conducted on the entire sample of 60 participants and on two subgroups—a "clinical group" and a "nonclinical group." The clinical group included participants seeking care for post-acute cognitive complaints from the WMCHealth Post-COVID-19 Recovery Program. The nonclinical group consisted of participants from the general community, none of whom were seeking care for post-acute COVID-19 symptoms.

Data were analyzed using SPSS software.[41] These included descriptive statistics (frequency, mean, standard deviation); Chi-square for group comparisons on categorical variables; and independent and one-sample *t*-tests and analysis of covariance for group comparisons on continuous variables. Significant group differences in moderators such as age and number of medical comorbidities were used as covariates in group comparisons. Pearson correlations were used to explore associations between immune markers and clinical variables. Logistic regression was used to identify independent predictors of extremely low NP test scores, using PAOF memory, language, and cognition scores, as well as medical and psychiatric variables that differed between clinical and nonclinical groups as predictors.

## RESULTS

### Characteristics of the Total Sample

The participants had a mean age of 41 years, approximately 67% were female, 75% were White or Hispanic, 67% were in a relationship, and 75% were employed. On average, participants had a college level education (Table 1).

From a medical standpoint (Table 2), the participants had acute COVID-19 illness on average 7 months before the assessment. The most prevalent acute symptoms were fatigue (92%), respiratory symptoms (90%), neurological symptoms (87%), anosmia (67%), and memory/cognitive problems (57%). Seven participants had been hospitalized for complications of COVID-19; 6 of them reported respiratory distress, 5 cognitive problems or weakness, and 3 flu-like symptoms. None were admitted to intensive care or required ventilator support. Aside from COVID-19, participants reported on average 1.5 comorbid medical comorbidities, including obesity (25%), asthma (23%), hypertension (17%), sleep apnea (15%), hypothyroidism (15%), migraines (10%), diabetes (7%), and hyperlipidemia (5%). Reported acute versus current COVID-19 symptoms declined; however, half of the participants reported current clinically significant fatigue as measured by the Chalder Fatigue Scale. Fifty participants underwent serological testing for IL-6, CRP, and TNF-α (Table 2). Availability of results

**TABLE 1. Sociodemographic Characteristics**

| Measure | Total sample | Post-COVID nonclinical | Post-COVID clinical | Stat., df, sig. (*P*, 95%)* |
|---|---|---|---|---|
| N | 60 | 28 | 32 | - |
| Age, M (SD) | 41.4 (13.5) | 33.7 (11.0) | 48.1 (12.8) | t = −4.6, df = 58, $P < 0.001$ |
| Female, N (%) | 41 (68) | 16 (57) | 25 (78) | Chi Sq. = 3.0, df = 1, $P = 0.08$ |
| Race (%) | | | | Chi Sq. = 7.1, df = 4, $P = 0.13$ |
| White | 30 (56.6) | 17 (65.4) | 13 (48.1) | |
| Hispanic | 11 (20.8) | 5 (19.2) | 6 (22.2) | |
| Asian | 5 (9.4) | 2 (7.6) | 3 (11.1) | |
| Black | 5 (9.4) | 0 (0.0) | 5 (18.5) | |
| Other | 2 (3.8) | 2 (7.7) | 0 (0.0) | |
| Education, yrs, M (SD) | 16.0 (2.2) | 16.4 (2.2) | 15.8 (2.1) | t = 1.1, df = 58, $P = 0.28$ |
| Relationship status, N (%) in relationship | 38 (63) | 18 (64) | 20 (63) | Chi Sq. = 0.02, df = 1, $P = 0.89$ |
| Employed currently, N (%) | 50 (83) | 26 (93) | 24 (75) | Chi Sq. = 3.4, df = 1, $P = 0.06$ |

M = mean; SD = standard deviation.

* *P* value represents comparison of nonclinical and clinical COVID-19 groups.

varied by test and was based on participant refusal, insufficient sample volume, or sample degradation. Of those with available results, approximately 40% had IL-6 or CRP levels above the reference range, and 20% had elevated TNF-α.

Psychiatrically (Table 3), 39% reported a pre-COVID-19 psychiatric history, including depression (30%), anxiety (25%), and attention deficit-hyperactivity disorder (8%). Seventeen percent had a history of substance use disorder (predominately marijuana and alcohol), all in remission. Twenty-five percent were currently taking antidepressants, 8% stimulants, 7% benzodiazepines, and 6% hypnotics, lamotrigine, or gabapentin. Based on cutoff scores for the PHQ-9, Generalized Anxiety Disorder-7, and Posttraumatic Stress Disorder Checklist for DSM-5, 47% screened positive for clinically significant depression, 28% for anxiety, and 20% for PTSD.

NP test findings (Table 4) indicated that the sample had a high-normal estimated premorbid

**TABLE 2. Medical Characteristics**

| | Total sample | | Post-COVID nonclinical | | Post-COVID clinical | | Stat., df, sig. (*P*, 95%)* |
|---|---|---|---|---|---|---|---|
| | | N | | N | | N | |
| Number of medical comorbidities, M (SD) | 1.5 (1.4) | 60 | 1.0 (1.1) | 28 | 1.9 (1.6) | 32 | t = −2.3, df = 59, $P = 0.02$ |
| Days since diagnosis, M (SD) | 209.3 (133.5) | 60 | 172 (120) | 28 | 250 (132) | 32 | t = −2.4, df = 59, $P = 0.02$ |
| Acute illness CDC symptom score, M (SD) | 16.5 (5.9) | 60 | 13.7 (5.2) | 28 | 18.9 (6.0) | 32 | F = 10.8, df = 3, $P < 0.001$† |
| Current CDC symptom score, M (SD) | 5.7 (4.6) | 60 | 2.5 (2.8) | 28 | 8.4 (4.0) | 32 | F = 13.5, df = 3, $P < 0.001$† |
| Hospitalized during COVID illness, N (%) | 7 (12) | 60 | 1 (4) | 28 | 6 (19) | 32 | Fishers Exact $P = 0.11$ |
| Chalder Fatigue Scale, M (SD) | 20.67 (7.71) | 59 | 16.7 (7.6) | 27 | 23.7 (6.5) | 32 | F = 5.8, df = 3, $P = 0.002$† |
| Clinical fatigue (Chadler Fatigue Scale ≥ 21), N (%) | 30 (51) | 59 | 8 (28) | 27 | 22 (69) | 32 | Chi Sq = 8.9, df = 1, $P = 0.003$ |
| Instrumental activities of daily living score, M (SD) | 7.6 (1.0) | 60 | 8.0 (0) | 28 | 7.3 (1.2) | 32 | F = 4.8, df = 3, $P = 0.006$† |
| IL-6 above reference range, N (%) | 18 (45) | 40 | 5 (25) | 20 | 12 (60) | 20 | Chi Sq = 4.4, df = 1, $P = 0.04$ |
| TNF-α above reference range, N (%) | 10 (20) | 50 | 7 (29) | 24 | 3 (14) | 26 | Chi Sq = 2.4, df = 1, $P = 0.12$ |
| CRP above reference range, N (%) | 14 (41) | 40 | 5 (25) | 22 | 9 (64) | 18 | Chi Sq = 7.9, df = 1, $P = 0.02$ |

CDC = Centers for Disease Control and Prevention; CRP = C-reactive protein; IL-6 = interleukin-6; M = mean; SD = standard deviation; TNF-α = tumor necrosis factor-alpha.

* *P* value represents comparison of nonclinical and clinical COVID-19 groups.

† Covariates include age and number of medical comorbidities.

**TABLE 3. Psychiatric and Behavioral Measures**

| | Total sample | Post-COVID nonclinic | Post-COVID clinic | Stat., sig (*P*, 95%) |
|---|---|---|---|---|
| N | 60 | 28 | 32 | - |
| Prior psychiatric history, N (%) | 24 (39) | 11 (39) | 13 (39) | Chi Sq = 0.01, df = 1, $P = 0.91$ |
| SUD history, N (%) | 10 (17) | 5 (18) | 5 (16) | Chi Sq = 0.05, df = 1, $P = 0.82$ |
| PHQ-9, M (SD) | 9.28 (6.17) | 6.4 (5.2) | 12.1 (5.8) | F = 7.1, df = 3, $P < 0.001$* |
| GAD, M (SD) | 6.17 (4.67) | 5.59 (5.06) | 6.77 (4.24) | F = 2.8, df = 3, $P = 0.05$* |
| PCL-5, M (SD) | 19.51 (14.45) | 13.5 (14.1) | 25.3 (12.5) | F = 7.6, df = 3, $P < 0.001$* |
| Endicott QOL % score, M (SD) | 47.5 (10.8) | 70.0 (17.0) | 51.3 (18.4) | F = 7.5, df = 3, $P < 0.001$* |
| Depression (PHQ-9 ≥ 11), N (%) | 28 (47) | 6 (21) | 22 (69) | Chi Sq = 13.4, df = 1, $P < 0.001$ |
| Anxiety (GAD-7 ≥ 10), N (%) | 17 (28) | 6 (21) | 11 (34) | Chi Sq = 1.2, df = 1, $P = 0.27$ |
| PTSD (PCL-5 ≥ 33), N (%) | 12 (20) | 3 (10) | 9 (28) | Chi Sq = 2.8, df = 1, $P = 0.09$ |

GAD-7 = Generalized Anxiety Disorder-7; M = mean; PCL-5 = Posttraumatic Stress Disorder Checklist for DSM-5; PHQ-9 = Patient Health Questionnaire-9; PTSD = posttraumatic stress disorder; QOL = quality of life; SD = standard deviation; SUD = substance use disorder.

*P* value represents comparison of nonclinical and clinical COVID-19 groups.

* Covariates include age and number of medical comorbidities.

intellectual function on the Test of Premorbid Function. Subjective cognitive function on the PAOF indicated mild-moderate perceived cognitive problems in the areas of memory, language, and cognition. Compared with age-adjusted norms, performance of the overall sample on the RBANS total score as well as subtests of immediate and delayed memory and language was significantly lower than normative values. Based on study criteria, just over one fourth (N = 16, 27%) had extremely low test scores (less than or equal to second percentile on at least one test). Among those 16 individuals, mean IADL was significantly lower than that for the rest of the cohort (6.8 vs. 7.9, respectively, $P < 0.03$), suggesting increased functional difficulty, particularly in the areas of medication management, handling money, shopping, and cooking.

## Comparison of Nonclinical and Clinical Groups

### *Sociodemographics*

The clinical group was significantly older than the nonclinical group but did not differ significantly on other sociodemographic characteristics (Table 1). The groups had nearly identical educational attainment and relationship status.

### *Medical*

The clinical group reported significantly more underlying chronic comorbid conditions, but none were medically unstable (Table 2). Given the group differences in age and comorbid conditions, these intrinsic patient characteristics that existed before the COVID-19 illness were included as covariates in subsequent group comparisons on continuous assessment measures (indicated in Tables 2–4). The clinical group was further from their COVID-19 diagnosis compared with the nonclinical group (8.3 vs. 5.7 months). They reported significantly more acute and current COVID-19 symptoms, higher levels of fatigue, and diminished IADLs. The clinical group also reported more current gastrointestinal symptoms ($P < 0.04$) and shortness of breath ($P < 0.02$). They were also significantly more likely to have CRP and IL-6 above the reference range.

### *Psychiatric*

The two groups were nearly identical in terms of psychiatric and substance use disorder history (Table 3). However, the clinical group had higher levels of depressive symptoms on the PHQ-9 and were over three times more likely to screen positive for clinically significant depression (69% vs. 21%). They also reported significantly more anxiety and PTSD symptoms, but the groups did not significantly differ in proportion with clinically significant Generalized Anxiety or PTSD.

### *Neuropsychological*

The two groups were nearly identical in terms of estimated premorbid intellectual function; however, the clinical group reported significantly more subjective cognitive complaints in the areas of memory, language, and cognition (executive functions) on the PAOF

**TABLE 4. Estimate of Premorbid Function, Patient Assessment of Their Current Cognitive Function and Neuropsychological Test Outcomes as Compared to Published Normative Data**

| | Total, N = 60 | | Post-COVID nonclinical, N = 28 | | Post-COVID clinical, N = 32 | |
|---|---|---|---|---|---|---|
| | | | | | | Sig (*P*, 95%)* |
| Test of premorbid cognitive function (TOPF), M (SD) | | | | | | |
| Scaled | 108.9 (12.9) | | 108.7 (14.1) | | 108.8 (11.3) | 0.33† |
| Predicted | 107.4 (7.9) | | 109.3 (6.9) | | 106.3 (8.0) | 0.72‡ |
| Patient assessment of own function (PAOF), M (SD) | | | | | | |
| Memory | 1.88 (1.1) | | 1.4 (0.9) | | 2.3 (1.2) | 0.002§ |
| Language | 1.47 (1.0) | | 1.1 (0.8) | | 1.8 (1.1) | 0.006‖ |
| Cognition | 1.50 (1.2) | | 0.8 (0.7) | | 2.2 (1.3) | 0.001¶ |
| | | **t, df, sig. (*P*, 95%)#** | | **t, df, sig. (*P*, 95%)#** | | **t, df, sig. (*P*, 95%)#** |
| RBANS total, M (SD) | | | | | | |
| Scaled score | 94.3 (14.5) | −3.0, 59, 0.004 | 9.46 (12.1) | −0.24, 27, 0.82 | – | – |
| Subgroups, M (SD) | | −1.1, 59, 0.29 | | | | |
| Attention | 97.8 (16.0) | −1.1, 59, 0.29 | 103.6 (15.5) | 1.2, 27, 0.22 | 92.6 (14.9) | −2.8, 31, 0.009 |
| Immediate memory | 90.8 (15.0) | −4.7, 59, <0.001 | 94.3 (11.5) | −2.6, 27, 0.01 | 87.8 (17.1) | −4.0, 31, 0.001 |
| Delayed memory | 93.1 (14.3) | −3.8, 59, <0.001 | 97.0 (12.8) | −1.2, 27, 0.23 | 89.6 (14.8) | −4.0, 31, 0.001 |
| Visuospatial | 104 (16.4) | 1.9, 59, 0.06 | 109.1 (10.7) | 4.5, 27, 0.001** | 99.6 (19.2) | −0.12, 31, 0.91 |
| Language | 94.3 (16.2) | −2.8, 59, 0.008 | 95.5 (17.3) | −1.3, 27, 0.18 | 93.1 (15.3) | −2.5, 31, 0.02 |
| Trail Making Test, M (SD) | | | | | | |
| A (T) | 47.3 (11.6) | −1.8, 59, 0.08 | 48.6 (11.0) | −0.67, 27,0.51 | 46.2 (12.2) | −1.8, 31, 0.09 |
| B (T) | 45.6 (10.9) | −3.1,59, 0.003 | 48.4 (11.6) | −0.75, 27,0.46 | 43.1 (9.8) | −4.0, 31, 0.001 |
| Verbal fluency, M (SD) | | | | | | |
| Category mean (T) | 49.3 (10.6) | −0.5, 59, 0.62 | 51.0 (11.8) | 0.47, 27, 0.65 | 47.8 (9.5) | −1.3, 31, 0.20 |
| Letter mean (T) | 47.7 (10.8) | −1.7, 59, 0.09 | 50.4 (10.7) | 0.22, 27, 0.83 | 45.4 (9.5) | −4.0, 31, 0.01 |
| Stroop Color Word Score, M (SD) (T) | 48.7 (11.9) | −3.5, 59, 0.001 | 54.6 (12.1) | 2.0, 27, 0.05** | 43.6 (9.2) | −3.9, 31, 0.001 |
| Extremely low Neuropsychological Test Score(s) | 16 (27%) | – | 4 (14%) | – | 12 (38%) | Chi Square = 4.2, df = 1, *P* = 0.04 |

M = mean; RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; SD = standard deviation.

* *P* value represents comparison of post-COVID-19 nonclinical group to clinical group.

† Covariates include age and number of medical comorbidities: F = 1.2, df = 3, *P* = 0.33.

‡ Covariates include age and number of medical comorbidities: F = 7.6, df = 3, *P* = 0.72.

§ Covariates include age and number of medical comorbidities: F = 5.7, df = 3, *P* = 0.002.

‖ Covariates include age and number of medical comorbidities: F = 4.6, df = 3, *P* = 0.006.

¶ Covariates include age and number of medical comorbidities: F = 9.2, df = 3, *P* < 0.001.

# *P* value represents statistical comparison of post-COVID-19 nonclinical group, clinical group, and total sample to published normative data using one-sample *t*-test.

** Performance of the nonclinical group on the visuospatial subtests of the RBANS and Stroop Color Word Test was significantly *better* than published norms.

(Tables 4 and 5). When the two groups were compared with age- and education-adjusted normative values, the nonclinical group scored lower than normative values on only 1 test—immediate memory on the RBANS—while scoring *higher* than expected on RBANS visuospatial functioning and Stroop Color Word tests. In contrast, the clinical group scored significantly lower than normative values on 8 of 11 tests, including domains of attention, language, immediate and delayed memory of the RBANS, as well as executive functioning as assessed by Letter Fluency, Trail Making Test Part B, and Stroop Color-Word Test. Thus, decreased NP test performance noted for the entire sample was primarily accounted for by the clinical group. Consistent with this, the clinical group had a significantly higher proportion scoring with extremely low NP scores (Table 4, n = 12, 38% clinical, vs. n = 4, 14% nonclinical, *P* = 0.04).

**TABLE 5. Logistic Regression Analysis Predicting Neuropsychological Impairment by Key Clinical Variables**

| Statistic / Clinical variable | Wald statistic | df | Sig. (*P*, 95%) |
|---|---|---|---|
| Acute COVID symptom score | 3.89 | 1 | 0.05 |
| Current COVID symptom score | 3.55 | 1 | 0.06 |
| PHQ-9 score | 6.02 | 1 | 0.01 |
| GAD-7 score | 3.38 | 1 | 0.07 |
| Chalder Fatigue Scale score | 1.42 | 1 | 0.23 |
| Number of medical comorbidities | 4.93 | 1 | 0.03 |
| Patient assessment of own functioning-cognition | 8.45 | 1 | 0.004 |
| Patient assessment of own functioning-memory | 9.62 | 1 | 0.002 |
| Patient assessment of own functioning-language | 5.73 | 1 | 0.02 |

GAD-7 = Generalized Anxiety Disorder-7; PHQ-9 = Patient Health Questionnaire-9.

### *IADL and Quality of Life*

The clinical group had significantly more difficulty with IADLs than the nonclinical group and significantly diminished quality of life on the Endicott QLESQ (Tables 2 and 3).

## Predictors of NP Test Scores

To determine which clinical factors might predict extremely low NP scores, we conducted a logistic regression analysis, with extremely low NP scores ($\leq 2^{nd}$ percentile) as the dependent variable (Table 5). Independent variables included acute COVID-19 symptoms, current COVID-19 symptoms, PHQ-9 score, GAD-7 score, Chalder Fatigue Scale score, number of medical comorbidities, and PAOF memory, language, and cognition scores. Inflammatory markers were not included in this model as the smaller N would limit predictive power. In the regression model, peak COVID-19 symptoms, PHQ-9, number of medical comorbidities, and PAOF memory, language, and cognition scores were significant predictors of extremely low NP scores, correctly categorizing 78% (12/16, $P = 0.004$).

## Exploratory Correlations of Proinflammatory Cytokines

Because of the limited number of inflammatory marker results, we calculated Pearson correlation coefficients (r) to explore associations between IL-6, TNF-$\alpha$, and CRP and medical, psychiatric, and NP variables of interest. IL-6 was significantly correlated with acute COVID illness score (r = 0.32, $P < 0.05$), number of medical comorbidities (r = 0.58, $P < 0.001$) and Chalder Fatigue Scale score (r = 0.42, $P < 0.01$), but inversely correlated with Stroop Color Word Test t-score (r = −0.38, $P < 0.02$), and Trail Making Test Part B t-score (r = −0.30, $P < 0.05$). CRP was correlated with current COVID illness score (r = 0.38, $P < 0.01$) and PHQ-9 score (r = 0.32, $P < 0.05$) but inversely correlated with Endicott QLESQ (r = −0.32, $P < 0.05$). TNF-$\alpha$ had no statistically significant correlations.

# DISCUSSION

Data from this sample suggest that individuals reporting cognitive complaints months after acute COVID-19 may have extremely low NP test performance (scored less than or equal to the second percentile) relative to those without such symptoms. These cognitive difficulties may lead such individuals to seek treatment. When comparing a clinical sample of individuals seeking care for cognitive complaints and other post-COVID symptoms, we found diminished performance in multiple neurocognitive domains relative to age- and education-adjusted norms that were not present in the nonclinical group, including attention, processing speed, memory, and executive function. A significantly higher proportion of these individuals had extremely low NP scores. This pattern and degree of performance difficulty is like that documented in prior studies of COVID-19 with smaller sample sizes and shorter timeframe after acute illness, particularly among those who were hospitalized.[6,23–25] We also found that the clinical group had high levels of clinically significant depression and fatigue, diminished quality of life, and

more limitations in IADLs than the nonclinical group, even after covarying for age and medical comorbidity. This suggests that group differences were both statistically and *clinically* significant, affecting function and quality of life, and that these clinical symptoms or their combination appear to lead individuals to seek treatment.

The inclusion of a measure of subjective neurocognitive complaints (the PAOF) allowed for investigation of whether the perceived impairment correlates with the actual impairment. It is important to note that prior studies have found subjective cognitive complaints do not correlate reliably with NP test impairment,[42] leading to skepticism about whether subjective complaints are "real." However, the current data suggest that perception of cognitive problems, even months after acute COVID-19, may be a reliable sign of actual cognitive difficulty and should be investigated. It could be argued that 38% with an extremely low NP test performance in a sample of individuals with cognitive complaints is relatively low and that, conversely, 62% were in the normal range. Nonetheless, the significant differences found in the clinical group on individual NP tests relative to published norms may indicate that individuals with cognitive complaints may detect a decline in NP function relative to what would be considered normal for their age and premorbid functioning.

When investigating a potential profile of risk factors for extremely low NP scores in the sample, independent predictors in a logistic regression model included severity of acute COVID-19 illness symptoms, depressive symptoms, number of medical comorbidities, and subjective perception of memory, language, and cognitive (executive function) problems. It is not surprising that severity of acute COVID-19 illness would be associated with NP test scores as found in previous research[23,25]; however, prior studies have not incorporated standardized measures of COVID-19 symptoms, medical comorbidity, estimate of premorbid intellectual functioning and subjective cognitive complaints. Medical comorbidities such as obesity, hypertension, and diabetes are known to increase risk for NP dysfunction and severe COVID-19 illness hospitalization and mortality.[43]

It is important to note that, while current depressive symptoms were independently predictive of extremely low NP test scores, the causal relationship is not clear. It is possible that extremely low NP performance was caused by depression, as depression is associated with deficits in processing speed, memory, verbal fluency, and executive function.[44] Depression is also associated with later decline in cognition even in those with no baseline deficit.[45] The fact that participants with a history of depression before COVID-19 were not more likely to have extremely low test scores does not support this contention. It is also possible that the presence of neurocognitive decline, along with persistence of COVID-19-related symptoms and psychosocial stresses, causes depression. Finally, it is possible that depression and NP dysfunction in COVID-19 co-occur and may be due to the same underlying pathogenic mechanisms.

We investigated correlations between serum IL-6, TNF-α, and CRP levels and psychiatric, medical, and neurocognitive measures to explore whether evidence of systemic inflammation might be associated with these outcomes. The data indicated significant positive correlations between IL-6, COVID-19 symptoms at the time of diagnosis, number of medical comorbidities, fatigue, and measures of executive function. Furthermore, the elevated IL-6 level was more prevalent in the clinical group. In contrast, CRP was significantly correlated with current COVID-19 symptoms and depressive symptoms but inversely correlated with quality of life. It is not clear how to interpret these disparate findings. IL-6 may be more associated with acute COVID severity and the underlying medical comorbidity leading to fatigue and executive function impairment, while CRP may be a marker of current COVID symptom burden and depression, leading to diminished perceived quality of life. IL-6 and CRP have been cited extensively as markers of COVID-19 illness severity and prognosis.[46] These proinflammatory cytokines may predict or cause the neuropsychiatric sequelae described here. While proinflammatory cytokines have been studied extensively in psychiatry,[29] such research in COVID-19 is limited. Zhou et al. (2020) found that CRP was correlated with elevated reaction time in a sample of individuals recovered from COVID-19, while IL-6 was not correlated with NP scores.[47] These results are not consistent with the results documented in this study, but study methodologies differed. Taken together, these preliminary results support further research in this area.

Study strengths included standardized assessments across NP, medical, and psychiatric domains; however, the

study has important limitations. The study sample is relatively small and was skewed toward a clinical population, so the results may not be generalizable to the entire post-COVID population. While an estimate of premorbid intellectual function was obtained, pre-COVID-19 NP performance was not available for comparison. The study did not include a COVID-19-negative comparison group matched for age, medical, and other comorbidities. However, comparison to age- and education-corrected norms is an accepted methodology in clinical practice and NP studies.[48] Data for this study are cross-sectional, so the onset, course, and causal associations of clinical variables and extremely low NP test performance could not be determined. Inflammatory markers were not available for all participants and could not be included as predictors of NP impairment in logistic regression analysis. The IADL, while correlated with NP performance, is not an objective measure of occupational and social functioning. Neuroimaging, encephalographic, and other central nervous system studies were not uniformly available in study participants.

Despite the limitations cited previously, these data support the existence of clinically relevant neurocognitive difficulty months after acute COVID-19 illness and that cognitive complaints warrant clinical investigation. The results mirror our clinical experience in caring for patients in the WMCHealth Post-COVID Recovery Program where cognitive complaints are frequent and distressing. Despite finding significant correlations of clinical variables with inflammatory markers, our results are preliminary. Longitudinal follow-up of this cohort is in progress.

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