



A systematic review of neuropsychological and psychiatric sequelae of COVID-19: implications for treatment

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Purpose of review

COVID-19 impacts multiple organ systems and is associated with high rates of morbidity and mortality. Pathogenesis of viral infection, co-morbidities, medical treatments, and psychosocial factors may contribute to COVID-19 related neuropsychological and psychiatric sequelae. This systematic review aims to synthesize available literature on psychiatric and cognitive characteristics of community-dwelling survivors of COVID-19 infection.

Recent findings

Thirty-three studies met inclusion/exclusion criteria for review. Emerging findings link COVID-19 to cognitive deficits, particularly attention, executive function, and memory. Psychiatric symptoms occur at high rates in COVID-19 survivors, including anxiety, depression, fatigue, sleep disruption, and to a lesser extent posttraumatic stress. Symptoms appear to endure, and severity of acute illness is not directly predictive of severity of cognitive or mental health issues. The course of cognitive and psychiatric sequelae is limited by lack of longitudinal data at this time. Although heterogeneity of study design and sociocultural differences limit definitive conclusions, emerging risk factors for psychiatric symptoms include female sex, perceived stigma related to COVID-19, infection of a family member, social isolation, and prior psychiatry history.

Summary

The extant literature elucidates treatment targets for cognitive and psychosocial interventions. Research using longitudinal, prospective study designs is needed to characterize cognitive and psychiatric functioning of COVID-19 survivors over the course of illness and across illness severity. Emphasis on delineating the unique contributions of premorbid functioning, viral infection, co-morbidities, treatments, and psychosocial factors to cognitive and psychiatric sequelae of COVID-19 is warranted.

Keywords

cognition, COVID-19, neuropsychology, psychiatric disorders, SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

INTRODUCTION

The novel coronavirus (SARS-CoV-2) that causes coronavirus disease (COVID-19) impacts multiple organ systems [1]. Mortality rates are staggering, and morbidity trends have been the focus of numerous investigations. Persisting symptoms following infection are increasingly reported, including psychiatric symptoms and cognitive concerns [2,3], which are likely salient contributors to morbidity and disability. Although the etiology is still largely unknown, cognitive deficits may arise from stroke, meningitis, hypoxia, and inflammatory injury [4–8] or from the invasive interventions required to treat

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KEY POINTS

- Neuropsychological weaknesses are not uncommon among COVID-19 survivors, particularly in the domains of attention and executive functioning.
- COVID-19 is associated with high rates of psychiatric symptoms, including anxiety, depression, fatigue, sleep disruption, and posttraumatic stress, and consistent risk factors for psychiatric symptoms include the history of a psychiatric disorder and female gender.
- Rates of anxiety and depression are similar, if not higher, among patients who were never hospitalized compared to those who required inpatient hospitalization, whereas rates of posttraumatic stress appear higher among previously hospitalized patients.
- Literature on neuropsychological functioning in COVID-19 is scarce, and the heterogeneity of patient samples, methods, and timeframe of assessment limit the characterization of neuropsychological and psychiatric sequelae among COVID-19 survivors.
- There is a pressing need for prospective research studies that recruit large patient populations and comparison samples, comprehensively define medical and treatment course, and utilize gold-standard measures to characterize cognitive and psychiatric functioning across specific domains over time.

severe illness from COVID-19 [9]. Psychiatric illness may arise from a combination of biological, psychosocial, and environmental factors. Early findings on COVID-19 are consistent with existing literature on patients with severe and unexpected illness who experience psychiatric symptoms related to medical illness, functional disability, and psychosocial stressors [10].

Here, we review the nascent literature on the neuropsychological and psychiatric sequelae of COVID-19 among community-dwelling individuals. We included studies that reported on postacute infection, including individuals who were never hospitalized and those who were previously hospitalized. We highlight trends, discuss treatment implications, and provide a roadmap for further research on long-term psychiatric and cognitive impairment after COVID-19.

METHODS

A systematic literature search of articles published in English between December 2019 and February 2021 was conducted according to PRISMA standards using PubMed. Medical Subject Headings and keywords pertaining to cognitive and psychiatric symptoms in community-dwelling adults with COVID-19

were used to identify original research articles. Case reports, studies with a sample size of $N < 10$, and studies examining acute psychiatric and cognitive consequences of infection, with data exclusively collected during hospitalization, were excluded.

Titles were initially screened by five reviewers. Abstracts were then independently examined by two reviewers, and two additional independent reviewers evaluated full-text articles to verify inclusion eligibility (Fig. 1). Differences were reconciled by consensus conference. We extracted sample characteristics, study design, assessment measures, primary outcomes, and study limitations (Table 1).

RESULTS

Neuropsychological and cognitive sequelae

Objective neuropsychological assessment

Abnormal cognitive performance was documented in approximately 15.0–40.0% of participants 10–105 days following hospital discharge [11[■],12[■],13[■],14[■],15–17]. Comparison of cognitive function in COVID-19 patients to matched controls found significant differences in performance on measures of sustained attention [13[■]], executive function and visuospatial processing [11[■]], attention, memory, and language [12[■]]. Notably, most studies relied on cognitive screening measures (e.g., Montreal Cognitive Assessment, Mini Mental State Exam, Telephone Interview for Cognitive Status).

Executive dysfunction was implicated in patients who were treated in the intensive care unit (ICU) and oxygen therapy was associated with lower scores in the domains of memory, attention, working memory, processing speed, executive function, and global cognition [14[■]]. Specific COVID-19 related symptoms were associated with differential patterns of cognitive performance. Neurological symptoms were associated with lower working memory scores, headache with lower scores on memory coding, attention, complex working memory, processing speed, executive function, and global cognition, diarrhea with lower scores in delayed visual memory, working memory, and complex working memory [14[■]]. Poor cognitive performance was associated with increased inflammatory markers in one study [13[■]]. Brain Magnetic Resonance Imaging in one study was not indicative of severe neurological injury in patients 2–3 months post recovery in comparison to healthy controls. However, recovered patients demonstrated increased bilateral thalamic T2 signal on susceptibility-weighted imaging and increased mean diffusivity in the posterior thalamic radiations and sagittal striatum, suggesting possible increased burden of

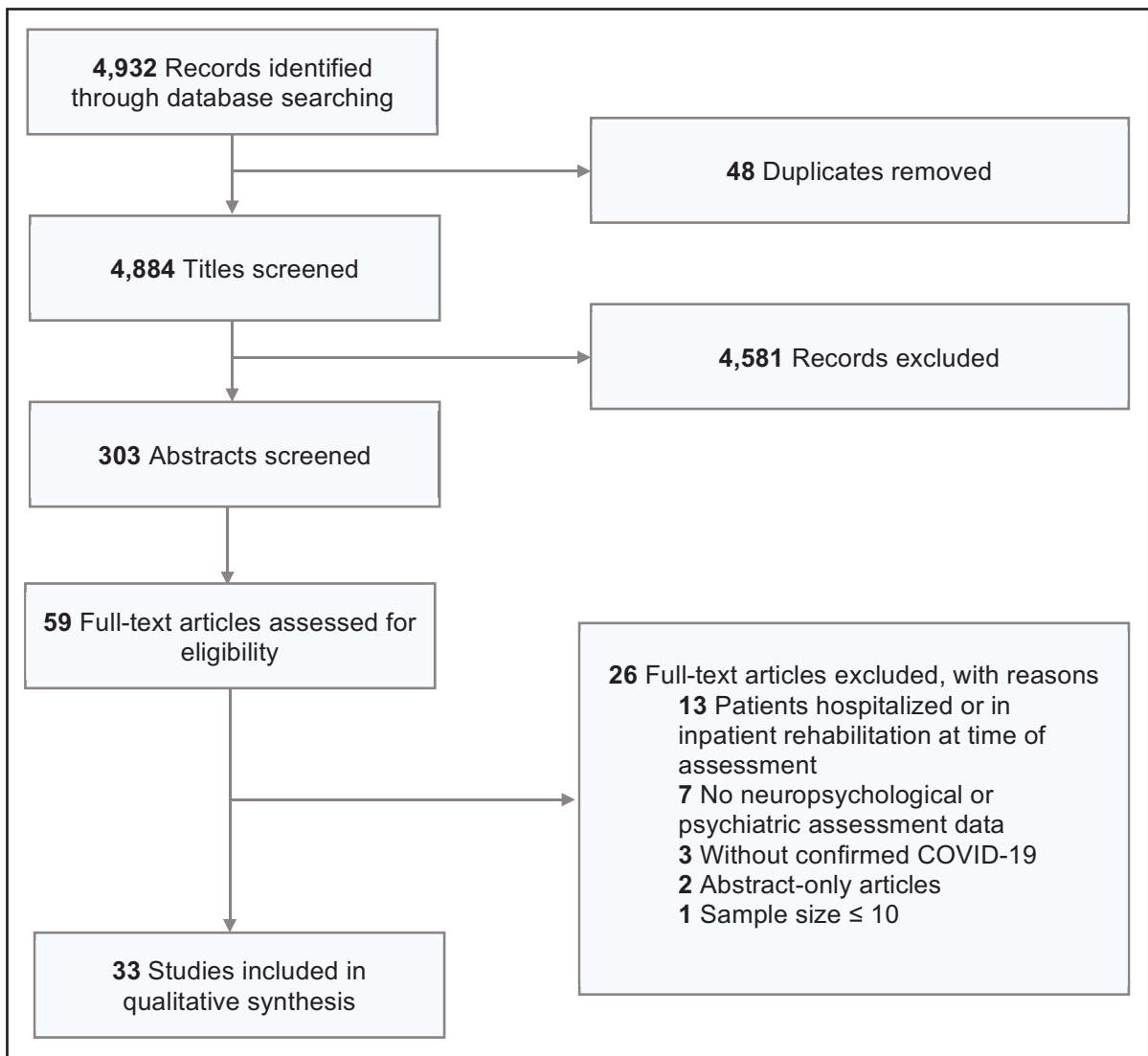


FIGURE 1. Flowchart of study selection.

microvascular events. Notably these findings were associated with markers of inflammation but not cognitive performance [11[•]].

Self-reported cognitive functioning

Self-report or observer report of cognitive difficulties was collected 4–15 weeks post discharge from hospital or recovery from COVID-19. Memory complaints were reported in 19.5–34.0% of participants and attention difficulties were reported in 24.4–28.0% of participants [18,19]. de Graaf [20] reported cognitive complaints in 25.0% of participants. Medical comorbidities were associated with more frequent report of concentration difficulties and memory loss [19]. Observation of patients from home healthcare workers indicated general improvements in cognitive status 1 month post hospital discharge [21].

Psychiatric sequelae of COVID-19

In addition to general mental health difficulties [22,23], there are elevated rates of depression, anxiety, Post Traumatic Stress (PTS), fatigue, and sleep difficulties among COVID-19 survivors.

Depression

In 19 of 33 studies assessing depression [2,11[•],12[•],13^{••}, 14^{••},16,17,20,24,28,29[•],30,31–34], symptom rates ranged from 10.0 to 68.5%. Previously hospitalized patients experienced high rates of depression both in the near- and long-term following hospital discharge. In the month following hospitalization, many patients endorsed subclinical levels of depression [12[•],14^{••},26], and 10.0–19.0% of patients reported moderate to severe depression [28,30]. Two to three months following discharge, rates of moderate to

Table 1. Overview of cited studies

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
Almeria <i>et al.</i> (2020)	35 patients without a history of prior cognitive impairment, psychiatric illness, or other CNS disease Barcelona, Spain 45.7% male	M = 47.6 SD = 8.9 Range = 24-60	Not listed	10–35 days post discharge from hospital	TAVEC: list learning, interference, recognition WMSIV: Visual reproduction Digit-Span Letters and Numbers TMT SDMT Stroop Verbal fluency BNT HADS	34.3% of the patients reported cognitive complaints No differences in neuropsychological performance between patients who reported cognitive complaints compared to those who did not endorse cognitive complaints Higher levels of anxiety and depression were found among individuals who endorsed cognitive complaints Neurological symptoms such as headache as well as loss of smell and taste were strongly associated with impaired attention, memory, and executive function	Small sample size Older individuals were excluded to avoid age-related cognitive impairment. Assessed shortly after discharge home Some data was extracted from the EMR rather than being assessed directly
Bellani <i>et al.</i> (2021)	238 previously hospitalized patients Italy 59.7% male	Median = 61 Range = 50-71	Not listed	3–4 months post discharge from hospital	IESR	Most patients did not endorse posttraumatic stress: 57.1% were within normal range, 25.6% reported mild symptoms, 11.3% reported moderate, and 5.9% reported severe symptoms Male sex was the only factor independently associated with the presence of moderate to severe PTS symptoms	Only contacted patients who necessitated inpatient hospitalization High rate of patients declining participation Evaluation was limited to assessment of posttraumatic stress
Bonazza <i>et al.</i> (2020)	261 previously hospitalized patients (35.2% received intensive care) Italy 68.2% male	M = 58.9 SD = 13.3	Not listed	2 months post discharge from hospital	HADS IESR	High prevalence of patients reported anxiety (28%), depression (16%), as well as posttraumatic stress (36.4%) Psychological distress was associated with female gender. Younger patients are more likely to have anxiety No correlations were found between duration of hospitalization or the intensity of care, and psychological outcomes	Participants assessed within quarantine setting Underlying reasons for high endorsement of PTS remains unclear
Bowles <i>et al.</i> (2020)	1409 hospitalized patients New York, US 51% male	M = 67 SD = 15	27% White; 28% Black; 35% Hispanic; 9% other	Not listed	OASIS-D1 mandatory assessment tool	Improvements in cognitive functioning and anxiety usually within one month post hospital discharge 1.6% increase in cognitive functioning and 35% decrease in anxiety	Information on rehospitalization and death after hospital discharge was not available
Cai <i>et al.</i> (2020)	126 hospitalized patients Shenzhen, China 47.6% male	M = 45.7 SD = 14	Not listed	Not listed	Self-report of PTSD Self-report of depression Self-report of anxiety	54% reported psychiatric distress Comorbidity of clinically significant stress response, anxiety and depression was 11.9% 31% had clinically significant stress response; 22.2% had clinical anxiety; 38.1% had clinical depression Older survivors (over age 60) reported lower levels of stress response than younger individuals Significantly higher rates of psychiatric symptoms than seen following previous major disasters	23 participants had prior history of psychiatric illness All patients were discharged from hospital into a mandatory quarantine facility, and were assessed while in quarantine
Daher <i>et al.</i> (2020)	33 hospitalized patients not requiring mechanical ventilation Germany 67% male	M = 64 SD = 3	Not listed	6 weeks post discharge from hospital	EQ-5D-5L PHQ-9 GAD-7	Most common endorsement was mild depression and anxiety On quality-of-life measures, patients reported slight to moderate difficulties with mobility, self-care, completing ADLs as well as elevated levels of pain/discomfort and anxiety/depression	Patients had multiple medical comorbidities, and did not identify premorbid psychiatric disorders Primary outcome was respiratory function; assessment of psychiatric concerns was secondary aim

Table 1 (Continued)

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
de Graaf <i>et al.</i> (2021)	81 hospitalized patients (42% requiring ICU admission); only 59 completed psychological assessments Netherlands 51% male	M = 60.8 SD = 13 Range = 27-88	Not listed	6 weeks post discharge from hospital	GAD-7 PHQ-9 PCL-5 Cognitive Failures Questionnaire IQ CodeN semi structured clinical interview	17% reported elevated symptoms of depression; 5% endorsed elevated anxiety; 10% met criteria for PTSD 40% reported previous mental health treatment 25% of patients endorsed cognitive impairments	Small Sample size Less than 50% of sample were admitted to the hospital participated in the study Lack of baseline data
De Lorenzo <i>et al.</i> (2020)	185 patients (68.1% requiring inpatient hospitalization) Italy 66.5% male	M = 57 Range = 48-67	90.8% European; 8.6% Hispanic; 0.5% African-American	Median of 23 days post discharge from hospital	WHQOL-BREF IES-R STAI-Y WHIRS Unstructured clinical interview	Cognitive impairment was observed in 25% of patients despite no history of cognitive disorder 22.2% of patients met criteria for PTSD	Lack of objective assessment of cognition Use of unstructured clinical interviews Only previously hospitalized patients were recruited
Garrigues <i>et al.</i> (2020)	129 hospitalized patients France 75% male	M = 63.2 SD = 15.7	Not listed	Mean of 110.8 (SD = 11.1) days post admission	EQ-5D-5L Brief phone interview of clinical symptoms	Most patients reported persistent symptoms of fatigue (55%), memory loss (34%) concentration difficulties (24%), and sleep disorders (30.8%)	Exclusive use of self-reported measures Lack of baseline functioning Only previously hospitalized patients were recruited
Guo <i>et al.</i> (2020)	259 patients China 46.9% male	<18 = 1.6% 18-46 = 53.1% 46-49 = 43.3% >69 = 2%	Not listed	One month post discharge from hospital	SF-36	Role limitations due to emotional problems were related to male sex and positive nucleic acid duration Significant differences were found in vitality and mental health of patients aged 46-69 with positive nucleic acid duration longer than 14 days	High rate of attrition across follow-up period Lack of standardized, granular mental assessment Only previously hospitalized patients were recruited
Huang <i>et al.</i> (2021)	1733 patients China 52% male	M = 57	Not listed	Median of 184 (Range = 175-199) days after symptom onset	mMRC EQ-5D-5L EQ-VAS	23% of reported depression or anxiety 63% reported fatigue/muscle weakness 25% reported sleep difficulties	Lack of baseline functioning Exclusion of patients with mild symptoms
Islam <i>et al.</i> (2021)	1002 patients (21% were previously hospitalized) Bangladesh 57.9% male	M = 34.7 SD = 13.9 Range = 18-81	Bangladeshi	Not listed	PHQ-9 Self-report treatment history Assessment of fear of reinfection	30.4% endorsed minimal symptoms of depression, 21.5% endorsed mild symptoms, 24.2% endorsed moderate symptoms, 19.4% endorsed moderate-severe symptoms, 4.6% endorsed severe symptoms 52.2% reported sleep disturbance Lower SES, poor health, sleep disturbance, asthma/respiratory problems, and fear of reinfection were associated with moderate-severe depression	Time of assessment was not provided Diagnostic status determined by self-report rather than utilization of PCR test
Janiri <i>et al.</i> (2020)	61 patients who were referred to postacute care clinic (9% previously required ICU admission) Italy 59% male	>60	Italian	Mean of 41 days (SD = 19) post discharge from hospital	TEMPSA-39 Difficulties in Emotion Regulation Scale Kessler Questionnaire-10	High likelihood of psychological distress was associated with female gender, Cyclothymic and Depressive scales of TEMPS, self-reported impulse control difficulties and lack of emotional clarity scales of DERS	Small sample size Statistical models in (ANCOVA with 7 covariates) in light of sample size
Jeong <i>et al.</i> (2020)	234 patients who were admitted to nonhospital facilities for isolation and monitoring (28.2% were asymptomatic and 71.8% were mildly symptomatic) South Korea 39.7% male	M = 37.78 SD = 15.57	South Korean	Not listed	HADS	During first week of quarantine, 19.8% endorsed mild depression or anxiety symptoms At 1 week follow-up, 1.4% reported depression or anxiety symptoms; significant decline in anxiety but not depression 20% of the asymptomatic group endorsed mood difficulties Anxiety and depression levels positively associated with quarantine durations	Small sample size Clinical outcomes of all the patients were not included Mental health data was collected via mobile-phone based survey. Patients without access was contacted by physicians via direct questioning

Table 1 (Continued)

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
Liu <i>et al.</i> (2020)	675 previously hospitalized patients (21.5% had mild symptoms, 60.1% had moderate symptoms, 17.2% had severe symptoms, 1.2% were critically ill) Wuhan, China 47% male	Median = 55 Range = 41-66	Not listed	Mean of 36.75 days post discharge from hospital	PHQ-9 GAD-7 PCL-5 5-item Perceived discrimination scale	12.4% of patients were provisionally diagnosed with clinically significant PTSD symptoms 10.4% were categorized as having moderate to severe anxiety symptoms, with 32.3% reporting mild symptoms 19% were categorized as having moderate to severe depression symptoms, with 46.7% reporting mild symptoms Perceived discrimination, disease severity, living with children, and death of family member were predictors of mental health symptoms; mechanical ventilation was not associated with mental health outcomes	Cross-sectional study which limits causal inference Mental health outcomes were cut off based on sum-score of diagnostic criteria, presenting potential threat to validity Medical comorbidities were not examined directly Lack of baseline psychological data
Liu <i>et al.</i> (2021)	324 patients: 6% asymptomatic, 73% had mild or moderate symptom 19% had severe/critical symptoms Shenzhen, China 47.8% male	Asymptomatic: M = 23.44 Mild/moderate: M = 38.61 Severe/critical: M = 57 Total: Range = 0.3-86	Not listed	Not listed	Not listed	Rates of anxiety was as follows: 11.94% among patients with mild/moderate symptoms, 10% among patients with severe/critical symptoms Rates of headache or insomnia were: 8.96% among patients with mild/moderate symptoms and 22.5% among patients with severe/critical symptoms	Anxiety measure was not reported, outcome was subsequently described as 'anxiety/depression' Timing of anxiety assessment remains unclear
Mandal <i>et al.</i> (2020)	384 previously hospitalized patients (14.5% required ICU admission) UK 62% male	M = 59.9 SD = 16.1	43% ethnic minority	Median of 54 days post discharge from hospital	PHQ-2	14.6% of patients endorsed depression a median of 54 days post discharge	Abbreviated measure of depressive symptoms
Manman <i>et al.</i> (2021)	1021 patients (10.9% were asymptomatic and 89.1% were symptomatically hospitalized) 384 previously hospitalized patients (14.5% required ICU admission) Bangladesh 75% male	0-9: N = 18 10-19: N = 50 20-29: N = 248 30-39: N = 309 40-49: N = 171 50-59: N = 126 >60: N = 96	Not listed	Received negative PCR result at least 4 weeks prior to the study	Phone interview	Most prevalent postrecovery complications included sleep disturbance (32%), weakened attention span (24.4%), anxiety and depression (23.1%), memory loss (19.5%), and complications with mobility (17.7%) Patients with medical comorbidity were found to be more likely to experience mobility problem (26%), weakness and problems performing usual activities (14%), anxiety and depression (28.5%), sleep disturbances (41.3%), concentration difficulties (28.5%), and memory loss (24.6%) than those without any comorbid conditions	Measures used to assess cognitive and psychological functioning were not reported
Moazza <i>et al.</i> (2020)	402 patients who were presented to ED (74.6% were admitted for inpatient hospitalization and 25.4% were discharged home) Milan, Italy 65.7% male	M = 57.8 Range = 18-87	Not listed	Mean of 31.29 (SD = 15.7) days post discharge from hospital, or mean of 28.56 (SD = 11.73) days after ED admission	IES-R PCL-5 BDI-13 STAI-Y WHIRS Obsessive-Compulsive Inventory Zung Depression Scale Medical Outcomes Study Sleep Scale	Rates of clinically significant psychopathology based on self-report: 28% for PTSD, 31% for depression, 42% for anxiety, 20% for obsessive-compulsive symptoms, and 40% for insomnia 55.7% endorsed clinical levels on at least 1 psychopathological dimension, with 36.8% endorsing clinical levels across 2 dimensions, 20.6% across 3 dimensions, and 10% across 4 dimensions Female patients with a previous psychiatric history, and patients who were discharged home reported greater difficulties on most measures	Cross-sectional study

Table 1 (Continued)

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
Park <i>et al.</i> (2020)	10 patients South Korea 80% male	M = 62.6 SD = 14.9	Not listed	1 month post discharge from hospital (median = 25 days, range = 13–50 days)	PHQ-9 GAD-7 IES-R	50% endorsed depressive symptoms during treatment 100% of patients denied significant anxiety after discharge At 1 month postdischarge, 10% endorsed symptoms of depression and PTSD Patients with high perceived stigma reported higher levels of PTSD symptoms Patients with a history of prior psychiatric treatment reported higher levels of PTSD symptoms, whereas levels of depression and anxiety did not differ as a function of treatment history	Small sample size
Raman <i>et al.</i> (2021)	58 hospitalized patients (95% required mechanical ventilation, 36% required ICU admission) 30 uninfected matched controls UK 58.6% male	M = 55.4 SD = 13.2	77.6% White, 22.4% Nonwhite	Median of 2.3 months from disease-onset, median of 1.6 months post discharge from hospital	PHQ-9 GAD-7 SF-36 MoCA MRC Fatigue Severity Scale	Executive/visuospatial impairments were greater among patients compared to controls. Severity of illness did not predict levels of depression or anxiety At 2–3 months from disease-onset, patients reported significantly reduced quality of life and endorsed greater levels of depression, anxiety, and fatigue than controls did	Small sample size Cross-sectional assessment Lack of correction for multiple comparisons Given that controls were not hospitalized, group differences may not be specific to COVID-19 infection
Soldati <i>et al.</i> (2021)	23 patients who were previously treated in the ICU Brazil 78.3% male	M = 53.6 SD = 11.7	Not listed	Ranged 43–136 days post discharge from hospital	TICS EuroQoL	60.9% of patients fell within normal limits on cognitive assessments 13% met criteria for MCI MCI diagnosis was negatively associated with EuroQoL scores No one exhibited severe levels of cognitive impairment on TICS Quality of education was inversely associated with cognitive functioning	Lack of control group
Speth <i>et al.</i> (2020)	114 patients Switzerland 45.6% male	M = 44.6 SD = 16.1	Not listed	M = 12.3 days (SD = 7.2, range = 0–31) following onset of COVID-19 symptoms	PHQ-2 GAD-2	Depressed mood and anxiety were positively associated with chemosensory dysfunction but not positively associated with symptoms of fever, cough and shortness of breath Older age and preexisting depressive and anxiety symptoms were positively associated with levels of depression and anxiety across disease course	Cross-sectional assessment Utilization of retrospective report Lack of objective measures of olfactory dysfunction
Sykes <i>et al.</i> (2021)	134 hospitalized patients (87% required supplemental oxygen or respirator support, 20% required ICU admission) UK 65.7% male	M = 59.6 SD = 14	91% White, 1.5% Black, 6% Asian, 1.5% Mixed/other	Median of 113 days (range: 46–167) post discharge from hospital	MRC EG-SD-5L	86% reported at least one residual symptom, with the most frequently reported complaint being fatigue Illness severity was not associated with self-reported symptom burden Female sex was positively correlated with level of residual symptoms, particularly anxiety and fatigue Persistent COVID-related complications may not be directly attributable to SARS-CoV2 infection but, rather, the neuropsychiatric sequelae of the virus	Severity of persistent symptoms was not assessed

Table 1 (Continued)

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
Tomasoni <i>et al.</i> (2021)	105 hospitalized patients (72% received minimal oxygen therapy whereas 22% were treated with CPAP, NIV or OTI) Milan, Italy 73.3% male	Median = 55	Not listed	1–3 months (Median = 46 days) after virological clearance	HADS MMSE	Among 25 patients who completed MMSE, 40% indicated cognitive impairment, which ranged from mild to severe Many patients continued to endorse anxiety (29%) and depression (11%) 1–3 months after virological clearance Clinical levels of HADS-A/D scores were positively associated with physical complaints	Small sample size Only included patients with confirmed virological recovery, patients with persistent positive PCR after clinical recovery were excluded Lack of baseline psychological data
Townsend <i>et al.</i> (2020)	128 patients (55.4% were hospitalized, 44.6% were outpatients) Dublin, Ireland 46.1% male	M = 49.5 SD = 15	Not listed	Outpatients: at least 6 weeks after abatement of acute COVID-19 symptoms Hospitalized patients: date of discharge	Chalder Fatigue Scale	Mean psychological fatigue was 4.72 (SD = 1.99) Treatment factors (hospitalization status, need for respiratory treatments) were not associated with fatigue levels Fatigue was positively associated with preexisting depression and use of antidepressant medications	Cross-sectional assessment
Van den borst <i>et al.</i> (2020)	124 patients (21.7% with mild disease, 41.1% with moderate, 20.9% with severe, 16.1% with critical disease); 78.2% required inpatient hospitalization Nijmegen, Netherlands 60% male	M = 59 SD = 14	Not listed	Outpatients: M = 13.0 weeks (SD = 2.2) symptom onset Hospitalized patients: M = 9.1 weeks (SD = 1.6) after discharge home	HADS TICS PCL-5 IESR SF-36 Cognitive Failures Questionnaire Nijmegen Clinical Screening Instrument	Approximately 33% exhibited cognitive difficulties or atypical mental status Disease severity grade was not associated with mental or cognitive status in this study Many patients reported chronic, and severe, problems across health domains Referred mild disease patients displayed a female predominance and reported more frequently severe problems than moderate-to-critical disease, in the domains of physical functioning, quality of life, and energy	Skewed distribution of prior health difficulties across disease severity groups; participants with mild disease had longstanding health impairments Diagnostic status not confirmed by PCR test for all participants
Wang, <i>et al.</i> (2020)	215 hospitalized patients Cleveland, US	Not listed	Not listed	Not listed	PTSD-5 GAD-7 CESD10	57% screened positive for PTSD, anxiety, or depression. Specific rates were as follows: 34% for PTSD, 24% for anxiety, and 42% for depression Among patients without a prior psychiatric history, 42% screened positive for one psychiatric disorder Among patients with a prior psychiatric history, 78% screened positive for one disorder	Utilization of self-report to characterize psychiatric history Not all patients were initially hospitalized due to COVID-19
Weerhandi <i>et al.</i> (2021)	152 hospitalized patients (45.3% required ICU admission, 36.7% required mechanical ventilation) New York, US 62.7% male	Median = 62 Range = 50–67	44.1% White, 21.7% Hispanic, 9/9% Asian, 11.2% Black, 8.7% Mixed/other, 4.4% unknown	Median of 37 days (range: 30–43) post discharge from hospital	the PROMIS Global Health-10	Poorer physical health and mental health were reported after hospital discharge compared to baseline functioning	Strict exclusion criteria
Woo <i>et al.</i> (2020)	18 patients with mild to moderate disease (61% required inpatient hospitalization) 10 age-matched healthy controls Hamburg, Germany 42.1% male	M = 42.2 SD = 14.3	Not listed	Median of 85 days (Range = 20–105 days) after recovery	TICS-M PHQ-9 Fatigue Assessment Scale	Patients exhibited greater difficulties on TICS-M as compared to healthy controls in the areas of short-term memory, attention, concentration/ language 50% reported attention deficits, 44.4% reported short-term memory deficits, 27.8% reported word-finding difficulties, 16.7% reported fatigue, 11.1% reported mood swings, and 5.6% reported fatigue, phonophobia, or incoherent thoughts Cognitive functioning was not associated with somatic symptoms Disease severity and treatment factors were not associated with cognitive impairments	Small sample size Screening measure of cognitive functioning

Table 1 (Continued)

Study	Population	Age (in years)	Race/ethnicity	Time of assessment	Measures	Findings	Limitations
Zorghami et al.(2020)	50 outpatients with mild symptomatology Fasa City, Iran	M = 43.62 SD = 15.81	Not listed	During home quarantine	PHQ-9 GAD-7 PSS-14 Semi-structured psychiatric interview	17.3% patients had prior history of psychiatric disorders Based on self-report measure, 34.6% endorsed depressive symptoms, 32.7% endorsed anxiety, and mean score for PSS-14 is 11.8 (scores range from 0–56) Based on clinical interview, 18.8% met criteria for a psychiatric disorder; specific rates were as follows: 5.8% for GAD, 21.2% for insomnia, 3.8% for MDD, and 9.6% for an adjustment disorder	Small sample size
Zhou et al. (2020)	29 recovered patients 29 healthy controls Zhejiang, China 62% male	M = 47 SD = 10.54 Range = 30-64	Chinese Han	2–3 weeks after infection	TMT Digit Span Sign Coding Test CPT GAD-7 PHQ-9	Cognitive impairments among patients with SARS-CoV-2 were mild and most prominent in the domain of sustained attention No significant difference between patient and healthy controls in TMT, SCT, or DST	Small sample size Participants excluded if they received fewer than nine years of education
Zhu et al. (2020)	432 previously hospitalized patients China 51% male	Median = 49 range = 35-60	Chinese Han and Tibetan	Not listed	Lawton IADL scale Barthel Index Zung's self-reported anxiety scale	36.8% of patients reported at least one IADL limitation, with 16.4% reporting moderate dependence and 5.6% reporting severe dependence 28.7% of patients met criteria for a probable anxiety disorder diagnosis Disease severity was associated with greater prevalence of disability and anxiety and was an independent risk factor for all outcomes	Lack of baseline data Lack of control group Reliance on self-report measures Cross-sectional assessment

BDI-13, Beck's Depression Inventory; BNT, Boston Naming Test; CES-D-10, Center for Epidemiological Studies Depression Scale; CPT, Continuous Performance Test; EQ-5D-5L, Euro Quality of Life-5 Dimensions-5 Levels; EQ-VAS, Euro Quality of Life- Visual Analogue Scale; GAD-7, Generalized Anxiety Disorder Scale; HAD, Hospital Anxiety and Depression Scale; IES-R, Impact of Event Scale-Revised; IQ Code-N, Informant Questionnaire on Cognitive Functioning in the Elderly; mMRC, modified British Medical Research Council dyspnea scale; MoCA, Montreal Cognitive Assessment; PCL, Posttraumatic Stress Disorder Checklist; PHQ-9, Patient Health Questionnaire 9; PSS-14, Perceived Stress Scale-14; SDMT, Symbol Digit Modalities Test; SF-36, 36-Item Short Form Survey; STAI-Y, State-Trait Anxiety Inventory form Y; TAVEC, Test de Aprendizaje Verbal España-Complutense; TEMPS, Temperament Evaluation of Memphis, Pisa, Paris, and San Diego; TICS, Telephone Interview of Cognitive Status; TMT, Trail Making Test A and B; WHIIRS, Women's Health Initiative Insomnia Rating scale; WHOQOL-BREF, World Health Organization Quality of Life; WMS, the Wechsler Memory Scale.

severe depression endured and ranged from 10.0 to 42.0% [2,11[■],16,24,25,28,29[■],32,33]. Survivors with higher depression severity endorsed greater perceived stigma related to COVID-19 [28,30], had a prior psychiatric history [29[■],33], and underwent quarantine posthospitalization [25].

In contrast, fewer studies focus on nonhospitalized COVID-19 survivors. Prevalence of depression in this group ranged from 15.0 to 68.5% [29[■],31,34]. Among mixed samples of previously hospitalized and never-hospitalized patients, prevalence rates ranged from 12.0 to 48.0% [17,27]. The wide range of prevalence rates are reflective of differences in assessment methods (e.g., screening questionnaires, clinical interview, self-report online surveys), used to capture symptoms of depression, differences in follow-up time frames, and global diversity of samples. Risk factors for depression in those with milder illness included female gender [29[■]], older age, and decreased sense of smell [31].

Anxiety

Of 33 studies, 25 included anxiety assessments. Estimates of clinical anxiety among patients with COVID-19 were broad and ranged from 5.0 to 55.2% [11[■],13[■],14[■],16–21,24–26,28,29[■],30–35,36[■],37–40]. Among hospitalized survivors, rates of anxiety ranged from 5.0 to 47.8% postdischarge, while some reported only subclinical symptoms of anxiety [26]. In the near term (<2months) following hospital discharge, anxiety rates were somewhat lower than in nonhospitalized survivors. In a sample of 402 COVID-19 survivors, 32.3% of previously hospitalized patients endorsed moderate to severe anxiety, whereas 44.2% of never-hospitalized patients endorsed similar levels one month after initially presenting to an emergency room in Italy [29[■]]. Others confirm greater rates of anxiety among never-hospitalized patients in the near term after infection [35]. Notably, those who were never hospitalized tend to be younger patients who have to return to family and work responsibilities shortly after recovery and these demands may exacerbate anxiety within this group. However, further, follow-up including prospective studies can confirm this finding and perhaps elucidate the etiology of higher rates of anxiety in nonhospitalized survivors.

Two to four months posthospitalization, survivors reported ongoing anxiety, with rates ranging from 14.0 to 47.8% [11[■],16,32]. The longest follow-up study to date (6 months postdischarge) indicated that 23.0% of previously hospitalized patients experienced anxiety or depression [36[■]]. Never-hospitalized patients experienced moderate to severe anxiety, at rates of 14.0–55.2%, up to four

months from symptom onset [31,34,37]. Risk factors for anxiety included illness severity [36[■]], medical comorbidities [19], reduced quality of life and persistent dyspnea [11[■]], younger age [14[■]], having close relatives with COVID-19 [25], prior psychiatric history [33], and decreased sense of smell [31].

Acute and posttraumatic stress

Eleven studies reported on acute stress reaction or PTS symptoms. One study found that, among adults in quarantine facilities in China, the prevalence rate of acute stress symptoms was 31.0% [25]. PTS prevalence among patients not held in a quarantine facility ranged from 7.0 to 36.4% [17,20,24,28,29[■],30,33–35,41]. On average, 10.0–28.0% survivors endorsed symptoms consistent with acute stress reaction [28,29[■],30,35]. Risk factors for greater severity of stress response included a history of psychiatric disorders, female gender, and COVID-19 infection of a close family member, whereas retirement status and older age were related to lower psychological distress [25].

Among studies that evaluated Post Traumatic Stress Disorder (PTSD), prevalence rates of 10.0% were reported 6 weeks postdischarge [20], whereas others reported rates of 36.4% 2 months posthospitalization [24]. Three to four months posthospitalization, 25.6% of survivors endorsed symptoms consistent with mild PTSD, 11.3% endorsed moderate symptoms, and 5.9% endorsed severe symptoms [41]. Among never-hospitalized patients with mild illness, 7.0% met the criteria for clinically significant PTSD while 10.0% endorsed acute stress symptoms [17].

Fatigue

Rates of fatigue- as measured both by formal assessment (i.e., Fatigue Assessment Scale [12[■]], Chalder Fatigue Scale or CFQ-11 [42[■]], Fatigue Severity Scale [11[■]], SF-36 energy/fatigue subscale [17] and Borg Rating Scale of Extreme Exhaustion [26], and by the patient report of symptoms [2,14[■],17,18,28,32,36[■]]) ranged from 12.7 to 88.6% across 11 studies. In one study, 10–35 days posthospitalization, 88.6% of patients endorsed fatigue [14[■]], however, two other studies report much lower rates (12.7–16.7%) 1 month after discharge [12[■],28]. Six weeks after symptom abatement or hospital discharge, 52.3% of COVID-19 survivors experienced fatigue, and 31.0% of those patients had not returned to work despite being medically cleared of COVID-19 related illness [42[■]].

Two to three months after hospital discharge, 40.0–69.0% of COVID-19 survivors endorsed ongoing fatigue that interfered with activities of daily

living and quality of life [2,11[■],17,18,26]. Sixty-three percentage of COVID-19 survivors endorsed ongoing fatigue or muscle weakness at six months [36[■]]. Risk factors for persistent fatigue included female sex and prior history of depression or anxiety [32,42[■]]. There was generally no association between fatigue and inflammatory markers or COVID-19 disease severity [32,42[■]]; however, one study reported that patients with moderate or severe illness endorsed worse fatigue than did those with mild illness [17].

Sleep difficulties

Estimates of sleep disturbance ranged from 26.0 to 52.2% across five studies [18,19,27,32,36[■]]. Those with multiple medical comorbidities were more likely to experience sleep disturbance (41.3%) than those without (32.0%) four weeks after hospital discharge [19]. Sleep disturbance was higher among women, and increased depression risk [32]. Further, sleep disturbance appeared to persist in 26.0% of survivors, 6 months postdischarge [36[■]].

DISCUSSION

In a systematic review of 33 studies evaluating the neuropsychological and psychiatric sequelae of community-dwelling patients recovering or recovered from COVID-19, we found high rates of depression, anxiety, fatigue, and sleep disruption, and somewhat lower, but still significant, rates of PTSD. Similar rates of depression and anxiety appear among patients who were previously hospitalized or never hospitalized; some studies even suggest these symptoms may be higher in never hospitalized survivors possibly due to the younger age range of these cohorts which developmentally may coincide with competing work/life responsibilities which older adults may not face. In contrast, rates of PTSD appear higher among hospitalized patients. Fatigue is the most prevalent and persistent symptom at longer-term follow-up time points and may contribute to difficulties returning to preillness roles. Though longitudinal studies are scarce, cross-sectional studies at different time points postinfection suggest that psychiatric symptoms may be enduring. Consistent risk factors for psychiatric symptoms include history of psychiatric disorder and female gender. Additional risk factors are infection of a family member, isolation, perceived stigma, and medical comorbidity. Findings on age as a risk factor are inconsistent.

Overall, few studies have formally assessed neuropsychological sequelae of COVID-19, and the substantial heterogeneity of study samples and methods undermine comprehensive

characterization of cognitive functioning within specific domains. Studies inconsistently excluded individuals with prior cognitive impairment. Notwithstanding, most studies included here indicate some degree of cognitive impairment among patients with previous diagnosis of COVID-19. Though rates vary, a substantial portion of survivors exhibit poor cognitive performance in the domains of attention, executive function, and memory. Our findings have several important implications for further research, clinical management, and treatment of COVID-19 survivors.

Implications for further research

Limited assessment of psychiatric symptoms to date does not allow for granular examination of psychiatric symptom range and acuity. Most studies to date use screening instruments to categorize and determine the severity of psychiatric disorders. Examination of patterns of symptoms or transdiagnostic processes (e.g., increased negative affect, decreased reward, rumination) may elucidate common underlying features of psychiatric sequelae post-COVID-19 to clarify mechanisms of psychiatric symptoms and inform treatment targets.

There is a need for prospective research studies that recruit large patient populations and comparison samples, comprehensively define medical and treatment course, and utilize gold-standard measures to characterize cognitive and psychiatric functioning across specific domains over time. Sample characteristics in the extant literature vary widely and often fail to characterize participants' medical comorbidities, premorbid cognitive functioning, and prior psychiatric and treatment history. Few studies examine the association between known COVID-19 risk factors (e.g., hypertension, diabetes, cardiovascular disease) and cognition or psychiatric symptoms, and studies do not consistently control for the impact of treatments.

There are few studies including nonhospitalized COVID-19 survivors. Elevated rates of psychiatric symptoms among patients who did not warrant hospitalization, as compared to those who did, suggest that, for some patients, environmental and psychological factors may contribute more to psychiatric sequelae than do disease characteristics or medical treatments. Identifying factors that contribute to psychiatric sequelae among never-hospitalized COVID-19 survivors is needed. Relatedly, prospective studies on populations that are quarantined per government directive may help to clarify the role of mood dysfunction stemming from COVID-related illness as compared to protracted isolation and perceived stigma.

This review did not focus on acute COVID-19 infection and treatment, and studies included here were predominantly conducted within the first few months of symptom abatement or hospital discharge. Longitudinal assessment across the course of viral infection/progression, treatment, and recovery is needed to document the nature of COVID-related cognitive and psychiatric difficulties over time. Such work will aid in the selection of appropriate interventions across stages of recovery.

Most studies relied on retrospective self-report assessment measures, which are susceptible to reporting biases [43]. Relatedly, neuropsychological functioning was often assessed using screening measures, thereby limiting the granular measurement of cognition. Future studies should utilize gold-standard measures of specific cognitive and psychiatric domains, which will help to elucidate specific treatment targets.

This review should be considered in the context of temporal and cultural factors that may limit generalizability. Many studies included in this review were conducted at the height of the pandemic, when understanding of the virus, its treatment, and the nature of the pandemic at large was limited. Prevalence rates of neuropsychological and psychiatric difficulty during the first peak of the pandemic may differ from those observed across subsequent waves of viral infection. Further, cultural differences, including stigma, quarantine procedures, access to, and the nature of, treatment, may underlie differing prevalence rates of neuropsychological and psychiatric symptoms across countries and regions.

Finally, given that COVID-19 disproportionately affects marginalized and ethnic minority communities, there is a critical need to explore factors that may contribute to increased risk of morbidity and mortality among this population. Treatment modalities may require modification according to the ethnocultural preferences of patients, to ensure treatment compliance, optimal recovery, and better outcomes.

Clinical assessment and treatment

Psychiatric symptoms should be considered highly common, distressing, and debilitating sequelae of COVID-19 that can endure, contribute to poor adherence to medical treatments, and require assessment and treatment. Survivors of COVID-19 should routinely be screened for psychiatric symptoms, and providers should not assume that those with milder forms of COVID-19 or those who were never hospitalized will not manifest psychiatric symptoms or cognitive deficits. Cognitive screening should be

performed routinely in COVID-19, with referral for more comprehensive neuropsychological assessment as indicated.

Among studies that use objective measures of cognition, memory was occasionally impaired whereas attention and executive functions appear to be commonly impaired. Cognitive remediation that introduces and practices strategies designed to support attention and executive functions may be helpful. Given the prevalence of COVID-19 infection and the varied rates of impairment, scalable interventions (e.g., digital therapeutics) that can be widely disseminated will be paramount in this population [44].

Cognitive-behavioral (CBT) and mindfulness-based approaches targeting depression, anxiety, and sleep difficulties are likely to be beneficial for survivors. Cognitive restructuring and mindfulness focused on self-compassion can target perceived discrimination while modified forms of behavioral activation can ameliorate depression symptoms. CBT for anxiety may be especially useful for individuals with ongoing shortness of breath postdischarge from the hospital. Activity pacing and graded increase in activities, together with medical management, may help those with fatigue symptoms. Sleep hygiene and CBT for insomnia are recommended to address ongoing sleep difficulties. Cognitive processing therapy or prolonged exposure therapy may be beneficial for ICU survivors who experience PTS symptoms. Given the rates of psychiatric symptoms reported to date, mechanisms for broad dissemination of interventions should be considered [45].

Limitations

Limitations of this review include a limited time frame (December 2019 to February 2021). Given the surge of research on COVID-19, timeframe restrictions on literature searches notably limit the inclusion of emerging data on the topic. Further, this review excluded studies with samples of hospitalized patients to minimize the review of neuropsychological and psychiatric sequelae stemming from factors related to inpatient hospitalization. In doing so, however, this review could not document cognitive and psychiatric deficits among acutely, and often critically, ill patients. Although outside the scope of the current paper, greater understanding of the nature of neuropsychological and psychiatric functioning across hospitalization course is needed. Indeed, delirium is common in patients treated in the ICU, which can cause severe and persistent cognitive dysfunction [46–48], and depression, anxiety, and PTSD are frequently experienced by survivors of critical illness [49,50].

CONCLUSION

This systematic review highlights cognitive deficits and psychiatric symptoms associated with COVID-19. Cognitive and psychiatric dysfunction has the potential to negatively impact survivors' social and occupational functioning during and after recovery. Primary findings from this paper shed light on important treatment targets for this population. Future research is essential to further delineate a granular characterization of cognitive and psychiatric functioning among COVID-19 survivors over time, which will enhance treatment specificity and efficacy across various stages of recovery.

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Conflicts of interest

There are no conflicts of interest.

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