seeking treatment for Post-Acute Sequelae of COVID-19 (PASC).
**Participants and Methods:** One hundred nineteen patients each completed a baseline neuropsychological evaluation, including clinical diagnostic interview, cognitive assessments, and a comprehensive battery of self-report questionnaires. Patients had a mean age of 50 years (*range*:18 to 74, *SD*=10.1) and a mean of 15.5 years (*SD*=2.54) of formal education. Patients were primarily female (74%) and of White/Caucasian race (75%).
Hierarchical agglomerative clustering was used to partition the data into groups based on cognitive performance. Euclidean distance was used as the similarity measure for the continuous variables and within-cluster variance was minimized using Ward's method. The optimal number of clusters was determined empirically by fitting models with 1 to 15 clusters, with the best number of clusters selected using the silhouette index. All analyses were conducted using the NbClust package, an R package for determining the relevant number of clusters in a data set.
**Results:** Clustering yielded two distinct clusters of cognitive performance. Group 1 (*n*=57) performed worse than Group 2 (*n*=62) on most cognitive variables (including a brief cognitive screener and tests of attention/working memory, executive function, processing speed, learning and delayed recall). Of note, there were no significant differences between groups on an infection severity scale, hospitalizations/ICU admissions, initial or current COVID-19 symptoms, or prior comorbidities. Groups did not differ in age or gender, but Group 1 had a lower education level than Group 2 (*M*=14.7, *SD*=2.45 vs. *M*=16.2, *SD*=2.42; p=.001). Group 1 also had significantly more minorities than Group 2 (40% vs. 8%; *p*<.001). No other demographic differences (income, living arrangement, or marital status) were observed. In comparison to Group 2 patients, Group 1 patients self-reported significantly higher levels of anxiety and depression and functional impairment (Functional Activities Questionnaire: *M*=11.3, *SD*=8.33 vs. *M*=7.65, *SD*=7.97), perceived stress (Perceived Stress Scale: *M*=24.7, *SD*=7.90 vs. *M*=20.3, *SD*=7.89), insomnia (Insomnia Severity Index: *M*=16.0, *SD*=6.50 vs. *M*=13.1, *SD*=6.76), and subjective cognitive functioning (Cognitive Failures Questionnaire: *M*=58.8, *SD*=16.9 vs. *M*=50.3, *SD*=18.6; *p*'s<.05).
**Conclusions:** Findings indicate two predominant subtypes of patients seeking treatment for PASC, with one group presenting as more cognitively impaired and reporting greater levels of anxiety, depression, insomnia, perceived stress, functional limitations, and subjective cognitive impairment. Future directions include follow-up assessments with these patients to determine cognitive trajectories over time and tailoring treatment adjuncts to address mood symptoms, insomnia, functional ability, and lifestyle variables. Understanding mechanisms of differences in cognitive and affective symptoms is needed in future work. Limitations to the study were that patients were referred for evaluation based on the complaint of "brain fog" and the sample was a homogenous, highly educated, younger group of individuals who experienced generally mild COVID-19 course.

**Categories:** Infectious Disease (HIV/COVID/Hepatitis/Viruses)
**Keyword 1:** cognitive functioning
**Keyword 2:** neuropsychological assessment
**Correspondence:** Kristine Lokken, Ph.D., University of Alabama at Birmingham, kristinelokken@uabmc.edu

## 4 Neurophenotypes and recovery trajectories following laboratory-confirmed SARS-CoV-2 infection

Divya Prabhakaran[1], Gregory S Day[1], Bala Munipalli[1], Beth Rush[1], Lauren Pudalov[1], Shehzad Niazi[1], Emily Brennan[1], Harry R Powers[1], Arjun Athreya[2], Karen Blackmon[1]
[1]Mayo Clinic, Jacksonville, FL, USA. [2]Mayo Clinic, Rochester, MN, USA

**Objective:** Cognitive sequelae are reported in 20-25% of patients following SARS-CoV-2 infection. It remains unclear whether post-infection sequelae cluster into a uniform cognitive syndrome. In this cohort study, we characterized post-COVID neuropsychological outcome clusters, identified factors associated with cluster membership, and examined 6-month recovery trajectories by cluster.

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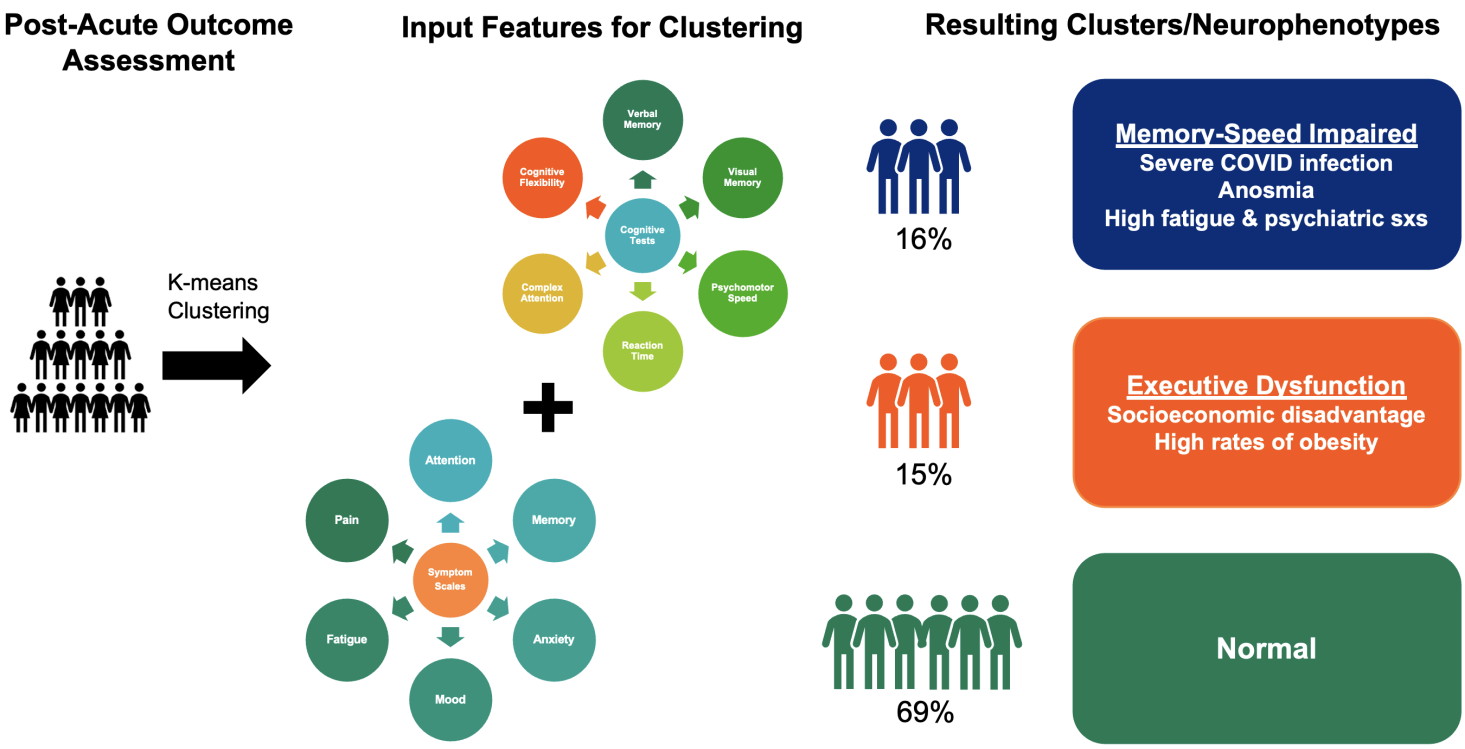


**Participants and Methods:** The Mayo Clinic Institutional Review Board approved study protocols. Informed consent was obtained from all participants. Participants (≥ 18 years old) were recruited from a hospital-wide registry of Mayo Clinic Florida patients who tested positive for SARS-CoV-2 infection from July 2020 to Feb 2022. We abstracted participant health history and COVID-19 disease severity (NIAID score) from the electronic health record and retrieved Area Deprivation Index (ADI) scores as a measure of neighborhood socioeconomic disadvantage. We assessed objective cognitive performance with the CNS Vital-Signs (CNSVS) and subjective neuropsychological symptoms with the Neuropsych Questionnaire-45 (NPQ-45). Results were used as input features in a K-means clustering analysis to derive neurophenotypes. Chi-square and analysis of variance (ANOVA) tests were used to identify clinical and sociodemographic factors associated with cluster membership. Participants repeated the CNS Vital Signs, NPQ-45, as well as the Medical Outcomes Survey (MOS SF-36) and a posttraumatic stress disorder (PTSD) checklist (PCL-C 17) 6 months following initial testing. Repeated-measures ANOVA was used to assess change in neurocognitive performance over time by cluster. Significance was set at $P < 0.05$.

**Results:** Our cohort consisted of 205 participants (171 ambulatory, 34 hospitalized) who completed post-acute outcome assessment a mean of 5.7 (± 3.8) weeks following testing positive for SARS-CoV-2. K-means clustering with elbow method fitting identified three subgroups (see figure). The first cluster (N = 31) is characterized by executive dysfunction, greater socioeconomic disadvantage, and higher rates of obesity. The second cluster (N = 32) is characterized by memory and speed impairment, higher COVID severity, prevalent anosmia (70%), and greater severity of memory complaints, depression, anxiety, and fatigue. The third and largest cluster (N = 142) is absent cognitive impairment. Approximately 39% of participants completed the 6-month outcome assessment (N=79). Regardless of cluster membership, verbal memory, psychomotor speed, and reaction time scores improved over time. Regardless of timepoint, cluster 1 (dysexecutive) showed lower scores on cognitive flexibility and complex attention and cluster 2 (memory-speed impaired) showed lower scores on verbal memory, psychomotor speed, and reaction time. Modeling of cluster by timepoint interactions showed a steeper slope of improvement in complex attention and cognitive flexibility in cluster 1 (dysexecutive). Cluster 3 (normal) showed significant improvement in fatigue while cluster 2 (memory-speed impaired)

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continued to report moderate-severe fatigue, worse medical outcomes, and higher PTSD symptom severity scores at six months.
**Conclusions:** Most participants were cognitively normal or experienced cognitive recovery following SARS-CoV-2 infection. The 25-30% of participants who showed cognitive impairment cluster into two different neurophenotypes. The dysexecutive phenotype was associated with socioeconomic factors and medical comorbidities that are non-specific to COVID-19, while the amnestic phenotype was associated with COVID-19 severity and anosmia. These results suggest that cognitive sequelae following SARS-CoV-2 infection are not uniform. Deficits may be influenced by distinct patient- and disease-specific factors, necessitating differentiated treatment approaches.

**Categories:** Infectious Disease (HIV/COVID/Hepatitis/Viruses)
**Keyword 1:** neuroimmunology
**Keyword 2:** memory disorders
**Keyword 3:** anoxia
**Correspondence:** Divya Prabhakaran, Mayo Clinic, Jacksonville, FL, USA, prabhakaran.divya@mayo.edu

## 5 Meta-Analysis of Cognitive Functioning Following Non-Severe COVID-19 Infection

Tara A Austin[1], Cooper Hodges[2], Emily Darowski[2], Michael L Thomas[3], Rachel Bergsmans[4], Sarah Parr[5], Crystal Lantrip[1,5], Elizabeth W. Twamley[6,7]
[1]VISN 17 Center of Excellence, Waco, Utah, USA. [2]Brigham Young University, Provo, Utah, USA. [3]Colorado State University, Fort Collins, CO, USA. [4]University of Michigan, Ann Arbor, MI, USA. [5]Baylor University, Waco, TX, USA. [6]VA San Diego Healthcare System, San Diego, CA, USA. [7]University of California San Diego, San Deigo, CA, USA

**Objective:** To effectively diagnose and treat cognitive post-COVID-19 symptoms, it is important to understand objective cognitive difficulties across the range of acute COVID-19 severity. The aim of this meta-analysis is to describe objective neuropsychological test performance in individuals with non-severe (mild/moderate) COVID-19 cases in the post-acute stage of infection (>28 days after initial infection).
**Participants and Methods:** This meta-analysis was pre-registered with Prospero (CRD42021293124) and utilized the PRISMA reporting guidelines, with screening conducted by at least two independent reviewers for all aspects of the screening and data extraction process. Inclusion criteria were established before the article search and were as follows: (1) Studies using adult participants with a probable or formal and documented diagnosis of COVID-19 in the post-acute stage of infection; (2) Studies comparing cognitive functioning using objective neuropsychological tests in one or more COVID-19 groups and a comparison group, or one group designs using tests with normative data; (3) Asymptomatic, mild, or moderate cases of COVID-19. Twenty-seven articles (n=18,202) with three types of study designs and three articles with additional longitudinal data met our full criteria.
**Results:** Individuals with non-severe initial COVID-19 infection demonstrated worse cognitive performance compared to healthy comparison participants (d=-0.412 [95% CI, -0.718, -0.176)], p=0.001). We used meta-regression to examine the relationship between both average age of the sample and time since initial COVID-19 infection (as covariates in two independent models) and effect size in studies with comparison groups. There was no significant effect for age (b=-0.027 [95% CI (-0.091, 0.038)], p=0.42). There was a significant effect for time since diagnosis, with a small improvement in cognitive performance for every day following initial acute COVID-19 infection (b=0.011 [95% CI (0.0039, 0.0174)], p=0.002). However, those with mild (non-hospitalized) initial COVID-19 infections performed better than did those who were hospitalized for initial COVID-19 infections (d=0.253 [95% CI (0.372, 0.134)], p<0.001). For studies that used normative data comparisons, there was a small, non-significant effect compared to normative data (d=-0.165 [95% CI (-0.333, 0.003)], p=0.055).
**Conclusions:** Individuals who have recovered from non-severe cases of COVID-19 may be at risk for cognitive decline or impairment and may benefit from cognitive health interventions.

**Categories:** Infectious Disease (HIV/COVID/Hepatitis/Viruses)

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