



Published in final edited form as:

J Am Assoc Nurse Pract. ; 34(3): 499–508. doi:10.1097/JXX.0000000000000647.

Describing Cognitive Function and Psychosocial Outcomes of COVID-19 Survivors: A Cross Sectional Analysis

Ashley Henneghan, PhD, RN, FAAN^a, Kimberly A. Lewis, PhD, RN^{b,c}, Eliana Gill, BSN, RN^{d,e}, Oscar Y. Franco-Rocha, BSN, RN^f, Ruben D. Vela^g, Sarah Medick, MPH, RN^f, Shelli Kesler, PhD^h

^a-Assistant Professor, School of Nursing, Department of Oncology, Dell Medical School, The University of Texas at Austin, 1710 Red River St. Austin, TX, U.S., 78712.

^b-Nurse Scientist, Department of Nursing Research, Ascension Texas, Austin, TX

^c-Postdoctoral Scholar, Department of Physiological Nursing, University of California at San Francisco, CA 94143.

^d-Predoctoral Student, School of Nursing, The University of Texas at Austin, 1710 Red River St. Austin, TX, U.S., 78712.

^e-Registered Nurse, Ascension Seton Medical Center Austin, 1201 W. 38th St. Austin, TX 78705.

^f-School of Nursing, The University of Texas at Austin. 1710 Red River St. Austin, TX, 78712.

^g-Department of Diagnostic Medicine, Dell Medical School, The University of Texas at Austin, Austin, TX.

^h-Associate Professor, School of Nursing, Department of Diagnostic Medicine, Dell Medical School, University of Texas at Austin, Austin, TX

Abstract

Background: Neurological and psychological symptoms are increasingly realized in the post-acute phase of COVID-19.

Purpose: To examine and characterize cognitive and related psychosocial symptoms in adults (21–75 years) who tested positive for or were treated as positive for COVID-19.

Methodology: In this cross-sectional study, data collection included a cognitive testing battery (Trails B; Digit Symbol Substitution; Stroop; Immediate and Delayed Verbal Learning) and surveys (Demographic/clinical history; self-reported depressive symptoms, fatigue, anxiety, sleep

Correspondence: Ashley Henneghan, PhD, RN, FAAN. Assistant Professor, School of Nursing, Department of Oncology, Dell Medical School, The University of Texas at Austin, 1710 Red River St. Austin, TX, U.S., 78712. Ph: 512-471-5412. ahenneghan@utexas.edu.

Alternative Correspondence: Kimberly A. Lewis, PhD, RN. Postdoctoral Scholar, Department of Physiological Nursing, University of California at San Francisco, CA 94143. Kimberly.Lewis@ucsf.edu.

Author contributions: Conceptualization (AMH, SRK, KAL); Data curation (AMH,RV); Data collection (OFR, RV, SM), Formal Analysis (AMH, KAL); Funding acquisition (AMH, SRK); Investigation (AMH, KAL, SRK); Methodology (AMH, KAL, SRK); Project administration (AMH, RV, OFR, SM); Resources (AMH, KAL, SRK); Supervision (SRK; AMH, KAL); Validation (AMH, KAL, SRK); Visualization (AMH); Writing – original draft (AMH, SRK); Writing – review & editing (AMH, KAL, OFR, EG, RV, SM, SRK)

Disclosures or disclaimers: The authors have no disclosures or disclaimers. The information reported here has not been reported elsewhere.

disturbance, social role performance, and stress). Results were compared to published norms, rates of deficits (more than 1 standard deviation from the norm) were described, and correlations explored.

Results: We enrolled 52 participants (mean age 37.33 years; 78.85% female) who were, on average, 4 months post illness. The majority had a history of mild or moderate COVID-19 severity. Forty percent of participants demonstrated scores that were 1 standard deviation or more below the population norm on 1 or more of the cognitive tests. A subset had greater anxiety (21.15%), depressive symptoms (23.07%), and sleep disturbance (19.23%) than population norms. Age differences were identified in Stroop, Digit Symbol, and Trails B scores by quartile ($p < .01$), with worse performance in those aged 28 – 33 years.

Conclusions: Cognitive dysfunction and psychological symptoms may be present in the weeks or months following COVID-19 diagnosis, even in those with mild to moderate illness severity.

Implications: Clinicians need to be aware and educate patients about the potential late/long term cognitive effects of COVID-19, even in mild to moderate disease.

Keywords

COVID-19; survivors; cognitive outcomes; psychological symptoms; executive function

Introduction

Growing evidence supports that persons diagnosed with COVID-19 can exhibit ongoing physical, cognitive, and psychosocial symptoms referred to as “post-COVID Syndrome” or “long COVID” (Oronsky et al., 2021). The majority of those with symptomatic COVID-19, experience ongoing symptoms 2 to 6 months after initial infection (Carvalho-Schneider et al., 2020; Datta et al., 2020; Davis et al., 2020; Huang et al., 2021). Davis et al. (2020) reported 96% of 3,762 surveyed survivors had symptoms beyond 90 days. Understanding the late and long-term effects of COVID-19 is critical, since it is estimated that 148,174,749 people worldwide have tested positive for this virus (as of April 27, 2021; (Dong et al., 2020)).

Although COVID-19 is primarily thought of as a respiratory disease, neurological involvement is now well documented in hospitalized patients (Bougakov et al., 2021). It is estimated that about 30–60% of patients exhibit neurological symptoms including loss of smell and taste, headaches, dizziness, confusion, impaired level of consciousness, ataxia, seizures, acute cerebrovascular illness, and delirium (Alnefeesi et al., 2020; Bougakov et al., 2021; Roman et al., 2020). The virus can access and interfere with neurobiological functioning directly (Pero et al., 2020) as well as indirectly via immune activation. Cytokine storm and immunosuppression in the periphery can cause inflammatory dysregulation, leakage of the blood brain barrier and neuroinflammation (Bougakov et al., 2021; Ogier et al., 2020; Oronsky et al., 2021; Pero et al., 2020). Prothrombic states can lead to hypoxemia, cerebral microvascular damage, coagulopathy, and endothelial dysfunction that could impact neurobiology and associated cognitive functioning (Miners et al., 2020; Moonis et al., 2020). Neuroimaging data of inpatient COVID-19 patients show acute cerebral infarcts,

leukoencephalopathy, hypoxic injury, demyelinating encephalomyelitis, and cranial nerve enhancement (Moonis et al., 2020).

Neurological symptoms are becoming increasingly realized in the post-acute phase of COVID-19, especially those with severe infections requiring hospitalization. In one study, 1/3 of survivors 100 days post COVID-19 complained of memory and concentration problems (Garrigues et al., 2020). In another report, the majority of 3,762 survivors reported cognitive dysfunction 6 months later (Davis et al., 2020). Less is known about underlying mechanisms of cognitive abnormalities of survivors, however, disrupted brain structure and function was reported in 55% of survivors (n= 60) three months post infection (Lu et al., 2020).

There is also increasing evidence of persistent psychological symptoms including anxiety, depression, insomnia, fatigue, and post-traumatic stress disorder (Willi et al., 2021) in COVID-19 survivors. One study reported that 30% of survivors displayed clinical anxiety/depression up to 3 months later (Tomasoni et al., 2020). Mazza et al. (2020) reported that a significant portion of 402 adult survivors had clinical levels of post-traumatic stress disorder (28%), depressive symptoms (31%), insomnia (40%), and anxiety (42%). Huang et al. (2021) reported that fatigue, anxiety, and depression were among the most common symptoms reported in their large sample of survivors 6 months post discharge.

In this pilot study we examined and characterized cognitive and related psychosocial symptoms in persons who tested positive for or were treated as positive for COVID-19. We aimed to 1) determine the feasibility of recruiting COVID-19 survivors and remotely collecting cognitive functioning (performance and perception) and psychosocial symptoms (depressive symptoms, anxiety, fatigue, sleep disturbance, social role performance, and stress) and 2) to describe the cognitive functioning and related psychosocial symptoms of survivors compared to established population norms.

Methods and Materials

The study was an observational, cross-sectional analysis. The University of Texas at Austin Institutional Review Board (IRB) provided oversight for all research procedures related to this study (IRB ID: STUDY00000246). Research was conducted in accordance with the Helsinki Declaration; however, no personal health information was collected, therefore the IRB determined that informed consent was not necessary.

Inclusion/Exclusion Criteria

Adults ages 21 to 75 who tested positive for COVID-19, or presumed positive by the medical team, were willing and able to complete remote data collection (cognitive testing; questionnaires), and who spoke English or Spanish were included. Persons with a pre-COVID diagnosis of significant neurological disorders or active COVID-19 infection were excluded.

Study Procedures

Patients were recruited from a central Texas hospital system from January 2021—February 2021. The hospital identified positive COVID-19 cases that were admitted or assessed in the emergency department between March 2020 and July 2020. Study flyers were directly mailed to these individuals from the hospital research department, distributed through the nursing department at this hospital, and through social media postings. Those interested in participating contacted our study team and were screened for eligibility.

Study data were collected and managed using REDCap electronic data capture tools (Harris et al., 2019; Harris et al., 2009). Questionnaires were administered via REDCap surveys in either English or Spanish. After survey completion, instructions for the cognitive testing battery were sent. The entire assessment battery took less than 1 hour to complete, and participants were given a \$25 gift card honorarium for participation.

Outcome Measures

Demographics, Medical and COVID-19 Clinical History—We leveraged instruments that have been published by the National Institutes of Health (NIH) to facilitate COVID-19 related research (“NIH Public Health Emergency and Disaster Research Response (DR2),” 2021). We used the *UPenn Patient Health- General Health Questionnaire* to capture participant’s health history, and the *COVID-19 Experiences (COVEX)* to measure COVID-19 specific diagnosis and symptoms (See supplementary materials for COVID-19 symptom and/or severity items). We added a categorical question regarding receipt of a COVID-19 vaccine. We used the *OSUMC Impact Questionnaire* to measure demographics (“NIH Public Health Emergency and Disaster Research Response (DR2),” 2021).

Cognitive Functioning—We administered the BrainCheck Memory battery (Yang et al., 2017), an FDA approved and validated web-based battery of cognitive tests, to measure memory (immediate and delayed recognition), attention, and executive functioning (Groppell et al., 2019). The battery requires approximately 10 minutes to complete, is available in both English and Spanish, and can be administered on any computer. BrainCheck yields standardized scores that are normalized for age and education.

The Patient Reported Outcome Measures Information System (PROMIS) Item Bank v2.0 – Cognitive Function- Short Form 8a (PROMIS Cognitive) was used to assess perceived cognitive function using built in REDCap scoring. This validated (Jensen et al., 2017) 8-item scale assesses frequency of cognitive symptoms and T scores were used, with a mean of 50 representing the larger general population and a 10-point standard deviation. Lower scores indicate worse cognitive functioning (*Cognitive Function*, 2019).

Psychosocial Symptoms—The PROMIS 57 Profile v2.0 (Cella et al. (2010) was administered to capture depressive symptoms, fatigue, anxiety, sleep disturbance, and social role performance. Each item has response options ranging in from one to five. There are 8 sub-scores for this profile (pain and physical functioning not reported here). Raw scores were converted to T scores per the PROMIS scoring tables with 50 representing the larger general population mean with a 10-point standard deviation. For the social role performance

subscale, higher scores indicated better performance. For anxiety, depressive symptoms, fatigue, sleep disturbance, higher scores indicated worse symptoms or functioning (*PROMIS Adults Profile Instruments*, 2020). The Perceived Stress Scale (PSS) was used to measure stress (Cohen et al., 1983). Total scores for this 10-item scale can range from 0–40, with higher scores indicating more perceived stress.

Open ended questions—In addition to the above instruments, we asked questions regarding study burden and what could be improved upon to evaluate feasibility and acceptability of this study.

Data Analyses

The sample size reflects the primary aim of this study which was to determine the feasibility of recruiting COVID-19 survivors and collecting all data remotely.

Feasibility—We calculated frequencies and descriptive statistics to determine the number of potential participants screened and enrolled and the number of participants completing all data collection. Open ended questions regarding study burden and participant suggestions were analyzed using qualitative content analysis.

Cognitive and Psychosocial Outcomes—Descriptive statistics were to describe the demographic and clinical variables of the sample. Distributions, central tendencies, and frequencies were examined for the cognitive and psychosocial outcomes. Correlations were also used to explore the relationships between clinical factors and cognitive functioning, psychosocial symptoms in the sample (Pearson’s correlations for continuous variables, Spearman’s rho for ordinal variables, and Kendall’s tau for categorical variables). Alpha level was set at $p < 0.05$.

Results

Sample

The 52 participants that enrolled and completed data collection ranged in age from 22 to 62 years old. The majority were female (78.85%), identified as being White/Caucasian (71.16%), with a Bachelor’s or higher degree (69.23%), were married or living with a partner (57.68%). The majority reported mild or moderate COVID-19 severity ($n=48$, 92%), with an average of 8 or more ($SD: 3.7$) symptoms experienced across their illness. For an overview of COVID-19 symptoms experienced by disease severity see Supplementary Figure 1. The average days since their most recent COVID-19 diagnosis was 120 ($SD: 95$). See Table 1 for demographic and clinical variables.

Feasibility

A total of 116 participants contacted the study team with interest in the study between January 4 and February 28, 2021. Fifty-seven (49%) agreed to participate and were sent the study information. Of these, 52 completed all data collection (retention rate of 91.22%).

Responses to Open-ended questions

The overall response to the study was positive. Ninety-eight percent of those who answered would recommend the study to someone they know. The majority of respondents did not recommend any changes for improvement. Some offered suggestions for improvement—adding or clarifying measures, strategies for recruitment of a diverse sample, study length, data collection strategies, and adding a baseline, pre-COVID measure for comparison or describing changes in outcomes over time.

Cognitive Outcomes

Although mean BrainCheck scores were within what is considered the normal range (Table 2), 40% of participants demonstrated scores that were 1 standard deviation or more below the population norm on 1 or more of the cognitive tests (Table 3). The largest number of participants performed poorly on the Stroop test (30.77%), a measure of executive functioning (Golden, 2005). The mean T score for PROMIS Cognitive (*mean* 43.24, *SD*: 8.65) was close to 1 SD below the mean, and 30.77% reported cognitive deficits greater than the norm (See Table 3).

No significant correlations were found between the cognitive test and PROMIS Cognitive scores ($p > .05$). Correlations were also examined among age, days since diagnosis, symptom total, disease severity, and total number of comorbidities, and all cognitive outcomes. One significant correlation was found between PROMIS Cognitive and symptom total ($r = -0.31, p = .023$), suggesting greater number of COVID-19 symptoms is related to worse perceived cognitive functioning. The correlation matrix can be found in Supplementary Table 1.

Psychosocial Outcomes

The means of all PROMIS subscales were within 1 standard deviation of the general population mean; however, the ranges for these subscales indicate that some participants had much lower (and in some cases much higher) rates of psychosocial symptoms. Some had greater anxiety (21.15%), depressive symptoms (23.07%), and sleep disturbance (19.23%) than the general population norm (See Table 4).

Correlations were also examined among some of the demographic and clinical variables (age, gender, non-White race/ethnicity, years of education, income greater than \$100K/year, number of comorbidities, days since diagnosis, symptom total, disease severity), the PROMIS measures, and the PSS. For demographic variables, relationships were identified between age and PROMIS Fatigue ($r = -0.28, p < .05$), PROMIS Social Role Performance ($r = -0.40, p < .01$) and PSS ($r = -0.34, p < .05$); number of comorbidities and PROMIS Sleep disturbance (*Kendall's Tau* = $-0.25, p < .05$); and income greater than \$100K/year and PROMIS Fatigue (*Kendall's Tau* = $0.29, p < .05$). For clinical variables, significant correlations were found for symptom total and PROMIS Depressive ($r = 0.31, p < .05$), PROMIS Fatigue ($r = 0.30, p < .05$), PROMIS Sleep Disturbance ($r = -0.39, p < .01$), PROMIS Social Role Performance ($r = 0.31, p < .05$), and PSS ($r = 0.32, p < .05$). See Supplementary Table 2 for correlation matrix.

Post Hoc Analyses

Our descriptive statistics led us to explore group differences in rates of cognitive deficits (presence of 1 or more score below SD of population norm = 1, no scores below SD of population norm = 0) and individual cognitive outcomes using Chi square (X^2) for categorical variables, and students T tests (for two groups) or ANOVA (for more than 2 groups) for continuous variables.

No group differences in rates of cognitive deficits were found between those who identified as White versus those who identified as Non-White ($X^2 = .001, p = .97$); those who identified as female versus those who identified as male ($X^2 = .15, p = .70$); among quartiles of time since COVID-19 diagnosis ($X^2 = 3.27, p = .35$) or between groups based on disease severity ($X^2 = 1.63, p = 0.65$). No group differences in individual cognitive outcomes for these same group comparisons (student t tests p values $>.05$).

No group differences in rates of cognitive deficits were found by age groups quartiles (1st: ages 22 to 27; 2nd: ages 28–33; 3rd: ages 34 to 49; and 4th: ages 50 to 62) ($X^2 = 4.24, p = .24$); however, some differences were identified when we examined individual cognitive scores. Significant age differences were identified in Stroop ($F(3,48) = 4.63, p = .006, \eta^2 = .225$), Digit Symbol (*Kruskal Wallis statistic (df 13)* = 13.6, $p = .004$), and Trails B ($F(3,46) = 4.63, p = .006, \eta^2 = .193$). Posthoc tukey's t tests of Stroop showed a significant difference 2nd and 3rd quartiles (*mean difference* = -27.55 , *standard error* = 7.52, $t = -3.66$, *Cohen's D* = $-1.46, p = .003$); of Digit Symbol showed significant difference between 2nd and 3rd quartiles (*mean difference* = -18.94 , *standard error* = 5.11, $t = -3.71$, *Cohen's D* = $-1.32, p = .003$); and of Trails B showed a significant difference between 2nd and 3rd quartiles (*mean difference* = -14.40 , *standard error* = 4.40, $t = -3.27$, *Cohen's D* = $-1.06, p = .011$). See Table 5.

For consistency, we examined age group differences in the psychosocial variables using ANOVA tests but found no significant group differences ($p > 0.05$).

Discussion

In this pilot study we determined the feasibility of recruiting COVID-19 survivors from a community setting and assessing their cognitive and psychosocial functioning using remote data collection. We were able to recruit approximately half of the participants who expressed interest in our study and of those who enrolled, almost all completed data collection over the course of 2 months. Those who did not enroll never responded to the study teams' communications so it is unclear why they did not enroll. Participant feedback also supported that the study was feasible and acceptable. Our findings provide new evidence that cognitive dysfunction and psychological symptoms (anxiety, depressive, sleep disturbance) may be present in the weeks or months following COVID-19 diagnosis.

The majority of neurologically focused COVID-19 research to date has focused on those with severe COVID-19 infections, typically requiring hospitalization. Our findings add preliminary insights regarding those who had mild or moderate disease not requiring hospitalization. Consistent with other reports of COVID-19 survivors' cognitive function

(Ferrucci et al., 2021; Gennaro et al., 2021; Helms et al., 2020; Zhou et al., 2020), we found that a subset of survivors demonstrated poorer performance on cognitive tests adjusted for age and education. Our findings are similar to Helms et al. (2020) and Zhou et al. (2020), who reported deficits in survivors compared to matched controls, but lower than Gennaro et al. (2021) and Ferrucci et al. (2021), who found higher rates of deficits in survivors (60–78%). Similar to Helms et al. (2020) and Gennaro et al. (2021), we found more deficits in the cognitive domain of executive functioning, however this pattern is different than Zhou et al. (2020), who reported deficits in sustained attention but not executive functioning in a sample of 29 survivors, and from Ferrucci et al. (2021), who found significant deficits in processing speed and memory in a sample of 38 survivors.

The difference in our findings could be due to sample sizes and characteristics—our sample was younger and mostly female. It is possible that different patterns of cognitive deficits could emerge with different gender and/or age distributions. Also, our differences could be due to cognitive measurement. We used computerized versions of well-known neuropsychological tests that have been validated in both general and clinical populations (Groppell et al., 2019; Yang et al., 2017). Tests delivered without supervision and via internet browser are different from tests administered by trained professionals and could yield different results. Our cohort was also highly educated (almost 70% had college degrees), which can mask cognitive deficits because of increased cognitive reserve (Corral et al., 2006).

We did not identify group differences in cognitive outcomes (i.e., gender, minority status, educational attainment, time since diagnosis, COVID-19 severity), unlike previous findings that survivors had different cognitive outcomes when grouped by gender and illness severity (Hu et al., 2020). This could be a function of our sample size and/or unequal distribution for statistical tests. We did find a pattern of worse performance in younger versus older survivors in our sample, but the relationship between age and cognitive function appears nonlinear. When we dichotomized the sample into younger survivors (age 22 to 33) and older survivors (age 34 or older) the pattern remained (student's *t* tests in Supplementary Table 3). These findings are unexpected since in general, older age is a risk factor for cognitive decline, and in COVID-19 survivors 5 months post infection, Ferrucci et al. (2021) described the opposite pattern of worse verbal memory in survivors > 55 years old. It is possible that younger adults with COVID-19 have neurological vulnerability that we do not currently understand.

When the pandemic began, it was believed that young and healthy individuals were not at risk of developing symptomatic disease. Therefore, those in this age group may not have taken the same precautions as older adults and may have had more exposure to the virus. Similarly, many frontline workers (e.g., healthcare providers, teachers, civil servants) fall in this age group, and thus are at higher risk for exposure. Pandemic age distributions from June to August 2020, showed highest rates of confirmed cases and 20% of new cases of COVID-19 in persons 20 to 29 years of age (Boehmer et al., 2020). We did not identify any significant clinical or demographic differences to explain the differences in cognitive outcomes we found between the younger and older survivors, but we discovered that more of the participants in the younger group were frontline workers, mainly nurses, through

examination of open-ended question responses (15 of the 25 younger compared to 7 of the 20 older survivors; $X^2= 6.18, p = .013$). It is possible that increased exposure to the virus, higher viral load, other immune related-responses or environmental factors are underlying mechanisms of the increased cognitive deficits seen in this group.

Approximately 30% of our sample perceived they had worse cognitive function than the general population. This is consistent with Ferucci et al. (2021) who also reported that COVID-19 survivors 4 to 5 months post hospital discharge described increased forgetfulness (26%), needing increased time to perform cognitive tasks (23%), and difficulty learning new things (20%). Similar to objective cognitive performance, we found a pattern of worse perceived cognitive functioning in younger survivors, that were related to COVID-19 symptom load, but no other clinical or demographic variables in this study. Few correlations among the cognitive outcomes and clinical and demographic variables could be due to the high variability in these measures, especially age and time since diagnosis, and power. We also found no correlations between perceived cognitive function and the cognitive tests. Previous studies on cognitive function in COVID-19 survivors (Ferrucci et al., 2021; Gennaro et al., 2021; Zhou et al., 2020) did not examine (or report) relationships between self-report measures and cognitive test scores. However, this disassociation is common in other clinical populations such as oncology (Bray et al., 2018).

Expanding on previous findings of COVID-19 survivors (Gennaro et al., 2021; Guo et al., 2020; Hu et al., 2020; Tomasoni et al., 2020), we found rates of anxiety, depression, and sleep disturbance higher than the general population in approximately 20% of our sample. Gennaro et al. (2021) reported 35% of COVID-19 survivors had clinically relevant self-reported depressive, anxiety, symptoms of post-traumatic stress and obsessive-compulsive disorder, up to 3-months post hospital discharge with a trend for improvement in symptoms over time. Another group (Tomasoni et al., 2020) reported that 30% of patients 1 to 3 months post viral clearance displayed pathological anxiety/depression. When compared to non-COVID controls, Guo et al. (2020) found that survivors who had a history of mild disease (average age of 42), had significantly higher levels of depression, anxiety, and post-traumatic stress symptoms ($p < 0.001$). Both Mazzo et al. (2020) and Matalon et al. (2021) reported trends in improvement of depressive symptoms and anxiety in COVID-19 survivors over time, which could explain our lower rates of psychosocial symptoms, since our sample was even longer post recovery.

We also identified some correlations among the psychosocial symptoms and demographic and clinical variables. In this sample, younger age was related to more stress and fatigue, and older age was associated with social role performance. This could be a function of work-related factors— our younger sample was comprised of mostly frontline workers and thus likely more stressed and fatigued. We also found that income less than \$100K/year was associated with greater depressive symptoms. Other studies with COVID-19 survivors reported correlations between psychosocial symptoms, gender, and perceived illness severity (Hu et al., 2020). We did not find any gender differences in our psychosocial outcome measures, but we did find that more COVID-19 related symptoms were associated with more depressive symptoms, fatigue, and perceived stress, similar to Tomasoni et al. (2020)

and Huang et al.(2021) who reported higher proportion of physical symptoms in survivors with abnormal anxiety and/or depressive symptoms than those with without.

Our findings expand on neurocognitive findings in COVID-19 survivors and add new data on possibly cognitive vulnerability in survivors of mild to moderate disease severity (not requiring hospitalization) and younger adults. These findings could have important clinical and public health implications since the majority of COVID-19 cases are not severe, and according to the CDC incidence of COVID-19 continues to be the highest in young adults (ages 18 to 24; (*COVID-19 Stats: COVID-19 Incidence,* by Age Group† — United States, March 1–November 14, 2020, 2021*)). True incidence rates of non-severe disease are likely much higher, as seropositive surveys in the U.S. and Europe estimate that true exposure to SARS-CoV-2 is 10-fold the rates of those actually diagnosed and reported (Havers et al., 2020; Stringhini et al., 2020). Cognitive deficits are important in this younger age group who are at a critical developmental life stage— launching careers, starting families, and establishing stability. Furthermore, many frontline workers fall within this age group (Carvalho-Schneider et al., 2021).

Even though our findings provide new insights on younger COVID survivors and those without severe disease, study limitations must be considered. We did not have a pre-COVID baseline of cognitive or psychosocial functioning, therefore we cannot determine if deficits existed prior to COVID exposure. We also did not have a matched non-COVID control group to determine if deficits were unique to COVID-19 exposure or broader societal changes due to the pandemic. Our sample was small and heterogenous, limiting internal validity, and our analyses cross sectional limiting causal inference. Our sample included only voluntary responders, therefore there was recruitment bias, and a larger proportion of the sample were healthcare/frontline workers representing bias of prior knowledge of COVID related symptoms. Future studies should include matched healthy controls for comparison, more clinical/biological data to investigate biological mechanisms, a longer follow up assessment, and neuroimaging data to explore neural architecture and functioning in prospective assessment of larger more balanced samples of COVID survivors. Evidence of ongoing cognitive dysfunction following COVID-19 is growing, yet many questions remain as to who is likely to develop cognitive dysfunction and what are the underlying mechanisms. Healthcare providers need to be aware of the neurocognitive sequelae of COVID-19 and educate patients about potential late/long term cognitive effects, even in patients with mild to moderate disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health [grant numbers K01NR018970, 2020–2023 (AMH); and T32NR019035, 2020–2025(EG)]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References

- Alnefeesi Y, Siegel A, Lui LMW, Teopiz KM, Ho RCM, Lee Y, Nasri F, Gill H, Lin K, Cao B, Rosenblat JD, & McIntyre RS (2020). Impact of SARS-CoV-2 Infection on Cognitive Function: A Systematic Review. *Front Psychiatry*, 11, 621773. 10.3389/fpsy.2020.621773
- Boehmer T, DeVies J, Caruso E, & al., e. (2020). Changing Age Distribution of the COVID-19 Pandemic — United States, May–August 2020 (Morbidity and Mortality Weekly Report Issue).
- Bougakov D, Podell K, & Goldberg E. (2021, Feb). Multiple Neuroinvasive Pathways in COVID-19. *Mol Neurobiol*, 58(2), 564–575. 10.1007/s12035-020-02152-5 [PubMed: 32990925]
- Bray VJ, Dhillon HM, & Vardy JL (2018, May 4). Systematic review of self-reported cognitive function in cancer patients following chemotherapy treatment. *J Cancer Surviv*. 10.1007/s11764-018-0692-x
- Carvalho-Schneider C, Laurent E, Lemaïgnen A, Beaufils E, Bourbao-Tournois C, Laribi S, Flament T, Ferreira-Maldent N, Bruyere F, Stefik K, Gaudy-Graffin C, Grammatico-Guillon L, & Bernard L. (2020, Oct 5). Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*. 10.1016/j.cmi.2020.09.052
- Carvalho-Schneider C, Laurent E, Lemaïgnen A, Beaufils E, Bourbao-Tournois C, Laribi S, Flament T, Ferreira-Maldent N, Bruyere F, Stefik K, Gaudy-Graffin C, Grammatico-Guillon L, & Bernard L. (2021, Feb). Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect*, 27(2), 258–263. 10.1016/j.cmi.2020.09.052 [PubMed: 33031948]
- Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D, Bode R, Buysse D, Choi S, Cook K, Devellis R, DeWalt D, Fries JF, Gershon R, Hahn EA, Lai JS, Pilkonis P, Revicki D, Rose M, Weinfurt K, Hays R, & Group PC (2010, Nov). The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. *J Clin Epidemiol*, 63(11), 1179–1194. 10.1016/j.jclinepi.2010.04.011 [PubMed: 20685078]
- Cognitive Function. (2019). Patient-Reported Outcomes Measurement Information System. Retrieved Mar. 15, 2021 from https://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Cognitive_Function_Scoring_Manual.pdf
- Cohen S, Kamarck T, & Mermelstein R. (1983, Dec). A global measure of perceived stress. *J Health Soc Behav*, 24(4), 385–396. <https://www.ncbi.nlm.nih.gov/pubmed/6668417> [PubMed: 6668417]
- Corral M, Rodriguez M, Amenedo E, Sanchez JL, & Diaz F. (2006). Cognitive reserve, age, and neuropsychological performance in healthy participants. *Dev Neuropsychol*, 29(3), 479–491. http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16671863 [PubMed: 16671863]
- COVID-19 Stats: COVID-19 Incidence,* by Age Group† — United States, March 1–November 14, 2020. (2021). (Morbidity and Mortality Weekly Report, Issue).
- Datta SD, Talwar A, & Lee JT (2020, Dec 8). A Proposed Framework and Timeline of the Spectrum of Disease Due to SARS-CoV-2 Infection: Illness Beyond Acute Infection and Public Health Implications. *JAMA*, 324(22), 2251–2252. 10.1001/jama.2020.22717 [PubMed: 33206133]
- Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, Redfield S, Austin JP, & Akrami A. (2020). Characterizing Long COVID in an International Cohort: 7 Months of Symptoms and Their Impact. *medRxiv*, 2020.2012.2024.. 10.1101/2020.12.24.20248802 [PubMed: 20248802]
- Dong E, Du H, & Gardner L. (2020, May). An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*, 20(5), 533–534. 10.1016/S1473-3099(20)30120-1 [PubMed: 32087114]
- Ferrucci R, Dini M, Groppo E, Rosci C, Reitano MR, Bai F, Poletti B, Brugnera A, Silani V, D'Arminio Monforte A, & Priori A. (2021, Feb 13). Long-Lasting Cognitive Abnormalities after COVID-19. *Brain Sci*, 11(2). 10.3390/brainsci11020235
- Garrigues E, Janvier P, Kherabi Y, Le Bot A, Hamon A, Gouze H, Doucet L, Berkani S, Oliosi E, Mallart E, Corre F, Zarrouk V, Moyer JD, Galy A, Honsel V, Fantin B, & Nguyen Y. (2020, Dec). Post-discharge persistent symptoms and health-related quality of life after hospitalization for COVID-19. *J Infect*, 81(6), e4–e6. 10.1016/j.jinf.2020.08.029 [PubMed: 32853602]

- Gennaro MM, Mariagrazia P, De Lorenzo R, Cristiano M, Sara P, Roberto F, Fabio C, Patrizia RQ, & Francesco B. (2021, Feb 24). Persistent psychopathology and neurocognitive impairment in COVID-19 survivors: effect of inflammatory biomarkers at three-month follow-up. *Brain Behav Immun*. 10.1016/j.bbi.2021.02.021
- Golden C. (2005). Stroop Color and Word Test. Psychological Assessment Resources.
- Groppell S, Soto-Ruiz KM, Flores B, Dawkins W, Smith I, Eagleman DM, & Katz Y. (2019, Mar 21). A Rapid, Mobile Neurocognitive Screening Test to Aid in Identifying Cognitive Impairment and Dementia (BrainCheck): Cohort Study. *JMIR Aging*, 2(1), e12615. 10.2196/12615
- Guo Q, Zheng Y, Shi J, Wang J, Li G, Li C, Fromson JA, Xu Y, Liu X, Xu H, Zhang T, Lu Y, Chen X, Hu H, Tang Y, Yang S, Zhou H, Wang X, Chen H, Wang Z, & Yang Z. (2020, Aug). Immediate psychological distress in quarantined patients with COVID-19 and its association with peripheral inflammation: A mixed-method study. *Brain Behav Immun*, 88, 17–27. 10.1016/j.bbi.2020.05.038 [PubMed: 32416290]
- Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, McLeod L, Delacqua G, Delacqua F, Kirby J, Duda SN, & Consortium RE (2019, Jul). The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform*, 95, 103208. 10.1016/j.jbi.2019.103208
- Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, & Conde JG (2009, Apr). Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support [Research Support, N.I.H., Extramural]. *J Biomed Inform*, 42(2), 377–381. 10.1016/j.jbi.2008.08.010 [PubMed: 18929686]
- Havers FP, Reed C, Lim T, Montgomery JM, Klena JD, Hall AJ, Fry AM, Cannon DL, Chiang CF, Gibbons A, Krapinaya I, Morales-Betoulle M, Roguski K, Rasheed MAU, Freeman B, Lester S, Mills L, Carroll DS, Owen SM, Johnson JA, Semenova V, Blackmore C, Blog D, Chai SJ, Dunn A, Hand J, Jain S, Lindquist S, Lynfield R, Pritchard S, Sokol T, Sosa L, Turabelidze G, Watkins SM, Wiesman J, Williams RW, Yendell S, Schiffer J, & Thornburg NJ (2020, Jul 21). Seroprevalence of Antibodies to SARS-CoV-2 in 10 Sites in the United States, March 23-May 12, 2020. *JAMA Intern Med*. 10.1001/jamainternmed.2020.4130
- Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, Collange O, Boulay C, Fafi-Kremer S, Ohana M, Anheim M, & Meziani F. (2020, Jun 4). Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*, 382(23), 2268–2270. 10.1056/NEJMc2008597 [PubMed: 32294339]
- Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, Zhang Z, & Ding L. (2020, Oct). Factors related to mental health of inpatients with COVID-19 in Wuhan, China. *Brain Behav Immun*, 89, 587–593. 10.1016/j.bbi.2020.07.016 [PubMed: 32681866]
- Huang C, Huang L, Wang Y, Li X, Ren L, Gu X, Kang L, Guo L, Liu M, Zhou X, Luo J, Huang Z, Tu S, Zhao Y, Chen L, Xu D, Li Y, Li C, Peng L, Li Y, Xie W, Cui D, Shang L, Fan G, Xu J, Wang G, Wang Y, Zhong J, Wang C, Wang J, Zhang D, & Cao B. (2021, Jan 16). 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*, 397(10270), 220–232. 10.1016/s0140-6736(20)32656-8 [PubMed: 33428867]
- Jensen RE, Potosky AL, Moynour CM, Lobo T, Cella D, Hahn EA, Thissen D, Smith AW, Ahn J, Luta G, & Reeve BB (2017, Jun 10). United States Population-Based Estimates of Patient-Reported Outcomes Measurement Information System Symptom and Functional Status Reference Values for Individuals With Cancer. *J Clin Oncol*, 35(17), 1913–1920. 10.1200/JCO.2016.71.4410 [PubMed: 28426375]
- Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, Jia T, Zhao Y, Wang D, Xiao A, & Yin B. (2020, Aug). Cerebral Micro-Structural Changes in COVID-19 Patients - An MRI-based 3-month Follow-up Study. *EClinicalMedicine*, 25, 100484. 10.1016/j.eclinm.2020.100484
- Matalon N, Dorman-Ilan S, Hasson-Ohayon I, Hertz-Palmor N, Shani S, Basel D, Gross R, Chen W, Abramovich A, Afek A, Ziv A, Kreiss Y, Pessach IM, & Gothelf D. (2021, Feb 16). Trajectories of post-traumatic stress symptoms, anxiety, and depression in hospitalized COVID-19 patients: A one-month follow-up. *J Psychosom Res*, 143, 110399. 10.1016/j.jpsychores.2021.110399
- Mazza MG, De Lorenzo R, Conte C, Poletti S, Vai B, Bollettini I, Melloni EMT, Furlan R, Ciceri F, Rovere-Querini P, & group C-BOCS (2020, Jul 30). Anxiety and depression in

COVID-19 survivors: Role of inflammatory and clinical predictors. *Brain Behav Immun*. 10.1016/j.bbi.2020.07.037

- Miners S, Kehoe PG, & Love S. (2020, Dec 30). Cognitive impact of COVID-19: looking beyond the short term. *Alzheimers Res Ther*, 12(1), 170. 10.1186/s13195-020-00744-w [PubMed: 33380345]
- Moonis G, Filippi CG, Kirsch CFE, Mohan S, Stein EG, Hirsch JA, & Mahajan A. (2020, Nov 25). The Spectrum of Neuroimaging findings on CT and MRI in Adults with Coronavirus Disease (COVID-19). *AJR Am J Roentgenol*. 10.2214/AJR.20.24839
- Ogier M, Andéol G, Sagui E, & Dal Bo G. (2020, May). How to detect and track chronic neurologic sequelae of COVID-19? Use of auditory brainstem responses and neuroimaging for long-term patient follow-up. *Brain Behav Immun Health*, 5, 100081. 10.1016/j.bbih.2020.100081
- Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, & Reid TR (2021, Feb 20). A Review of Persistent Post-COVID Syndrome (PPCS). *Clin Rev Allergy Immunol*, 1–9. 10.1007/s12016-021-08848-3
- Pero A, Ng S, & Cai D. (2020, Jul 25). COVID-19: A Perspective from Clinical Neurology and Neuroscience. *Neuroscientist*, 1073858420946749. 10.1177/1073858420946749
- PROMIS Adults Profile Instruments. (2020). Patient-Reported Outcomes Measurement Information System. Retrieved March, 15, 2021 from https://www.healthmeasures.net/images/PROMIS/manuals/PROMIS_Adult_Profile_Scoring_Manual.pdf
- Roman GC, Spencer PS, Reis J, Buguet A, Faris MEA, Katrak SM, Lainez M, Medina MT, Meshram C, Mizusawa H, Ozturk S, Wasay M, & Group WFNENS (2020, Jul 15). The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. *J Neurol Sci*, 414, 116884. 10.1016/j.jns.2020.116884
- Stringhini S, Wisniak A, Piumatti G, Azman AS, Lauer SA, Baysson H, De Ridder D, Petrovic D, Schrempft S, Marcus K, Yerly S, Arm Vernez I, Keiser O, Hurst S, Posfay-Barbe KM, Trono D, Pittet D, Getaz L, Chappuis F, Eckerle I, Vuilleumier N, Meyer B, Flahault A, Kaiser L, & Guessous I. (2020, Aug 1). Seroprevalence of anti-SARS-CoV-2 IgG antibodies in Geneva, Switzerland (SEROCoV-POP): a population-based study. *Lancet*, 396(10247), 313–319. 10.1016/S0140-6736(20)31304-0 [PubMed: 32534626]
- Tomasoni D, Bai F, Castoldi R, Barbanotti D, Falcinella C, Mule G, Mondatore D, Tavelli A, Vegni E, Marchetti G, & d'Arminio Monforte A. (2020, Aug 25). Anxiety and depression symptoms after virological clearance of COVID-19: a cross-sectional study in Milan, Italy. *J Med Virol*. 10.1002/jmv.26459
- Willi S, Luthold R, Hunt A, Hanggi NV, Sejdiu D, Scaff C, Bender N, Staub K, & Schlagenhauf P. (2021, Feb 22). COVID-19 sequelae in adults aged less than 50 years: A systematic review. *Travel Med Infect Dis*, 40, 101995. 10.1016/j.tmaid.2021.101995
- Yang S, Flores B, Magal R, Harris K, Gross J, Ewbank A, Davenport S, Ormachea P, Nasser W, Le W, Peacock WF, Katz Y, & Eagleman DM (2017). Diagnostic accuracy of tablet-based software for the detection of concussion. *PLoS ONE*, 12(7), e0179352. 10.1371/journal.pone.0179352
- Zhou H, Lu S, Chen J, Wei N, Wang D, Lyu H, Shi C, & Hu S. (2020, Oct). The landscape of cognitive function in recovered COVID-19 patients. *J Psychiatr Res*, 129, 98–102. 10.1016/j.jpsychires.2020.06.022 [PubMed: 32912598]

Table 1

Descriptive statistics of demographic and clinical variables for sample (N=52)

Variable	Mean (SD)	Frequency (%)	25 th %	50 th %	75 th %
Age	37.33 (12.12)		28	34	50
Non-white Race/Ethnicity		15 (28.85%)			
Female Gender		41 (78.85%)			
Educational Attainment					
GED/High School		3 (5.76%)			
Associates		4 (7.69%)			
Bachelor's		28 (53.84%)			
Graduate Degree		8 (15.38%)			
Some College		6 (9.62%)			
Working Remotely		12 (23%)			
Insured		49 (94.23%)			
Married/Living with a Partner		30 (57.68%)			
Enough Money to Pay Bills		48 (92.30%)			
Income Levels					
\$20,000 to \$34,999		7			
\$35,000 to \$49,999		5			
\$50,000 to \$74,999		8			
\$75,000 to \$99,999		8			
\$100,000 to \$199,999		14			
\$200,000 or more		5			
Prefer Not to Answer		3			
Days Since Diagnosis	120.25 (94.63)		39	84	212.5
COVID-19 Severity					
Mild ^a		29 (55.77%)			
Moderate ^b		19 (36.54%)			
Severe ^c		3 (5.77%)			
Critical ^d		1 (1.9%)			
1+ Comorbidity		51 (98.1%)			
Immune-Related Comorbidity		28 (53.85%)			
Received COVID-19 Vaccine		22 (44.3%)			
Total Number of COVID-19 Related Symptoms	8.42 (3.7)		6	8	11

Abbreviations: GED: Graduate Equivalency Degree; COVID-19: also called SARS-CoV-2. Non-white includes anyone who identified as African America/Black; American Indian/Alaskan Native; Hawaiian/Pacific Islander, Asian American, Hispanic, or Other

^a Mild illness (dry cough, headache, nausea/diarrhea, aches and pains, low-grade fever - no need to see a doctor or hospitalization)

^b Moderate illness (coughing, high fever (above 100.0 degrees Fahrenheit or above 37.8 degrees Celsius), chills, feeling that you can't get out of bed, shortness of breath)

^c Severe illness (breathlessness, complications leading to pneumonia)

^d Critical illness (respiratory failure, septic shock, and/or organ dysfunction or failure)

Table 2

Descriptive statistics for standard scores of cognitive measures (N=52)

Cognitive Measure	Valid	Mean	Standard deviation	Minimum	Maximum	Number of scores below 1 SD of the population norm	% of scores of scores below 1 SD of the population norm
Trails B	50 [^]	104.86	11.86	62	132	4	7.69
Digit Symbol	52	102.96	14.12	64	137	6	11.54
Stroop	52	94.21	20.70	41	136	16	30.77
Immediate Recall	52	105.52	12.75	58	117	3	5.77
Delayed Recall	52	103.90	17.4	27	117	7	13.46
PROMIS Cognitive Function	52	43.24	8.65	25.4	63.9	16	30.77

Footnote: Trails B—mental flexibility, Digit Symbol Substitution, Stroop—executive functioning, Immediate and delayed memory with a verbal learning test. Standardized scores used. —mean score of the population is 100 (SD:15), and higher score are better. The PROMIS cognitive function scale scores are T scores standardized with a mean of 50 (SD:10), and higher scores are better.

Abbreviations. PROMIS: Patient Reported Outcome Measures Information System

[^] 2 participants “timed out” of taking the trails b, taking more than the given time to complete the test.

Table 3

Total number of cognitive test scores below 1 SD (15 points) of the population norm

Number of Test Scores	Frequency	Percent
0	31	59.615
1	12	23.077
2	5	9.615
3	2	3.846
4	2	3.846

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 4

Descriptive statistics for standard scores of psychosocial measures (N=52)

Psychosocial Measure	Valid	Mean	Standard deviation	Minimum	Maximum	Number of scores above or below 1 SD of the population norm	% of scores of scores above or below 1 SD of the population norm
PROMIS Anxiety	52	50.42	9.68	38.2	68.7	11	21.15%
PROMIS Depressive Symptoms	52	53.44	10.03	33.1	77.8	12	23.07%
PROMIS Fatigue	52	51.14	7.61	35.3	67.4	6	11.54%
PROMIS Sleep Disturbance	52	50.49	9.33	25.9	65.4	10	19.23%
PROMIS Social Role Performance	52	56.45	10.27	37.1	73	4	7.69%
Perceived Stress [^]	52	17.5	8.59	1	34	-	-

Footnote: For Anxiety, Depressive, Fatigue, and Sleep Disturbance a T-score of 60 is one SD worse than average. For Social Role Performance, a T-score of 60 is one SD better than average.

Abbreviations: PROMIS: Patient Reported Outcome Measures Information System

[^] No published norms for the Perceived Stress Scale

Table 5.

Age group differences (quartiles) in cognitive scores evaluated parametrically with ANOVA and non-parametrically with Kruskal Wallis

Cognitive Test	ANOVA F Statistic	P value	Effect size (η^2)
Delayed	.65	.17	.039
Immediate	5.63 [^]	.13	-
Stroop	4.63	.006	.225
Digit Symbol	13.6 [^]	.004	-
Trails B	3.66	.019	.193
PROMIS Cognitive	.62	.60	.037

Footnote. Age quartiles: 1st includes ages 22 to 27; 2nd includes ages 28–33; 3rd includes ages 34 to 49; and 4th includes ages 50 to 62.

Abbreviations. PROMIS: Patient Reported Outcome Measures Information System

[^] = Significant Levene’s test found for ANOVA test, non-parametric Kruskal Wallis statistic used instead

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript