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Original Research Article

Cognitive Dysfunction, Psychiatric Distress, and Functional Decline After COVID-19



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Background: There is a limited understanding of the cognitive and psychiatric sequelae of COVID-19 during the post-acute phase, particularly among racially and ethnically diverse patients. **Objective:** We sought to prospectively characterize cognition, mental health symptoms, and functioning approximately four months after an initial diagnosis of COVID-19 in a racially and ethnically diverse group of patients. **Methods:** Approximately four months after COVID-19 diagnosis, patients in the Johns Hopkins Post-Acute COVID-19 Team Pulmonary Clinic underwent a clinical telephone-based assessment of cognition, depression, anxiety, trauma, and function. **Results:** Most Johns Hopkins Post-Acute COVID-19 Team patients assessed were women (59%) and members of racial/ethnic minority groups (65%). Of 82 patients, 67% demonstrated ≥ 1 abnormally low cognitive score. Patients requiring intensive care unit (ICU) stays displayed greater breadth and severity of impairment than those requiring less intensive treatment. Processing speed (35%), verbal fluency (26%–32%), learning (27%), and

memory (27%) were most commonly impaired. Among all patients, 35% had moderate symptoms of depression (23%), anxiety (15%), or functional decline (15%); 25% of ICU patients reported trauma-related distress. Neuropsychiatric symptoms and functional decline did not differ by post-ICU versus non-ICU status and were unrelated to global cognitive composite scores. **Conclusions:** At approximately 4 months after acute illness, cognitive dysfunction, emotional distress, and functional decline were common among a diverse clinical sample of COVID-19 survivors varying in acute illness severity. Patients requiring ICU stays demonstrated greater breadth and severity of cognitive impairment than those requiring less intensive treatment. Findings help extend our understanding of the nature, severity, and potential duration of neuropsychiatric morbidity after COVID-19 and point to the need for longitudinal assessment of cognitive and mental health outcomes among COVID-19 survivors of different demographic backgrounds and illness characteristics.

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Key words: COVID-19, cognitive impairment, critical illness, depression, anxiety, functional decline.

INTRODUCTION

The potential for neuropsychiatric complications of COVID-19 was appreciated early in the pandemic based on observations from prior coronavirus infections. Both the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) epidemics were characterized by delirium, cognitive impairment, mood disturbances, and anxiety that persisted beyond the acute phase of illness.¹ Against this background, early reports of neurologic symptoms and delirium coupled with an ever-growing infection rate raised concerns that cognitive and

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Cognitive Dysfunction After COVID-19

mental health sequelae of COVID-19 could have significant individual and population health implications.^{2,3}

While critical illness and hospitalization alone represent risk factors for impaired cognition and neuropsychiatric sequelae, combined hypoxemia, coagulopathy, need for greater sedation, social isolation, and related limits in access to rehabilitation services implies a potential for compounded neuropsychiatric risk in both short- and long-term outcomes.³⁻⁸ At present, most available data characterize psychiatric and cognitive symptoms during the acute phase of COVID-19 illness, including delirium/altered mentation at presentation or during hospitalization.^{9,10} Existing knowledge of post-acute neuropsychiatric symptoms associated with COVID-19 infection is limited and primarily focused on psychiatric rather than cognitive outcomes. When assessed one month after hospital discharge, more than half of patients in one study produced scores in the clinically elevated range across measures of anxiety (42%), insomnia (40%), depression (31%), and post-traumatic stress (28%).¹¹ Among COVID-19 patients who lack prior psychiatric histories, data suggest heightened risk of new-onset psychiatric diagnosis within 90 days of a positive COVID-19 test relative to that occurring after a range of other medical events.¹²

To date, most studies have relied on brief cognitive screening measures or small case series rather than detailed neuropsychological test batteries in samples of sufficient size to permit detection of patterns of impairment and associated disease and treatment characteristics.¹³⁻¹⁷ Much remains to be learned about the nature and severity of cognitive and psychiatric functioning across patients of varying disease severity and at various time points over the course of recovery from COVID-19.¹⁸ Furthermore, it is appreciated that racial and ethnic minority groups are disproportionately impacted by the pandemic and may be at higher risk of poor clinical outcomes, yet little data exist on long-term cognitive and psychiatric functioning in these groups.¹⁹⁻²¹

In order to characterize post-acute neuropsychiatric functioning, we prospectively evaluated a broad range of cognitive abilities, mental health symptoms, and functioning at approximately four months after an initial diagnosis of COVID-19 in a racially and ethnically diverse group of patients.

MATERIALS AND METHODS

Study Design

A comprehensive battery of cognitive tests and measures of mental health and functional decline were administered as part of routine clinical care and analyzed retrospectively. The Johns Hopkins Medicine Institutional Review Board approved the study.

Study Population

Patients included adults receiving care in the Johns Hopkins Post-Acute COVID-19 Team (JH PACT) pulmonary clinic, requiring referral from a treating physician.²² Qualifying criteria for post-ICU clinic services included acute illness from COVID-19 requiring ≥ 48 hours of ICU care. Referrals to the JH PACT were a standard component of the ICU discharge procedures. Qualifying criteria for non-ICU clinic services included either (1) recovery from acute COVID-19 hospitalization (non-ICU) with ongoing pulmonary and/or rehabilitation needs at the time of hospital discharge or (2) persistent symptoms at 4-6 weeks after acute infection without hospitalization. Residual symptoms prompting JH PACT referral included persistent pulmonary issues, dyspnea, dysautonomia, fatigue, cognitive complaints, pain, and other nonresolving symptoms after COVID-19 infection.

Characterization

COVID-19 diagnosis was made via real-time reverse transcription PCR test. Demographic characteristics including age, sex, race, and ethnicity as well as years of educational attainment and occupational status were obtained through chart review and patient self-report. The Barona Index combined demographic variables (age, sex, race, education, occupational status, and geographic region) with correction for the tendency for intelligence test scores to increase over time, known as the Flynn effect, to predict Wechsler Adult Intelligence Scale 4th edition Full Scale IQ scores.²³ See [Supplementary Table 1](#).

Cognitive Assessment

Patients underwent a telephone-based neuropsychological assessment battery; telephone assessment has been shown to be feasible and provides valid assessment of cognitive function relative to in-person

examinations.^{24–26} This battery has been successfully implemented in diverse patient populations.^{27,28} Assessments occurred between July 6, 2020, and January 22, 2021.

The cognitive battery consisted of eight scores. The Rey Auditory Verbal Learning Test (RAVLT^{29,30}) assessed acquisition of a 15-item word list that was presented over multiple exposure trials as well as memory as indexed by delayed recall for word list items. Oral Trail Making Test parts A and B assessed processing speed by having patients count aloud to 25 as quickly as possible (part A) and executive functioning (part B) by having them do so while switching between numbers and letters.³¹ Attention and working memory were assessed with a number span task during which patients repeated increasingly lengthy digit strings in forward and backward sequences.²⁸ Letter-cued verbal fluency assessed speeded word retrieval in response to phonetic cues by asking patients to name as many words as possible beginning with a certain letter of the alphabet over two 60-second trials (cues F and L²⁸). Category-cued verbal fluency assessed rapid access to semantic information by asking patients to name as many items of a given semantic category as possible over two 60-second trials (cues animals and vegetables²⁸). Standardized scores were derived from age-adjusted published normative data.^{28,30,31} A global cognitive composite was computed as the mean of age-adjusted standardized scores across up to 8 available cognitive scores.

Mental Health and Functional Assessment

Patients completed the Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) on which scores ≥ 5 and ≥ 10 reflect the presence of clinically elevated mild and moderate symptoms of depression and anxiety, respectively.^{32,33} Trauma-related distress was assessed in post-ICU patients via the Impact of Events Scale-6, on which scores of ≥ 1.75 reflect symptomatic levels of post-traumatic distress.^{34,35} The Quick Dementia Rating Scale, patient version, (QDRS) assessed subjective change across 10 domains of cognition, mood, and daily functioning. Scores ≥ 1.5 and ≥ 6 reflect clinically meaningful mild and moderate functional decline, respectively.^{36,37}

Missing Data

One patient declined to report race, and two declined to report ethnicity. Four patients could not complete Oral

Trail Making Test part B, and one declined to attempt the task. An additional patient declined to complete the letter and category fluency tasks as well as the GAD-7. Those with missing cognitive data were similar to those with complete data with respect to age, sex, racial/ethnic minority status, education, estimated IQ, cognitive composite scores, and psychiatric and functional assessment scores ($P > 0.05$).

Statistical Analyses

Cognitive outcomes

Independent samples t-tests compared PACT clinics (non-ICU/post-ICU) by age, educational attainment, estimated IQ, and time since diagnosis. Chi-square analyses compared PACT clinics by sex, race, and ethnicity. These demographic and clinical characteristics were also explored in relation to global cognitive composite scores via independent samples t-tests, analysis of variance, and chi-square analyses. Analysis of covariance compared global cognitive composite scores by PACT clinic (non-ICU/post-ICU) adjusting for variables that were either imbalanced across clinics or associated with global cognitive composite scores. Frequencies were calculated for the proportion of individuals overall and within each PACT clinic producing ≥ 1 cognitive score in the impaired range. Mild/moderate and severe cognitive impairment were defined as performances ≥ 1.5 and ≥ 2 standard deviations below published age-adjusted normative means for each cognitive test and the global cognitive composite score. Because neurologically healthy individuals may produce one or more low test scores on a cognitive battery, reliance on a single low score may increase the likelihood of false-positive findings of impairment.^{38–40} The likelihood of obtaining one or more low scores increases along with the number of tests in the battery.^{39,40} Based on the binomial probability distribution, in a cognitive battery such as this yielding 8 primary scores, there is a 10% probability that 2 scores will exceed the ≥ 1.5 standard deviation cutoff for mild/moderate impairment and a 1% probability that 2 scores will exceed the ≥ 2 standard deviation cutoff for severe impairment.⁴¹ Tests for the significance of proportions determined whether the observed proportion of individuals within each clinic producing at least 2 scores ≥ 1.5 and ≥ 2 standard deviations below demographic means exceeded expectation (i.e., 10% and 1% probabilities, respectively).

Cognitive Dysfunction After COVID-19

Mental health and functioning

Independent samples t-tests compared scores on measures of the PHQ-9, GAD-7, and QDRS by PACT clinic. Frequencies were calculated for the proportion of individuals scoring above clinical cutoffs on mental health and functional outcome measures. Pearson correlations assessed the association between cognitive test performances and PHQ-9, GAD-7, Impact of Events Scale-6, and QDRS.

Statistical analyses were performed with IBM SPSS statistics version 25.

RESULTS

Characteristics

Of 82 PACT patients for whom English is the primary language, N = 48 (59%) required ≥ 48 hours of ICU care (i.e., post-ICU clinic). The majority were women (59%) and members of racial/ethnic minority groups. The mean (SD) age was 54.5 (14.6) years. The majority (95%) had at least a high school (12 years) education with mean (SD) 14.7 (3.1) years. The mean (SD) estimated IQ score was 98.2 (8.6). Post-ICU patients were older and had fewer years of education as well as lower estimated IQ scores than non-ICU patients but did not differ with respect to sex, race, ethnicity, or time since initial COVID-19 diagnosis. See [Table 1](#).

Cognitive Outcomes

Cognitive testing occurred approximately 4 months after the first positive test for COVID-19 (mean [SD], 126.5 [70.1] days). Mean age-adjusted standard scores are presented in [Figure 1](#). Overall, 67% of PACT patients produced ≥ 1 score in the mild/moderate or severe range of impairment (65% non-ICU, 69% post-ICU).

Global cognitive composite scores differed by ICU status (post-ICU versus non-ICU, $t(80) = 2.18$, $P = 0.03$), racial/ethnic minority status ($t(79) = 3.32$, $P = 0.001$), and estimated IQ ($F(1,79) = 14.47$, $P < 0.001$) but did not differ by age, sex, education, or time since initial COVID-19 diagnosis (all $P > 0.05$). After accounting for age, education, estimated IQ, and racial/ethnic minority status, post-ICU clinic patients produced lower cognitive composite scores than non-ICU patients (mean post-ICU = 90.6, SD = 11.0, mean non-ICU = 95.8, SD = 10.3, $F(1, 75) = 4.6$, $P = 0.04$). Among non-ICU patients, cognitive

composite scores did not differ between those who were hospitalized (n = 21, 62%) and those who were not hospitalized (n = 13, 38%, $t(32) = -0.19$, $P = 0.85$). Racial/ethnic minorities showed an insignificant trend toward disproportional receipt of care in the ICU (minority post-ICU = 65.4%, minority non-ICU = 34.6%, white post-ICU = 44.8%, white non-ICU = 55.2%, chi-square (1, n = 81) = 3.2, $P = 0.07$). Within racial/ethnic minority patients, those treated in the post-ICU clinic demonstrated a trend toward poorer global cognitive functioning relative to racial/ethnic minority patients treated in the non-ICU clinic (mean post-ICU = 87.9, SD = 10.1, mean non-ICU = 93.3, SD = 10.9, $t(50) = 1.77$, $P = 0.083$) while not differing with respect to age, education, or estimated IQ (all $P > 0.42$).

On a global cognitive composite measure, the average score among non-ICU patients was 0.28 standard deviations below demographic expectation, with 6% producing global cognitive functioning scores below the cutoff for mild/moderate impairment. The observed proportion of non-ICU patients producing ≥ 2 cognitive scores beyond the cutoff for mild/moderate impairment (32%) exceeded the expected 10% proportion ($P < 0.001$).⁴¹ Mild/moderate impairment was particularly common on Oral Trail Making Test part A, category-cued verbal fluency, RAVLT acquisition, and RAVLT delayed recall. The observed proportion of non-ICU patients producing ≥ 2 cognitive scores beyond the cutoff for severe impairment (15%) exceeded the expected 1% proportion ($P < 0.001$). Severe impairment was most common on the Oral Trail Making Test part A (21%). See [Figure 2](#), [Table 2](#), and [Supplementary Table 2](#).

Post-ICU patients performed, on average, 0.63 standard deviations below expectation on a global cognitive composite measure, with 19% producing global cognitive functioning scores below the cutoff for mild/moderate impairment. The observed proportion of post-ICU patients producing ≥ 2 scores below the cutoff for mild/moderate impairment (58%) exceeded the expected 10% proportion ($P < 0.001$). Elevated rates of impairment were observed across all domains with the exception of number span forward. More than one-third of post-ICU patients performed in the mild/moderately impaired range on the Oral Trail Making Test part A, letter- and category-cued verbal fluency, RAVLT acquisition, and RAVLT delayed recall. The observed proportion of post-ICU patients producing

TABLE 1. Baseline Demographic, Cognitive, and Mental Health Characteristics Overall and Differences in ICU Status

Variables	Overall (N = 82)	Non-ICU (N = 34)	Post-ICU (N = 48)	T/Chi-square statistic (df)	P value
Age, mean (sd); range, years	54.5 (14.6); 26–85	49.5 (13.0); 26–82	58.0 (14.8); 29–85	−2.7 (80)	<0.01
Male, n (%)	34 (41.5)	11 (32.4)	23 (47.9)	2.0 (1, 82)	0.16
Race, n (%)				4.2 (4, 82)	0.38
White or Caucasian	29 (35.4)	16 (47.1)	13 (27.1)		
Black or African American	44 (53.7)	15 (44.1)	29 (60.4)		
Asian	2 (2.4)	1 (2.9)	1 (2.1)		
Other	6 (7.3)	2 (5.9)	4 (8.3)		
Unspecified	1 (1.0)	—	1 (1.2)		
Ethnicity, n (%)				1.5 (2, 82)	0.47
Not Hispanic or Latino	78 (95.1)	33 (97.1)	45 (93.8)		
Hispanic or Latino	2 (2.4)	1 (2.9)	1 (2.9)		
Unspecified	2 (2.4)	—	2 (2.4)		
Education, mean (sd); range, years	14.7 (3.1); 2–22	15.7 (3.1); 12–22	14.0 (3.0); 2–21	2.5 (80)	0.02
Estimated IQ, mean (sd); range, years	98.2 (8.6); 70–114 [†]	100.7 (8.5); 84–114	96.4 (8.4); 70–112	2.3 (79)	0.02
Time from diagnosis, mean (sd); range, days	126.5 (70.1); 19–282	122.7 (75.7); 27–294	129.0 (66.9); 19–301	−0.4 (78)	0.69
RAVLT acquisition, mean (sd); range [#]	42.6 (11.2); 17–63	46.7 (10.8); 20–63	39.7 (10.7); 17–63	2.9 (80)	<0.01
RAVLT delayed recall, mean (sd); range [#]	7.5 (3.5); 0–14	8.4 (3.5) 0–13	6.9 (3.3); 1–14	1.9 (80)	0.06
Oral Trail Making Test Part A, mean (sd); range [#]	10.1 (6.7); 4–56	10.3 (9.0); 5–56	10.0 (4.6); 4–26	0.2 (80)	0.85
Oral Trail Making Test Part B, mean (sd); range [#]	42.5 (34.4); 13–231	37.2 (38.6); 13–231 [‡]	46.5 (30.7); 17–145 [§]	−1.2 (75)	0.24
Number span forward, mean (sd); range [#]	9.9 (2.7); 3–16 [*]	10.4 (2.4); 7–16	9.6 (2.9) 3–16	1.5 (80)	0.15
Number span backward, mean (sd); range [#]	7.2 (2.8); 1–15	7.6 (2.4); 3–13	6.9 (3.1); 1–15	1.1 (80)	0.28
Letter-cued verbal fluency, mean (sd); range [#]	23.2 (8.7); 5–48 [†]	27.0 (8.1); 11–48 [‡]	20.6 (8.2); 5–40	3.5 (79)	<0.01
Category-cued verbal fluency, mean (sd); range [#]	30.8 (9.3); 13–50 [†]	32.6 (9.2); 14–50 [‡]	29.5 (9.2); 13–48	1.5 (79)	0.15
PHQ-9, mean (sd); range	7.0 (5.0); 0–20	7.5 (5.5); 0–20	6.7 (4.6); 0–20	0.71 (80)	0.48
GAD-7, mean (sd); range	5.3 (4.7); 0–19	5.5 (4.6); 0–19	5.1 (4.9); 0–19	0.35 (79)	0.72
IES-6, mean (sd); range	—	—	1.2 (1.4); 0–7	—	—
QRDS, mean (sd); range	3.1 (2.9); 0–12	3.2 (3.3); 0–11	3.0 (2.7); 0–12	0.27 (80)	0.79

Abbreviations: GAD-7 = Generalized Anxiety Disorder-7; IES-6 = Impact of Events Scale-6; PHQ-9 = Patient Health Questionnaire-9; QRDS = Quick Dementia Rating Scale; RAVLT = Rey Auditory Verbal Learning Test.

* n = 77.

† n = 81.

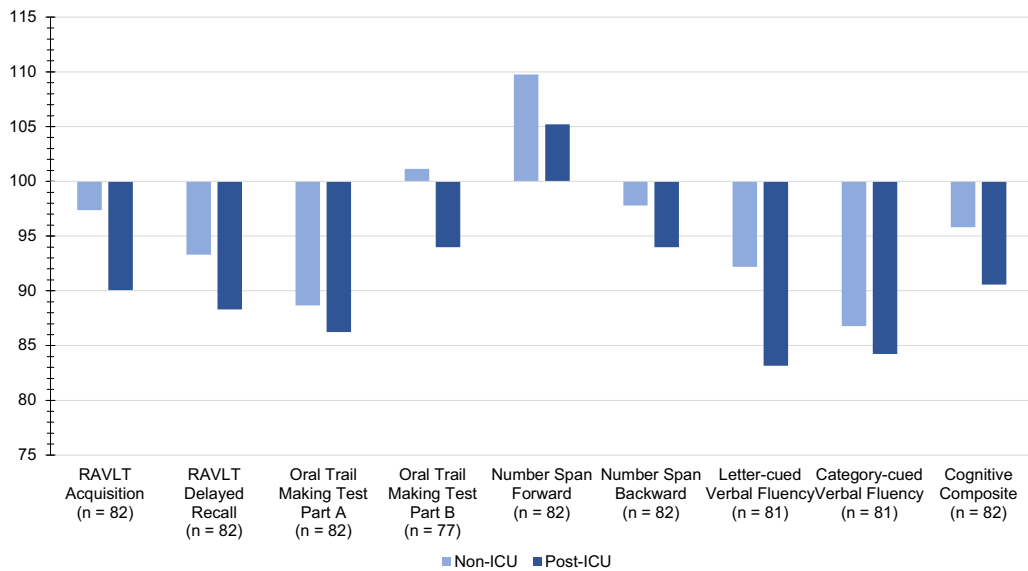
‡ n = 33.

§ n = 44.

|| n = 47.

Age-adjusted standard scores, M = 100, SD = 15; allowable range, 61–139.

FIGURE 1. Age-Adjusted Standard Scores by ICU Status. Age-adjusted standard scores have a mean of 100 and standard deviation 15, with higher scores reflecting better performance. The cognitive composite was computed as the mean of age-adjusted standard scores across the cognitive scores.



≥2 cognitive scores beyond the cutoff for severe impairment (31%) exceeded the expected 1% proportion ($P < 0.001$). Severe impairment was most common on a test of processing speed (29%).

Mental Health and Functioning

Scores on the PHQ-9, GAD-7, and QDRS did not differ based on ICU status (all $P > 0.05$). Overall, 78% of PACT patients produced ≥1 mildly elevated score across measures of psychiatric distress and functional decline (74% non-ICU, 81% post-ICU), with 35% producing ≥1 moderately elevated score across these measures (35% non-ICU, 35% post-ICU). Mildly elevated PHQ-9 or GAD-7 were reported by 70% of PACT patients, with 27% reporting moderate to severe elevations. In addition, 62% and 69% of patients reported mild functional declines on the QDRS across non-ICU and post-ICU clinics, with 18% and 13% reporting moderate functional declines, respectively. One quarter of post-ICU patients reported symptomatic levels of trauma-related distress on the Impact of Events Scale-6. See Table 3.

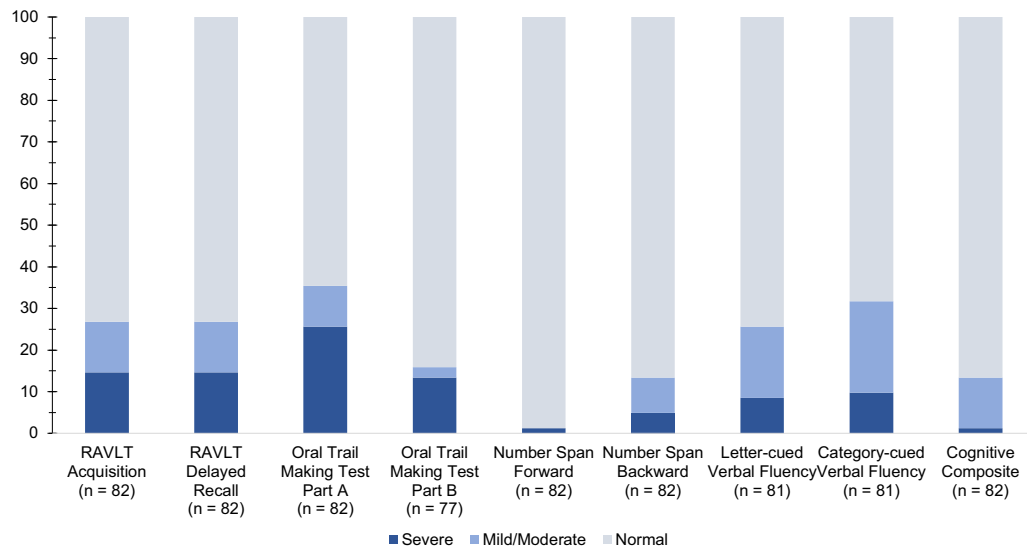
Global cognitive composite scores were not associated with scores on the PHQ-9, GAD-7, Impact of Events Scale-6, or QDRS (all $P > 0.08$).

DISCUSSION

At approximately 4 months after acute illness, two-third of COVID-19 patients presenting to a post-COVID-19 clinic showed impairment in one or more domains of cognition. Cognitive deficits were widespread in those with and without ICU stays and occurred most commonly on measures of oral processing speed and verbal fluency as well as learning and memory. Patients requiring at least 48 hours of ICU care demonstrated poorer global cognition and also demonstrated more frequent impairment in executive functioning and working memory relative to those requiring less intensive treatment. Psychiatric distress and functional decline were also common, with 35% of COVID-19 survivors producing at least one moderately elevated score across measures of anxiety, depression, trauma, and functional decline. One in four patients requiring treatment in the ICU reported trauma-related distress. Severity of psychiatric distress and functional decline were similar among patients requiring more and less intense COVID-19 treatment and were unrelated to cognitive functioning.

Our understanding of post-acute cognitive and mental health functioning remains in the early stages and is limited to a handful of studies that vary with respect to patient characteristics, COVID-19 severity,

FIGURE 2. Proportion of PACT Patients Producing Scores at or Below Cutoffs for Mild/Moderate and Severe Cognitive Impairment Across Cognitive Tests. Mild/moderate impairment is defined as scores ≥ 1.5 standard deviation below published age-adjusted normative means. Severe impairment is defined as scores ≥ 2 standard deviations below published age-adjusted normative means.



the time in which testing occurred relative to infection, and the breadth and depth of cognitive assessment. In an Italian study, 12 previously neurologically healthy adults (age 48–80 years) hospitalized for neurologic complications of COVID-19 performed more poorly than matched controls on an executive functioning composite and measures of reaction time and vigilance when tested near the end of their course of inpatient rehabilitation.⁴² More recently, 81% of patients (n = 57, mean age 65 years) recovering from COVID-19 infection on an inpatient rehabilitation unit showed mild to severe cognitive impairment on a battery assessing memory and executive functioning, with deficits occurring most frequently in working memory, set shifting, divided, attention, and processing speed.⁴³

Two studies have examined cognition in relatively younger and seemingly less severely ill patients early in the post-acute phase. Among 35 previously cognitively healthy COVID-19 survivors in Spain (age 24–60 years) who were tested 10 to 35 days after hospital discharge, severe impairments (T score ≤ 30) were most frequent on tests of letter-cued verbal fluency (11%), mental flexibility (9%), and working memory (9%), with less frequent deficits (6%) observed on tests of processing speed, category-cued verbal fluency, attention, learning, and memory.⁴⁴ Subjective cognitive complaints were associated with the severity of anxiety and depressive

symptoms, but not objective cognitive performance. A group of 29 hospitalized adults in China (age 30–64 years) underwent tablet-based cognitive testing of select cognitive domains 2 to 3 weeks after COVID-19 infection. Patients performed more poorly than age- and sex-matched peers on aspects of sustained attention but did not differ from controls with respect to processing speed, executive functioning, attention, or working memory nor did they report elevated symptoms of anxiety or depression.⁴⁵

Data on longer term cognitive outcomes after COVID-19 are just starting to take shape and suggest that outcomes may vary based on markers of disease severity. Of 179 previously cognitively and psychiatrically healthy patients in Spain (age 22–81 years) assessed roughly two months after hospital discharge, 58% demonstrated moderate deficits (T score ≤ 40) on at least one of four cognitive tests, most frequently learning and category-cued verbal fluency. Clinically elevated symptoms of depression, anxiety, and/or trauma were reported by 39% of patients.⁴⁶ In contrast, in an Australian sample of 78 patients tested two to three months after diagnosis and of whom only 12% required hospitalization, objective cognitive impairment was demonstrated by only 10% of patients, most frequently on a test of psychomotor speed, with most deficits (63%) being of mild severity.⁴⁷ Symptoms of

Cognitive Dysfunction After COVID-19

TABLE 2. Proportion of PACT Patients Performing at or Below the Mild/Moderate and Severe Ranges of Impairment Across Cognitive Tests by ICU Status

Domain	Overall (N = 82), % impaired*		Non-ICU (N = 34), % Impaired		Post-ICU (N = 48), % Impaired	
	Mild/Moderate	Severe	Mild/Moderate	Severe	Mild/Moderate	Severe
	RAVLT acquisition	26.8	14.6	14.7	8.8	35.4
RAVLT delayed recall	26.8	14.6	14.7	8.8	35.4	18.8
Oral Trail Making Test Part A	35.4	25.6	32.4	20.6	37.5	29.2
Oral Trail Making Test Part B	15.9 [†]	13.4 [†]	11.8 [§]	8.8 [§]	18.8	16.7
Number span forward	1.2	1.2	0	0	2.1	2.1
Number span backward	13.4	4.9	8.8	2.9	16.7	6.3
Letter-cued verbal fluency	25.6 [‡]	8.5 [‡]	11.8 [§]	2.9 [§]	35.4	12.5
Category-cued verbal fluency	31.7 [‡]	9.8 [‡]	26.5 [§]	5.9 [§]	35.4	12.5
Cognitive composite score	13.4	1.2	5.9	2.9	18.8	0

Abbreviations: ICU = intensive care unit; PACT = Post-Acute COVID-19 Team; RAVLT = Rey Auditory Verbal Learning Test.

* Mild/moderate and severe cognitive impairment were defined as performances ≥ 1.5 and ≥ 2 standard deviations below published age-adjusted normative means. Hence, 7% of normative control group participants would be expected to produce a score in the mild/moderate range of impairment on any single cognitive test, and 2% would be expected to produce a score in the severe range of impairment on any single cognitive test.

[†] n = 77.

[‡] n = 81.

[§] n = 33.

^{||} n = 44.

depression were reported by 21%. More recently, a prospective US cohort of 100 nonhospitalized patients found high rates of relatively young individuals (mean age 43 ± 11), females (70%), and those with pre-existing anxiety/depression (42%) and autoimmune disease (16%) presented to a post-COVID clinic. When assessed five to six months after the illness, there was no difference in subjective rates of “brain fog” or cognition-related quality of life between those who had tested positive versus negative for SARS-CoV-2. Among a smaller subset undergoing objective

assessment (n = 34), the groups did not differ in their performance on a brief cognitive battery although the SARS-CoV-2 positive group did underperform relative to demographic controls on measures of attention and working memory.⁴⁸

To date, predictions as to the potential for long-term neuropsychiatric sequelae of COVID-19 have been based largely on observations of neurologic symptoms and delirium in the acute stage of illness coupled with literature from prior coronavirus epidemics and observations made in the study of critical

TABLE 3. Proportion of PACT Patients Scoring in the Symptomatic Range Across Mental Health and Functional Outcomes by ICU Status

IES-6	Overall (N = 82), % symptomatic		Non-ICU (N = 34), % symptomatic		Post-ICU (N = 48), % symptomatic	
	Mild	Moderate	Mild	Moderate	Mild	Moderate
	PHQ-9	67.1	23.2	67.6	29.4	66.7
GAD-7	50.0*	14.8	52.9 [†]	15.2	47.9	14.6
QRDS	65.9	14.6	61.8	17.6	68.8	12.5

Abbreviations: GAD-7 = Generalized Anxiety Disorder-7; IES-6 = Impact of Events Scale-6; PHQ-9 = Patient Health Questionnaire-9; QRDS = Quick Dementia Rating Scale.

* n = 81.

[†] n = 33.

illness survivors. More than 15% of patients affected by the SARS and MERS epidemics demonstrated cognitive impairment and psychiatric disturbance 6–39 months after recovery.¹ Similarly, reports that at one year after hospitalization for critical illness, cognitive deficits persist in 24%–34%, symptoms of post-traumatic distress persist in 34%, and symptoms of depression persist in 29% suggest that long-term follow-up of COVID-19 patients is warranted.^{6–8} While depression has been found to independently predict long-term cognitive impairment in survivors of critical illness,⁴⁹ the present study did not find psychiatric symptoms to track with the intensity of treatment or severity of cognitive dysfunction. More work is needed to understand the mechanisms driving cognitive and psychiatric morbidity among individuals treated for COVID-19.

The present study reflects a detailed assessment of cognitive functioning, psychiatric distress, and functional decline in a sample of clinically referred COVID-19 patients during the post-acute phase. Patients spanned a wide age range and were of diverse racial and ethnic backgrounds. They varied in disease severity and level of care required during the acute phase of illness. Patients were not excluded based on pre-existing medical or neurological conditions; rather, findings reflect the neuropsychiatric functioning of patients who are likely to receive treatment in a post-acute COVID-19 pulmonary clinic. We used a comprehensive battery and methodologically rigorous definitions of cognitive impairment. Assessments also occurred later in the post-acute phase than has previously been explored and provide novel data on the potential duration of neuropsychiatric sequelae among COVID-19 survivors.

The study findings are limited by the selective nature of patients seen in the JH PACT clinic and are not generalizable to those who do not seek outpatient post-COVID-19 care. As these are clinically referred patients, we also lack baseline data that could help determine the extent to which observed cognitive and psychiatric dysfunction reflects sequelae of COVID-19 illness. Furthermore, ours is one of the first dedicated COVID-19 survivorship clinics in the United States, with data collection beginning relatively early in the pandemic.²² As such, we were unable to recruit healthy controls and instead relied on published normative data to establish rates of poor cognitive performance. The normative data for some tests were derived from samples that were relatively older and less racially and

ethnically diverse than our own.²⁸ The use of regression-based norms allowed for standardization of obtained cognitive scores for younger individuals who were not well represented in the normative data set. The finding that a substantial proportion of patients showed cognitive impairment even when applying norms for older adults suggests that the extent of cognitive dysfunction in younger COVID-19 survivors may be higher than appreciated in the present study. In addition, our finding that within racial/ethnic minority patients, those treated in ICU for ≥ 48 hours tended to perform more poorly than those requiring less intensive treatment, while not differing in age, education, or intelligence suggests that disease severity rather than systematic biases in clinic makeup underly the observation of poorer cognition outcomes in ICU survivors. Further work is needed to elucidate and combat systemic inequalities that are contributing to the disproportional impact of the COVID-19 pandemic among racial minority groups. We may have underestimated rates of executive functioning by excluding those who could not complete the tasks rather than classifying these individuals as impaired. Finally, study data were collected over seven months in which rapid advances were made in the treatment of COVID-19. It remains to be seen whether neuropsychiatric outcomes will improve in parallel with treatment advances.

CONCLUSIONS

The present study's findings of persistent cognitive deficits, psychiatric symptoms, and functional decline at approximately 4 months after the diagnosis help extend our understanding of the breadth, severity, and potential duration of neuropsychiatric morbidity among patients presenting to a post-COVID-19 clinic. Consistent with reports that racial and ethnic minority groups are disproportionately impacted by the pandemic, minority patients composed most individuals receiving care in the JH PACT clinic.^{20,21} This underscores the need for greater representation of minority groups in COVID-19 research to further understand the full impact of COVID-19 in vulnerable and traditionally underrepresented groups. Findings highlight the need for multidisciplinary integrated care teams aimed at providing comprehensive survivorship care for COVID-19 survivors throughout the recovery process. They also serve as a foundation for the

Cognitive Dysfunction After COVID-19

longitudinal assessment of cognitive and mental health outcomes among COVID-19 survivors of different demographic backgrounds and illness characteristics.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jaclp.2021.10.006>.

Conflict of Interest: E.B. reports receiving speaker fees/honoraria from the University of Rochester, Johns Hopkins University, and Montana Area Health Education Center. A.M.P. reports receiving legal consulting fees; speaker fees/honoraria from Vizient, Johns Hopkins, ASHA, HCL Healthcare India, and Global Tracheostomy Collaborative; and Data Safety Monitoring

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