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Research Article

Cognitive Decline in Recovered COVID-19 Patients: An Updated Systematic Review and Recommendations

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Abstract

Background: As the coronavirus disease 2019 (COVID-19) pandemic has advanced to its second year, the focus is shifting to the long-term impact of COVID-19 infections on the health of survivors, particularly cognitive decline following recovery from COVID-19 infection.

In this systematic review, we collate findings from current literature to describe the impact of COVID-19 infection on cognition after recovery in confirmed cases.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report findings. The following combination of keywords was used to search Pubmed, ClinicalKey, Scopus, and Cochrane Library: "cognitive OR cognition", "decline OR deficit OR impairment", and "COVID-19 OR corona OR SARS-CoV-2". The outcome was to assess whether recovered COVID-19 patients had a higher risk of cognitive impairment while noting the severity of initial infection.

Results: Of 1,874 records identified during database search, 92 were assessed using full-texts, and 9 studies were included in the qualitative analysis. We presented data for 1,936 patients. The incidence of cognitive impairment was determined for 1,875 out of 1,936 participants. Notably, 615 (32.8%) recovered COVID-19 patients presented with cognitive impairment.

Conclusion: Various contributors have been implicated in the post-COVID-19 cognitive impairment. Further elucidation is necessary to understand the neurotropic impact of the virus.

Keywords: Cognitive; COVID-19; Neurological; Neurotropism

1. Introduction

As the coronavirus disease 2019 (COVID-19) pandemic has advanced to its second year, the focus is shifting to the long-term impact of COVID-19 infections on the health of survivors. There has been a great emphasis placed on the cognitive decline following recovery from COVID-19 infection [1]. The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virion has been implicated for its infiltration of the central nervous system (CNS) [2]. The association of neurotropism and viruses is not new as neurotropism was also documented during the 1918 influenza pandemic [3]. However, attention of the CNS impact of COVID-19 infection had not been evaluated in longer-term clinical presentations until the last few months [4]. The number of recovered patients has been increasing, resulting in emerging data of cognitive decline. Studies have reported at least one-third of COVID-19 patients manifesting neurological symptoms and over 20% of hospitalized patients with delirium in the acute stages of infection, identified with signs including confusion and agitation [5, 6]. High-risk sub-groups include patients over 65 years of age and with underlying cognitive impairment due to ongoing neurocognitive decline [7]. Underlying inflammatory process implicated in severe COVID-19 infection has also resulted in an increased likelihood of infarctions, thrombosis, coagulopathy, and increased blood-brain barrier (BBB) permeability, possibly involved in cognitive decline [7].

Mechanistically, SARS-CoV-2 infection leads to direct infiltration of the CNS cells by binding the S1 subunit of the S protein, 1 of 4 structural proteins on the virion, to the angiotensin-converting enzyme 2 receptor (ACE-2) [8]. The binding of ACE-2 with the S1 subunit results in the entry of the virus into the cells of CNS, through fusion of host and viral cells [8]. Different mechanisms have been proposed that may act in conjugation to enhance the neurotropism of SARS-CoV-2, including

retrograde axonal transport after invading peripheral olfactory neurons, and breach of the blood-brain barrier (BBB) or choroid plexus endothelial cells [9]. The underlying pathology is associated with the cytokine storm, further compromising the BBB [9]. CNS manifestations have been attributed to different etiologies including inflammatory (e.g. meningo-encephalitis), and hematological (e.g. cerebrovascular disease) [10]. Taken together, the combination of the patient's risk factors, the severity of COVID-19 and treatment course contribute to the cognitive decline, independently or altogether. In this study, we review the current literature to describe the impact of COVID-19 infection on cognition after recovery in confirmed cases.

2. Methods

2.1 Search strategy and selection

We conducted a systematic review of the literature regarding cognitive decline after recovery from COVID-19 infection. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to report the findings. The following combination of keywords was used to search Pubmed, ClinicalKey, Scopus, and Cochrane Library from 2020 to April 30, 2021: "cognitive OR cognition", "decline OR deficit OR impairment", and "COVID-19 OR corona OR SARS-CoV-2". Studies prior to 2020 were excluded. Further screening was conducted using an umbrella review method to screen for eligible studies from the reference list of selected studies. Journals including the Lancet, JAMA, BMJ, NEJM, and Annals of Internal Medicine were manually screened for eligible studies. To minimize bias, two independent reviewers screened for the studies separately. Only studies that reported original data, including case reports, observational studies, and clinical trials were selected. Other article types including abstracts, editorials, and commentaries were excluded. Studies reporting the cognitive impairments of COVID-19 in sub-acute or long-term settings were selected. Duplicates were removed using the software Endnote X9.

2.2 Inclusion and exclusion criteria

Inclusion criteria comprised of 1) studies in English, 2) including COVID-19 recovered patients, 3) follow-up period specified, 4) cognitive function assessment. All other studies were excluded. Cognitive function was commonly assessed using the Montreal Cognitive Assessment (MoCA) score and other scores listed in Table 1. Cognitive impairment is defined as a MoCA score of <24 in the absence of a known history of neurocognitive disease.

2.3 Outcome and data tabulation

The outcome was to assess whether recovered COVID-19 patients had a higher risk of cognitive impairment while noting the severity of initial infection. To ensure optimal data tabulation and presentation for eligible studies, information including 1) author-year, 2) title, 3) study design- sample size, 4) tool/parameter used, 5) incidence of cognitive impairment, 6) severity of COVID-19 infection, and 7) duration of follow up, was documented. The relevant data can be found in Table 1.

No	Author-year	Title	Study Design (Sample Size)	Tool/Parameter used	Incidence of Cognitive Impairment	Severity of COVID-19	Duration of follow up
1	De Lorenzo *et al.* (2020)	Residual clinical damage after COVID-19: A retrospective and prospective observational cohort study	Retrospective and prospective observational cohort (n=185)	Montreal Cognitive Assessment (MoCA) score. Cognitive impairment was positive if the score was <24 in the absence of a known history of neurocognitive disease	Cognitive impairment was present in 47 (25.4%) patients of which 11 (18.6%) were discharged from the ED and 36 (28.6%) were hospitalized	126 (68.1%) patients were hospitalized, while 59 (31.9%) were discharged from ED	The Median (IQR) time from hospital discharge to follow-up was 23 (20–29) days
2	Bowles *et al.* (2020)	Surviving COVID-19 after hospital discharge: Symptom, functional, and adverse outcomes of home health recipients	Retrospective observational cohort (n=1409)	OASIS (Outcome and Assessment Information Set) version D-1 datasets	327 (23%) patients required prompting, while 92 (7%) required assistance and direction, or considerable assistance	137 (10%) patients were re-hospitalized, 1241 discharged (88.1%)	The mean duration of care was 32 (SD= 25.7) days*
3	Del Brutto *et al.* (2020)	Cognitive decline among individuals with a history of mild symptomatic SARS-CoV-2 infection: A longitudinal prospective study nested to a population cohort	Longitudinal prospective cohort (n= 93)	Montreal Cognitive Assessment (MoCA) score post and pre-pandemic assessments	12 (13%) patients presented with cognitive decline	All patients (100%) had mild symptomatic SARS-CoV-2 infection	The total person-years of follow-up from the last pre-pandemic MoCA test was 253.4 years (95% CI 242.5–264.2)
4	Hosp *et al.* (2021)	Cognitive impairment and altered cerebral glucose metabolism in the subacute stage of	Prospective cohort (n= 29)	Montreal Cognitive Assessment (MoCA) score < 26	18 of 26 (69.2%) patients had impaired MoCA scores with an emphasis on frontoparietal cognitive functions	27 (93.1%) patients were discharged, 1 (3%) was still hospitalized	Inpatients were followed for a total of 22 days, with cognitive symptoms onset at

		COVID-19					18.4 days (SD=2.3)
5	Zhou *et al.* (2020)	The landscape of cognitive function in recovered COVID-19 patients	Observational cross-sectional, 29 COVID-19 participants and 29 controls (n= 58)	iPad-based online neuropsychological tests (the Trail Making Test (TMT), Sign Coding Test (SCT), Continuous Performance Test (CPT), and Digital Span Test (DST)	COVID-19 patients vs Controls (Mean scores): TMT (47.82 vs 49.76), SCT (32.14 vs 34.48), CPT part 1, 2,3 had different reaction times, and DST (19.24 vs 18.97)**	None (0%) of the included patients had severe SARS-CoV-2 infection at the time of testing and only recovered (100%) ones were included	Neuropsychological assessments were conducted 2-3 weeks post-recovery from infection
6	Miskowiaka *et al.* (2021)	Cognitive impairments four months after COVID-19 hospital discharge: Pattern, severity, and association with illness variables	Prospective cohort (n= 29)	Screen for Cognitive Impairment in Psychiatry-Danish Version (SCIP-D), Trail Making Test-Part B (TMT-B), the Cognitive Failures Questionnaire (CFQ)	19 (65%) patients were classified as (selective and/or global) cognitively impaired	All patients (100%) were admitted to the hospital at the time of infection, but only 1 had required mechanical ventilation	Patients were followed for 3–4 months
7	Alemanno *et al.* (2021)	COVID-19 cognitive deficits after respiratory assistance in the subacute phase: A COVID- rehabilitation unit experience	Prospective cohort (n= 87)	Mini-Mental State Evaluation (MMSE), Montreal Cognitive Assessment (MoCA)	73 (83.9%) patients presented with cognitive defects	All included patients (100%) were previously admitted to the ED, ICU, RHDCU of infectious disease units	Follow-ups were performed 1 month after home discharge
8	Ferrucci *et al.* (2021)	Long-lasting cognitive abnormalities after COVID-19	Prospective cohort (n= 38)	Montreal Cognitive Assessment (MoCA), Brief Repeatable Battery of Neuropsychological Tests (BRB-NT)	23 (60.5%) patients showed cognitive abnormalities, {16 (42%) had slowing of cognitive processing speed and 7	Of 33, 21 patients had no ARDS, 10 had mild ARDS, and 2 were	Days between hospital discharge and cognitive assessment were 132.9 (SD=36.62)

					(20%) had long-term verbal and spatial memory dysfunctions}	classified as moderate ARDS	
9	Blazhenets *et al.* (2021)	Slow but evident recovery from neocortical dysfunction and cognitive impairment in a series of chronic COVID-19 patients	Prospective case series (n= 8)	Montreal Cognitive Assessment (MoCA) and ^{18}F-FDG PET scans	4 (50%) patients had cognitive impairments	All patients (100%) were hospitalized with 2 (25%) requiring ICU treatment	Patients were followed for around six months after symptom onset

* Follow-up was defined as the time until the first adverse event or the completion of study (until 15 September 2020)

**CPT was divided into three parts, showing continuous selection, selective attention, and impulse. Significant differences were found in CPT scores between COVID-19 patients and the control, with no significance between TMT, DST, or SCT.

ED: Emergency department, CI: Confidence interval, ICU: Intensive care unit, IQR: Interquartile range , MoCA: Montreal cognitive assessment, RHDCU: Respiratory high dependency care units.

Table 1: Characteristics of included studies.

3. Results

The PRISMA flowchart is shown in Figure 1. During the first round of screening, a total of 1,874 results were yielded. After duplicates were removed, 1,633 results were assessed for abstracts and titles. During the second round, 1,250 results were excluded as they met the exclusion criteria. In the final round, 92 records were assessed using full-texts, and 9 studies were included in the qualitative analysis. We presented data for a total of 1,936 patients from all included studies. The characteristics of all included studies are listed in Table 1.

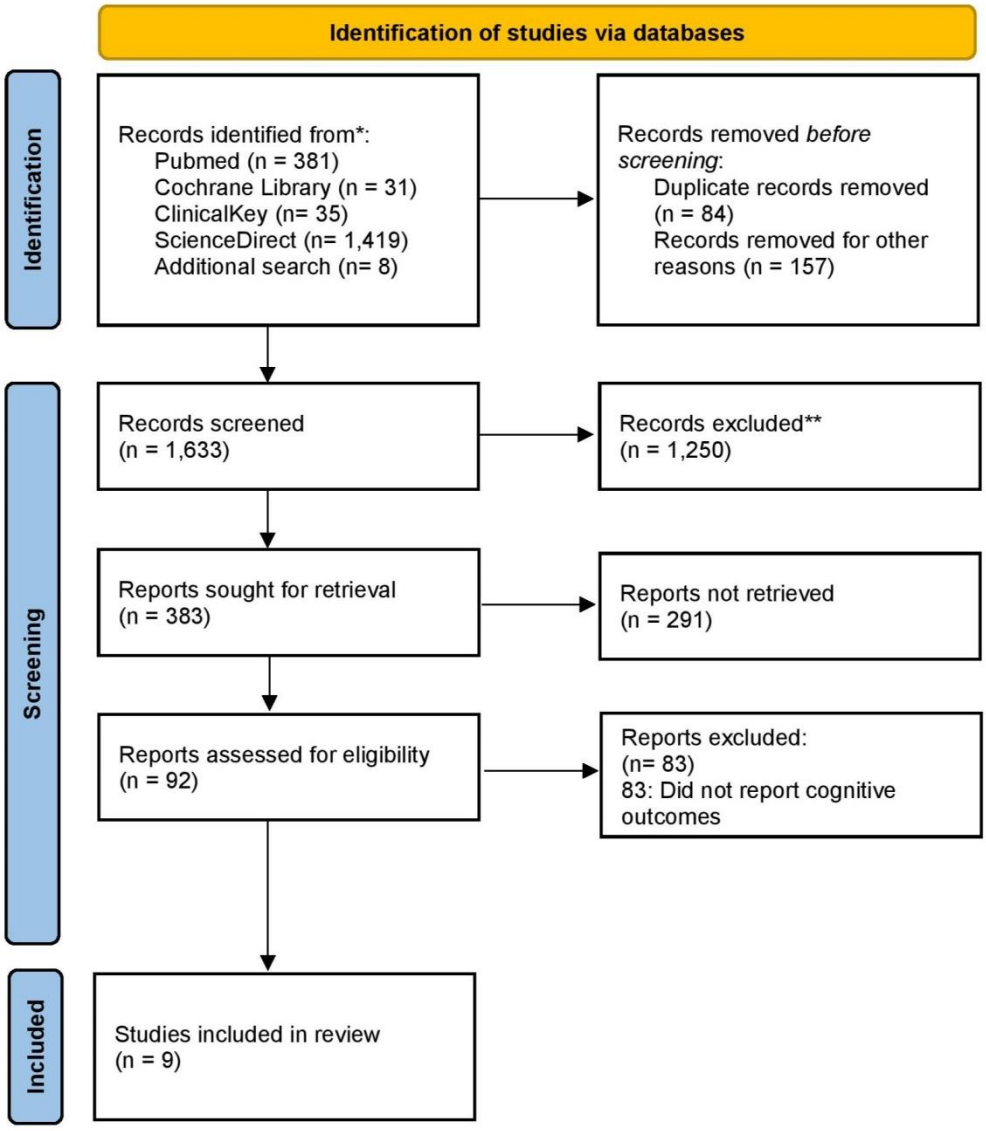

Figure 1: PRISMA flowchart.

All included studies were observational cohort studies or case series. The common tools used to assess cognitive impairment included primarily the Montreal Cognitive Assessment (MoCA) score, with others including iPad-based online neuropsychological tests, OASIS (Outcome and Assessment Information Set) version D-1 datasets, and Mini-Mental State Evaluation (MMSE). The incidence of cognitive impairment was determined for 1,875 out of 1,936 participants. Notably, 615 (32.8%) recovered COVID-19 patients presented with cognitive impairment. The severity of COVID-19 infection was variable among all included studies ranging from mild to moderate ARDS, requiring ICU treatment and mechanical ventilation. The standard duration of follow up ranged from 1 week to 6 months post-recovery (Table 1).

4. Discussion

We are still focusing on the acute life-threatening consequences of COVID-19 with the ongoing third wave of the pandemic. However, there has been a shift in attention to sub-acute and long-term impacts of COVID-19 among recovered individuals. The underlying pathogenesis of SARS-CoV-2 is associated with abrupt immune-inflammatory processes [11]. The penetration of the SARS-CoV-2 virus to the brain through the BBB may be potentially associated with longer-term consequences. As the recovered COVID-19 patients start manifesting potential complications, the healthcare system may witness patients with cognitive decline. As observed across studies, patients who have been discharged after recovery from COVID-19 have not been able to return to baseline cognitive function in the sub-acute phases [12]. The implicated cytokine storm syndrome in COVID-19 infection is suspected of causing small punctate strokes that may not manifest with overt neurological deficits [13]. However, these patients may complain of compromised memory, attention, or processing speed [13]. It is, therefore, advisable to follow these patients 6-8 months after discharge to observe the longevity of cognitive impairment. If is significant impairment in certain cognitive domains, it is necessary to consider neurocognitive rehabilitation to aid their return to baseline level [14]. Neurocognitive rehabilitation may prevent these patients from witnessing worse age-related cognitive decline later.

Importantly, evidence has consistently demonstrated the relevance of vascular risk among COVID-19 infections. Patients who have a higher risk of vascular complications such as diabetics, hypertensives, and obese patients, are more likely to manifest direr outcomes [15]. Given the limitations on the cognitive function data in the longer term after COVID-19 infection, there is increased emphasis on documenting these potential causal factors. So far, SARS-CoV-2 invasion has been recognized in the peripheral olfactory neurons, resulting in virally-induced acute anosmia [16]. The further transmission of the virus to the cortical regions is through the entorhinal cortex and hippocampus via the trans-synaptic route [17]. The potential link of these cortical regions impacting memory and spatial navigation cannot be undermined. In combination with other complications such as vascular and inflammatory pathologies, the risk of long-term cognitive decline among recovered COVID-19 patients is present. As the COVID-19 infection affects elderly patients severely, it poses an additional challenge of the acceleration of the onset of neurodegenerative dementia [18]. These neural pathways have also been overlapped with Parkinson's and Alzheimer's disease due to the potential involvement of the medial temporal lobe [19]. If such an overlap exists, it may serve as an anatomical basis for the acceleration of beta-amyloid and tau pathologies which are also associated with other viruses including

herpes virus and human immunodeficiency virus (HIV) [20].

As ACE-2 is widely distributed across multiple organs, the inflammatory process identified as the cytokine storm is associated with elevated cytokines and chemokines. The high levels of these cytokines are associated with increased vascular permeability, edema, and inflammation across different organs [21]. The involvement of the CNS system may be a combination of systemic inflammation, direct neurotropism, and cerebrovascular changes [22]. Direct invasion of the CNS has also been described in previous coronavirus outbreaks [23]. Consequently, it may be of great importance to assess the contribution of the SARS-CoV-2 virus to neurodegenerative or demyelination processes as a cause of cognitive decline [24]. It is important to note that while the biological mechanisms of COVID-19 infection have been discussed in the literature, the impact of psychological stress on the cognitive decline cannot be ignored. Patients who have recovered from COVID-19 infection in their sub-acute phases may have witnessed extreme levels of stress [25]. While chemokines and cytokines have been closely monitored during acute phases of infection, the release of stress hormones such as cortisol and steroids within the body may also result in sub-acute cognitive decline [26]. Highlighting the biopsychosocial model in COVID-19 infection is essential to assess patients at risk for cognitive decline in the long-term and is yet to be monitored [27].

4.1 Limitations

The present study is a systematic review that assessed factors contributing to the cognitive decline in recovered COVID-19 patients. However, the following limitations should be taken into account during the interpretation of our findings. Firstly, there was limited data on long-term cognitive decline among COVID-19 survivors, possibly due to lack of follow-up by the patient or the lack of neuro-symptomatology. Secondly, various observational studies included in the review utilized different tools/parameters to note cognitive decline, which possibly led to different definitions of cognitive decline in the post-infectious period. Thirdly, we could not determine whether any external contributors such as lack of access to healthcare or socioeconomic discrepancies affected cognitive functions, which should be explored further across all settings worldwide. Finally, we did not synthesize data on the influence of antiviral therapy on cognitive functions.

4.2 Recommendations

Potential effects of SARS-CoV-2 may theoretically manifest years later, following penetration at the neuronal level, disrupting the cellular mitochondrial function and protein folding [28]. Decades later among younger patients, the latent CNS SARS-CoV-2 virus may hypothetically lead to brain degeneration [28]. As discussed in this study, there is a need to identify the prevalence and underlying mechanisms of the long-term impact of COVID-19 infection on cognitive function. As such, *in vivo* and *in vitro* lab studies may be able to identify the neurotropism of the SARS-CoV-2 virion. Observational studies may be able to document epidemiological information including demographics, psychosocial, and biological risk factors. Extracting the direct and indirect impact of COVID-19 infection may be assessed through functional imaging of implicated brain regions. With more objective cognitive testing, the psychological and cognitive dysfunction may help eliminate psychological health challenges. With better insight into the acute stages of COVID-19 infection during the first wave of the pandemic, the second and further waves now require focus on the long-term cognitive impairment, which also incorporates the risk of dementia. Lessons learned during the first stage of the pandemic have improved acute clinical outcomes.

As the second stage unfolds, it is imperative that attention now should be on the implications of COVID-19 infection for long-term cognitive impairment and dementia risk. To aid prospective detection and intervention with pharmacological strategies, the engagement of public health bodies may be essential. A consistent approach such as documenting cognitive impairment among recovered COVID-19 patients in registries may allow for the identification of trends of potentially increased neurological diseases later in life.

5. Conclusion

Various factors have been implicated in the post-COVID-19 cognitive impairment. While these mechanisms seem compelling, further elucidation is necessary to understand the neurotropic impact of the virus. Ongoing scientific literature has hinted towards a longer-term cognitive impairment that cannot be ignored given the magnitude of the COVID-19 pandemic, now in its second year globally.

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