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Clearing the Fog: a Systematic Review on Cognitive Dysfunction in COVID-19

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[Objective] The systematic review aims to examine the association between COVID-19 and cognitive dysfunction, including the link between the severity of COVID-19 and the occurrence of cognitive impairment and the potential pathophysiological mechanisms related to brain fog among COVID-19 patients. [Methods] PubMed, Oxford University Press, ProQuest Health and Medical Complete, ScienceDirect, Ovid, HERDIN, Google Scholar, and Cochrane Library databases were accessed to retrieve literature using the PRISMA guidelines. [Results] After critical appraisal, 13 full journal articles were included in the study. The studies showed the most frequent cognitive impairment are attention, memory, and executive function in COVID-19 patients. Compared with healthy controls in three out of four studies, cognitive impairment was only evident in COVID-19 patients. Furthermore, two studies showed no correlation between brain fog and depression, and five studies showed a link between the severity of COVID-19 infection and cognitive impairment. Cases ranging from mild to severe illness presented manifestations of brain fog. However, a disparity in the evidence of the pathophysiology of COVID-19 and cognitive dysfunction exists, prompting the need to investigate further. Additionally, recent studies provide insufficient evidence for direct central nervous system invasion, and there are emerging studies that contrast the presumed pathogenesis of neurological complications from neuroinflammation. [Conclusion] There is an association between COVID-19

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and cognitive dysfunction. Manifestation of cognitive dysfunction is present regardless of illness severity. Moreover, there are existing pathophysiological mechanisms of the Coronavirus that lead to cognitive dysfunction in COVID-19 patients; however, additional studies are required to substantiate such mechanisms further. [PROSPERO registration number] CRD42022325669.

Keywords: brain fog, cognitive dysfunction, COVID-19, neuroinflammatory processes, pathophysiology, SARS-CoV-2 infection

INTRODUCTION

With millions of Coronavirus (COVID-19) cases worldwide, it is becoming apparent that more people are experiencing neurological symptoms associated with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. For this reason, researches into the putative link between SARS-CoV-2 and neurological manifestations continue to grow (Desai *et al.* 2021; Ghannam *et al.* 2020; Guadarrama-Ortiz *et al.* 2020). Cognitive dysfunction, also known as brain fog, is defined as the decrements in the cognitive status during continuous mental activity (García-Sánchez *et al.* 2022). Brain fog as a general term can present as confusion, difficulty finding the appropriate words, disorientation, memory problems, altered mental status, and trouble concentrating (Altuna *et al.* 2021; Asadi-Pooya *et al.* 2022; Hampshire *et al.* 2021). Such a decline can be measured using various neurocognitive assessments that can either reveal a cognitive impairment with a certain severity or discern, which specific cognitive domain is significantly affected. An example of a neurocognitive test is the Montreal Cognitive Assessment (MoCA), which includes different domains: orientation, attention, language, visuospatial function, memory, and executive function (Julayanont and Nasreddine 2017).

Gustatory and olfactory impairments are the most frequent sudden neurologic manifestations of COVID-19 associated with the peripheral nervous system, which occur in the early stages of SARS-CoV-2 infection (Cooper *et al.* 2020; Lechien *et al.* 2020; Salcan *et al.* 2021). These sensory impairments entail that SARS-CoV-2 is afflicting the nervous system (Iadecola *et al.* 2020). The discovery of the brain invasion of mice by the intranasal administration of the novel coronavirus (Kumari *et al.* 2021) and the existing knowledge about the previous detection of other coronaviruses in the human cerebrum (Cheng *et al.* 2020) led to a hypothesis that COVID-19 infection can be linked with neurocognitive complications. Preliminary studies suggest that cognitive deficits of hospitalized COVID-19 patients were dependent on two factors: the medical assistance they received (Ferrucci *et al.* 2021; Hampshire *et al.* 2021) and the degree of inflammation (Zhou *et al.* 2020) – that is, severe infections are assumed to contribute to severe cognitive impairments (Beaud *et al.* 2021; Tay *et al.* 2021; Wild *et al.* 2021). Moreover, several studies point out that more severe cases of the disease, hospitalization, and/or increased length of hospital stay were associated with post-COVID syndrome, such as cognitive deficits and fatigue (Ceban *et al.* 2022). However, there are still gaps in the studies regarding how COVID-19 infection increases cognitive impairment risk, severity, and progression. There is mounting evidence that brain fog is among the observed neurological manifestations of COVID-19 (Whittaker *et al.* 2020). However, the association of the symptom – including the possible mechanisms and the potential triggers – remains unclear. Consequently, if there is an association between the two, research about the extent of the impact on cognition and the affected cognitive domains of brain fog is limited (Zhou *et al.* 2020). Therefore, researchers have yet to determine whether cognitive systems are equally affected or some domains are more susceptible to SARS-CoV-2 infection. The primary purpose of this review is to assess cognitive dysfunction, more commonly known as "brain fog," as a symptom of COVID-19 to understand its etiology better. This encompasses the mechanisms that may cause the impairment and the prevalence of the emergent symptom. The current study also aims to determine the association between SARS-CoV-2 infection and cognitive dysfunction, elucidate the link between the severity of COVID-19 infection and brain fog, and describe the potential pathophysiological mechanisms related to cognitive dysfunction in COVID-positive individuals. This study gathered evidence that could provide clarity on the association between brain fog and COVID-19 infection.

METHODS

Study Setting

The study was carried out for six months (July–December 2021). Database searching was the initial step for identifying reports. Search strategies were employed, and primary identified records were based on the titles, database availability, and abstracts. Reviewers evaluated these based on predetermined inclusion criteria. Once reports have passed the inclusion criteria, a full-text report was obtained to assess its eligibility against the inclusion

criteria further. Irretrievable full-text reports were excluded. More specifically, a population, phenomenon of interest, and context or PICO approach was utilized to generate a sequence of terms (Lockwood *et al.* 2015; Munn *et al.* 2018).

Eligibility Criteria/ Criteria for Considering Studies for This Review

Types of studies. The studies included in this systematic review were observational studies – including case reports, case series, cross-sectional studies, case-control studies, and cohort studies. In addition, reports focusing on individuals with COVID-19 who suffer from brain fog were included. Only articles in the English language restriction were imposed.

Types of participants. Participants included in the study were patients who tested positive for COVID-19 through a reverse transcription polymerase chain reaction (RT-PCR), antigen test, or SARS-CoV-2-specific immunoglobulin G (IgG) in serum and experienced cognitive dysfunction. All COVID-19 positive patients were included regardless of sex, race, ethnicity, and age. In addition, healthy, non-COVID-19 patients were also included for comparison.

Types of phenomena of interest and context. This systematic review's main phenomena of interest included the manifestation of brain fog in COVID-19 patients and non-COVID-19 patients. Therefore, studies focusing on the link between COVID-19 severity and occurrence of brain fog and potential mechanisms that cause cognitive dysfunction as a symptom of COVID-19 were also included.

Search Methods for Identification of Studies

Information sources. The following databases were used to identify completed studies until December 2021: PubMed, Oxford University Press, ProQuest Health and Medical Complete, ScienceDirect, Ovid, HERDIN, Google Scholar, and Cochrane Library. Ongoing studies were recognized; however, these studies were not included in the systematic review. In addition, a date restriction was set for identifying studies: studies since the start of the COVID-19 pandemic – January 2020 up to December 2021 – were included in this systematic review.

Search strategy. The electronic literature search included the following key terms: COVID-19, SARS-CoV-2, neurocognitive impairment, brain fog, confusion, poor concentration, memory problems, brain fog pathophysiology, neurological mechanism, and cognitive dysfunction. Moreover, the Boolean search strategy ("AND," "NOT," "AND NOT," "OR") was employed to identify studies using the key terms. The search strategy for databases can be found in online Supplemental File A.

Selection process. Authors (NDB, MFDC, AMOD, TRFM, and OKSD) independently searched for studies that were included in the systematic review. The initial selection of studies consists of the examination of the titles, abstracts, and full-text, if available. Inclusion criteria implemented were observational studies on individuals with COVID-19 who experience cognitive dysfunction. The authors created the final list of included studies. Any disagreements that arose during the appraisal process were settled by discussing with another author.

Assessment of risk of bias in individual studies. Three authors (MFDC, TRFM, and OKSD) independently evaluated the risk of bias in each study. A fourth (NDB) and fifth (AMOD) author was assigned to resolve disagreements in assessments. To assess bias in included studies, they were segregated into observational studies such as case reports, case series, cross-sectional studies, case-control studies, and cohort studies. The risk of bias in the included studies was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (Vandenbroucke *et al.* 2007). The risk of bias was scored as "low," "moderate," or "high" risk. The overall quality of each study was given a rating based on the score from the STROBE statement. Furthermore, only studies with a low-risk rating were included in the study.

Data Analysis and Presentation

Formatted according to the extraction tool used to extract the data, a Microsoft Excel spreadsheet was used to tabulate results for representation of results. The characteristics of the included articles were described, which were previously discussed and agreed upon within the study team.

Evidence Synthesis

A narrative synthesis of overall evidence was undertaken by comparing and contrasting the data to express and synthesize the results of the included studies. Development of a preliminary synthesis, exploration of the relationships within and between studies, and the determination of the robustness of the synthesis were the three stages of the narrative synthesis undertaken by the research team (Popay *et al.* 2006). Data of the included studies were qualitatively described and presented. The authors frequently met to discuss the results and reach a consensus on the findings.

RESULTS

Description of the Studies

Literature search. Two hundred eighty-nine (289) studies were identified after a comprehensive search through databases (PubMed, ProQuest, Oxford University Press, ScienceDirect, Cochrane Library, Google Scholar, JSTOR, and Herdin). Duplicate records (n = 12) were removed based on their titles. After initial screening, 177 studies were excluded due to differences in study design (*e.g.* review paper, narrative review, hypothesis/theory article, and chart review) based on the title and abstract. In addition, 15 articles were not retrieved because the study is ongoing. A total of 85 full-text studies were assessed for eligibility. After critical appraisal, 13 studies were included in the final systematic review. An adapted PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart of the study selection is presented in Appendix Figure I.

Included studies. Characteristics of the included studies are tabulated in Table 1. The age of the study participants in the included studies was greater than 16 yr old. All study participants were diagnosed with COVID-19 through various diagnostic tests such as SARS-CoV-2 RT-PCR of a nasopharyngeal swab, SARS-CoV-2 antibody testing (*e.g.* SARS-CoV-2-specific IgG in serum), rapid antigen test, and PCR test for SARS-CoV-2 in upper and/or lower airway samples. Participants in four included studies were assessed during COVID-19 infection, seven during post-COVID-19 infection, four had follow-ups, and one examined patients *post mortem*. The duration of the follow-ups in the included studies ranges from 2–4 mo. Out of the 13 included observational studies, one is a case series, one is a case report, six were cross-sectional studies, and five were cohort studies.

Excluded studies. A total of 276 studies were excluded from the list of included studies due to the following reasons: different study design (n = 179), irrelevance to the systematic review (n = 59), unavailability of the full-text article (n = 16), duplications (n = 13), and focused on the psychological aspect (n = 9).

Risk of Bias in Included Studies

Observational studies were evaluated based on 10 domains: Introduction – [1] Objectives; Methods – [2] Participants; Results – [3] Participants, [4] Descriptive Data, [5] Outcome Data, and [6] Main Results; Discussion – [7] Key Results, [8] Limitations, [9] Interpretation, and [10] Generalizability. Of the 13 included observational studies, all were assessed as low risk of bias.

Qualitative Results

Eleven (11) studies focused on the association between COVID-19 and brain fog, five studies identified the link between the severity of COVID-19 and the occurrence of cognitive dysfunction, and seven studies described the possible pathophysiological mechanisms related to brain fog in COVID-19 patients.

Association between SARS-CoV-2 infection and neurocognitive dysfunction. The prospective cohort study conducted two MoCA tests with mean scores of 19.1 and 23.4 on the first and second exams, respectively (Blazhenets *et al.* 2021). The average scores showed significant improvement on the second exam. However, the MoCA performance of the second exam was still within the range of mild cognitive impairment (MCI). In a cross-sectional study, the average MoCA score of the COVID-19 patients was significantly lower than the healthy controls or HCs (Ortelli *et al.* 2021). In addition, the severity of cognitive impairment was mentioned in a study (Hosp *et al.* 2021), wherein 54% (14/26) of the participants were mild to moderately impaired, whereas 15% (4/26) were severely impaired (see Appendix Table I for details).

Seven of the included studies reported domain-specific cognitive deficits. The prospective cohort assessed all six cognitive domains that showed an insignificant decline in orientation and attention domains with 6.00 and 5.13 scores, respectively (Blazhenets *et al.* 2021). However, the MoCA domain scores on language (3.88), visuospatial function (3.13), memory (2.25), and executive function (2.50) revealed significant cognitive deficits.

Another cohort study also utilized the MoCA test (Hosp *et al.* 2021). The MoCA domain scores in this study revealed an impairment in executive function, visuospatial function, memory, and attention. The two other domains, language, and orientation, were not impaired. An extended neuropsychological test battery confirmed the deficit in executive function and memory but not in attention (Hosp *et al.* 2021).

In a cross-sectional study, two cognitive domains such as attention and executive function were assessed using three subtests of MoCA and frontal assessment battery (FAB), respectively (Ortelli *et al.* 2021). The reaction time (RT) of the COVID-19 patients in each subtest of MoCA was compared with that of the HCs. In two of the subtests – namely, stroop interference task (SIT) and navon task (NT) – the RTs were significantly longer in the patients than in the HCs. In contrast, the RTs of the patients and the HCs in the vigilance task (VT) did not have a significant difference. Furthermore, significantly lower FAB scores were observed in COVID-19 patients than in the HCs, indicating an executive function deficit (Ortelli *et al.* 2021).

Table 1. Characteristics of included studies (n = 13).

Author (year)	Sample size	Population mean age/ median age* (range)	Study design	Outcome/s
Beach *et al.* (2020)	4	75.25 yr (68–87)	Case series	Neuropsychological and neurophysiological features of fatigue were studied in post-COVID-19 patients. In addition, apathy, deficits in executive functions, and reduction in global cognition were found.
Blazhenets *et al.* (2021)	31	66.00 yr (39–89)	Cohort	MOCA *M* = 19.13; 23.38 Impaired language, visuospatial function, memory, and executive function.
M.A. Garcia *et al.* (2021)	18	56 yr* (20–79 yr; 14 healthy, 68 non-COVID-19 neurological disease controls)	Cross-sectional	Neuroinflammatory processes in COVID-19 CSF may be the result of a homeostatic neurological response rather than an adaptive, immune-mediated cytokine storm or inflammation caused by neurovirulence. Mild, moderate, severe, and critical cases exhibited cognitive deficits, regardless of severity.
M.H.C. Garcia *et al.* (2021)	199	43 yr (> 18 yr)	Cross-sectional	Mild to moderate cases of COVID-19 severity exhibited cognitive deficits.
Graham *et al.* (2021)	100	43.2 yr	Cohort	Patients and controls had mild to moderate cognitive dysfunction but showed no significant difference.
Hosp *et al.* (2021)	29	65.2 yr (> 18)	Cohort	MOCA *M* = 21.77 Impaired attention, visuospatial function, memory, and executive function.
Ortelli *et al.* (2021)	12	67 yr (48–80)	Cross-sectional	MOCA *M* = 17.80 Impaired attention *via* SIT and NT but unimpaired attention on VT.
Puchner *et al.* (2021)	23	57 yr (≥ 18)	Cohort	In 29% of tested patients, cognitive deficits in concentration, memory, and/or executive functions were found.
Vannorsdall *et al.* (2022)	82	54.5 yr (> 16)	Cohort	Impaired scores for oral trail making test, verbal fluency, and Rey auditory verbal learning test of critically ill patients exhibited cognitive deficits.
Virhammar *et al.* (2021)	19	64 yr (34–76)	Cohort	Majority of patients presented with increased CSF levels of neuronal injury markers. Results of the study show that there is no specific pattern in the manifestation of brain fog across illness severity.
Woo *et al.* (2020)	18	42.11 yr (17–71)	Cross-sectional	TICS-M: COVID-19 patients scored significantly lower than HC, especially in memory, attention, and language. Patients with mild to moderate case severity indicated manifestation of cognitive dysfunction.
Yesilkaya *et al.* (2021)	1	20 yr	Case report	Cognitive deficits in SARS-CoV-2 infection can result from glutamatergic dysfunction with decreased glutamate and NAA levels in the DLPFC confirmed by MRS.
Zhou *et al.* (2020)	29	47 yr (30–64)	Cross-sectional	CPT: COVID-19 patients performed significantly worse than HC No significance for TMT, SCT, and DST between the two groups.

Another study also utilized subtests of MoCA such as the trail making test (TMT), sign coding test (SCT), continuous performance test (CPT), and digit span test (DST) that revealed significant differences in the attention domain and no significant differences in executive function, visuospatial function, and memory between COVID-19 patients and HCs (Zhou *et al.* 2020). Meanwhile, in a cohort study, a neuropsychological assessment battery revealed specific cognitive deficits in non-ICU and post-ICU COVID-19 patients (Vannorsdall *et al.* 2022). Both groups showed significant cognitive impairment in three cognitive domains – namely, executive function, language, and memory but not in attention.

A different cognitive function assessment tool was used in another cohort study (Graham *et al.* 2021). In this study, the National Institutes of Health (NIH) Toolbox v2.1 instrument revealed a mild to moderate

cognitive impairment in both COVID-19 patients and HCs; however, it did not show any significant difference between the Toolbox T-scores of the two groups.

A modified telephone interview for cognitive status (TICS-M) is another screening tool for MCI used in another study (Woo *et al.* 2020). Cognitive deficits in orientation, memory, attention, and language in post-COVID-19 patients and HCs were reported. It was also revealed that the scores of the patients in three domains – specifically, memory, attention, and language – were significantly lower than the HCs (Woo *et al.* 2020).

Moreover, a cross-sectional study involving 199 patients from Lima, Peru, described the relationship between mild to moderate COVID-19 infection and neurological symptoms, wherein seven out of 199 patients (3.5%) presented impaired consciousness (M.H.C. Garcia *et al.* 2021). Meanwhile, in another study, 23 patients who had severe to critical COVID-19 were analyzed (Puchner *et al.* 2021). A neuropsychological evaluation was conducted on 14 out of the 23 patients, and four patients (29%) were found to have cognitive dysfunction in memory, executive function, and attention (Puchner *et al.* 2021). In addition, a case study reported a patient who tested positive for SARS-CoV-2 and did not have any neurologic or psychiatric evaluation history. The patient was evaluated using a neuropsychological battery test, including the global deterioration scale (GDS), California verbal learning test (CVLT), FAB, and TMT. The neurological battery tests suggested cognitive impairment (FAB score of 16; GDS stage 3) in executive function, concentration, and memory. At the patient's follow-up, no cognitive impairment was identified (FAB score of 13; GDS stage 1) (Yesilkaya *et al.* 2021).

Fourteen (14) COVID-19 patients underwent hospital anxiety and depression scale (HADS-D) that revealed no significant increase in their anxiety and depression symptoms despite detecting cognitive deficits in memory and executive functions (Puchner *et al.* 2021). A similar study that utilized the patient health questionnaire 9 (PHQ-9) depression scale revealed no significant correlation between depression and cognitive dysfunction (Woo *et al.* 2020). Meanwhile, one study used the Beck depression inventory (BDI), wherein scores of COVID-19 patients and HCs had a significant difference (Ortelli *et al.* 2021).

Elucidating the link between disease severity of COVID-19 infection and the manifestation of cognitive dysfunction. The NIH established a classification for the clinical spectrum of SARS-CoV-2 infection. Patients with COVID-19 may be grouped according to illness severity: asymptomatic or presymptomatic, mild, moderate, severe, and critical illness (Health 2020). Increasing evidence suggests that the severity of SARS-CoV-2 infection is linked with the occurrence of cognitive dysfunction in COVID-19 patients. After evaluation of retrieved and appraised journals, five studies correlate with this hypothesis (see Appendix Table II). In the cross-sectional study examining cerebrospinal fluid (CSF) of 18 COVID-19 subjects with neurological complications, 44% (8) were classified as critical, 28% (5) as severe, 22% (4) as moderate, and one patient as mild illness (M.A. Garcia *et al.* 2021). This review shows that across the case of 18 COVID-19 patients, all exhibited cognitive dysfunction regardless of case severity. Furthermore, a cohort study conducted among patients of the John Hopkins Post-Acute COVID-19 Team Pulmonary Clinic reveals that out of 82 patients classified for critical illness, 67% (54) demonstrated abnormally low cognitive scores ($\geq$ 1 deviation from published age-adjustive normative means) and is correlated to mild/moderate or severe range of cognitive impairment (Vannorsdall *et al.* 2022). In addition, the prospective-single center study involved 19 patients with a distribution of 11% (2) having a mild illness, 21% (4) having a moderate illness, another 21% (4) having a severe illness, and 47% (9) having critical illness severity (2021) were reported (Virhammar *et al.* 2021). Reports also showed that two out of nine critically ill patients manifested cognitive dysfunction, two out of four severely ill patients showed altered mental status, and two out of four moderately ill patients exhibited confusion and altered mental status (Virhammar *et al.* 2021). Findings show that there is no specific pattern for COVID-19-related cognitive dysfunction. Lastly, a cross-sectional study conducted at the University Medical Center Hamburg-Eppendorf involved 18 patients in either mild or moderate severity (Woo *et al.* 2020). Cognitive deficiencies were present among the involved patients: nine (50%) reported having attention deficiency, eight (44.4%) suffered from concentration deficits, eight (44.4%) experienced short-term memory deficiency, and five (27.8%) had trouble finding words. Results from 18 patients impacted with COVID-19 were compared to 10 healthy non-COVID patients. Findings also show that COVID-19 neurological sequelae are independent of hospitalization and illness severity (Woo *et al.* 2020).

Possible pathophysiological mechanisms leading to cognitive dysfunction. Seven studies analyzed cognitive dysfunction in COVID-19 patients on a molecular level and their potential pathogenesis. One study examined serum pro-inflammatory markers [interleukin-2 (IL-2), IL-4, IL-6, IL-10, tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), and C-reactive protein (CRP)] (Zhou *et al.* 2020). However, their findings revealed no significant correlation between the inflammatory markers and the cognitive function assessment results from the TMT, SCT, and DST. In contrast, all the 29 post-COVID-19 patients showed a trend of significant

difference for lower RT in the first and second parts of CPT, as well as a lower correct number in the second part of CPT than the 29 HCs. The serum CRP and RT in the CPT are positively correlated. Moreover, 11 post-COVID-19 patients demonstrated hyper-inflammation, evidenced by elevated CRP and interleukin-6 serum levels (Ortelli *et al.* 2021). The remarkable pro-inflammatory state induced by SARS-CoV-2 in all four cases and the cessation of carbidopa-levodopa in one patient case described in another study has been postulated to convey a dysregulated immune response and a potential precipitant of the abrupt mental confusion and emotional disarray (Beach *et al.* 2020).

One study analyzed the CSF of 19 patients with mild to critical COVID-19. Only one (5%) was positive for SARS-CoV-2. The analysis includes biomarkers of central nervous system injury [neurofilament light chain (NfL) protein, glial fibrillary acidic protein (GFAp), and total tau (T-tau)] and found increased CSF levels of NfL (63%), total tau (37%), and GFAp (16%). The amount of CSF NfL was higher in patients with central neurological symptoms, and the elevated level was associated with the severity of the disease, time spent in critical care, and level of consciousness (Virhammar *et al.* 2021).

Another study evaluated fluorodeoxyglucose positron emission tomography (FDG PET) images of eight COVID-19 patients (post-infection) and the MoCA scores to assess neuronal damage or synaptic dysfunction distribution (Blazhenets *et al.* 2021). They discovered that after the patients are no longer infectious and in the chronic stage (about 6 mo after symptom onset), their impaired neocortical glucose metabolism can return to normal levels – evidence of reversibility – which is critical for the pathophysiology of cognitive deficit. In the FDG PET scans of another study, 10 of the 15 patients had abnormal findings (Hosp *et al.* 2021). According to the observer, 10 of the subjects had cortical hypometabolism, with two cases having striatal hypermetabolism. Likewise, the second observer noted cerebral hypometabolism in six out of nine subjects. Striatal hypermetabolism is present in the other three cases. In addition, their findings demonstrated a highly significant linear association between MoCA and PET, with more robust pattern expression being related to poorer cognitive function. The same study found oligoclonal bands present with identical electrophoretic patterns in the serum in one patient but unremarkable protein and IgG levels in four out of 29 who agreed to undergo CSF analysis. Moreover, all CSF samples tested negative for SARS-CoV-2 (Hosp *et al.* 2021).

In a case study, the CSF analysis through lumbar puncture detected no presence of SARS-CoV-2. The N-acetylaspartate (NAA), glutamate, and glutamate/glutamine ratio were measured using MR-spectroscopy and bilateral DLPFC. A week and 3 mo following the initial diagnosis of SARS-CoV-2 infection, substantial increases in glutamate, glutamine, and NAA levels were discovered during follow-up, suggesting that the glutamatergic pathway might be implicated in the pathogenesis of cognitive impairment (Yesilkaya *et al.* 2021).

DISCUSSION

All studies that utilized the MoCA test showed MCI following COVID-19 infection. An included study reported a more severe global cognitive impairment among COVID-19 patients than HCs (Ortelli *et al.* 2021). Among the cognitive domains, attention, executive function, and memory are most likely to be impaired. These were also the domains that frequently showed significant differences between COVID-19 and non-COVID-19 patients in a recent study (Crivelli *et al.* 2022). This observation is congruent with another study reporting that the exact cognitive domains, except for memory, seem prone to impairments (Daroische *et al.* 2021). On the other hand, results on language, orientation, and visuospatial function varied in the included studies. This inconsistency may be due to the apparent heterogeneity in the tests used, time of evaluation, eligibility criteria, and the presentation of results.

Majority of the included studies utilized the MoCA test (n = 5), followed by NIH Toolbox (n = 1) and TICS-M (n = 1). Different tests with varying total scores, sensitivity, and specificity in comparing study populations can be attributed to the contradictory results. For instance, one study used three tests (SIT, NT, and VT) – all assessed the attention domain and discovered that only SIT and NT showed significantly different RTs between COVID-19 and HCs (Ortelli *et al.* 2021). However, the difference in VT was not statistically different. Furthermore, some studies either did not specify or utilized different cut-off scores. Two studies used the same test and total score. Still, different cut-off values in assessing visuospatial function, thereby affecting the consistency of the interpretation (Blazhenets *et al.* 2021; Hosp *et al.* 2021). This emphasizes the need for a standardized and accurate test specific to each cognitive domain.

A prospective cohort study with 31 participants showed a better MoCA performance of COVID-19 patients at the chronic stage than at the subacute stage (Blazhenets *et al.* 2021). The authors provided evidence that supports the association between COVID-19 infection and cognitive dysfunction, and these deficits can still be measured 6 mo after symptom onset of COVID-19. However, only eight patients underwent a second MoCA examination at the chronic stage of the disease. Similarly, another study

reported that only one-tenth of the patients had cognitive dysfunction at the 6-mo follow-up (Nalbandian *et al.* 2021). With that, the different assessment times of the included studies could be the result of the inconsistency. More research using the same methodology is necessary to evaluate the time frame of cognitive dysfunction after COVID-19 infection.

Several studies showed the comparison of results between COVID-19 and non-COVID-19 patients (HCs). Three of the four studies used HC and reported a cognitive impairment only in COVID-19 patients (Ortelli *et al.* 2021; Woo *et al.* 2020; Zhou *et al.* 2020). A similar review reported that its included studies had significantly more cases of cognitive impairment in COVID-19 patients than in HC (Daroische *et al.* 2021).

Of all included studies, only three studies measured depression, two of which stated no correlation between depression and cognitive dysfunction. However, one study reported a significant difference in depression between COVID-19 patients and HC (Ortelli *et al.* 2021). There is a higher prevalence of depression among post-COVID-19 patients compared to the frequency in the general population before the pandemic. Common factors of depression include sex, age, and psychiatric or chronic illness history (Renaud-Charest *et al.* 2021; Xiong *et al.* 2020). Contrary to the results, a systematic review found that symptoms of depression significantly affected cognitive function, wherein patients would more likely to perform poorer on neurological tests (Renaud-Charest *et al.* 2021). Additionally, previous studies hypothesized that cognitive dysfunction and depression were bi-directional (Miskowiak *et al.* 2021; Vinkers *et al.* 2020). Severe cognitive dysfunctions may produce more depression because of increased difficulty in daily life functions. In addition, more symptoms of depression can affect the performance in cognitive tests (Miskowiak *et al.* 2021). Therefore, there should be more significant consideration of mood and cognitive symptoms following COVID-19 infection.

Emerging reports indicate that a large population suffers from cognitive dysfunction due to COVID-19 infection. Results from the selected studies (Appendix Table II) showed that cognitive dysfunction is present among patients characterized by mild, moderate, severe, and critical illnesses. According to a report, cognitive impairments were most prevalent in hospitalized patients (Hampshire *et al.* 2021). However, non-hospitalized patients also exhibited cognitive dysfunction relating to COVID-19 infection. A recent study stated evidence of cognitive deficits in patients classified with mild to moderate illness (del Brutto *et al.* 2021). Cases exhibiting severe illness also provide proof of cognitive deficit (Hampshire *et al.* 2021; Negrini *et al.* 2021). Additionally, severe infections are assumed to contribute to severe cognitive impairments (Beaud *et al.* 2021; Tay *et al.* 2021; Wild *et al.* 2021). Moreover, another study reported that critically ill patients presented long-lasting complaints of inability to think and concentrate (brain fog) (Asadi-Pooya *et al.* 2022). In contrast with the current study results, other studies revealed that cognitive deficits were also observed in asymptomatic/presymptomatic cases (Amalakanti *et al.* 2021; Huang *et al.* 2021; Tenforde *et al.* 2020). Therefore, regardless of the intensity of clinical manifestations of COVID-19, patients may still develop brain fog; however, take into account that the link between the severity of COVID-19 and severity of brain fog was not elucidated. The correlation between the severity of COVID-19 disease and severity of cognitive dysfunction remains inconclusive due to a lack of studies, variation of patient characteristics, and breadth and depth of cognitive assessment. The establishment of standardized tests for obtaining cognitive scores should be developed to represent a normative data set to analyze the correlation of severity scale.

The presence of the virus in the systemic circulation, its spread and damage to the endothelium of the vascular bed, and direct damage to the central nervous system are potential mechanisms causing neurological complications in COVID-19 (Martynov *et al*. 2021). Cognitive impairment can be caused by endothelial injury and dysfunction (Hughes *et al.* 2018). Studies have reported elevated endothelial injury markers in COVID-19 patients, which might be caused by endothelial cells being directly infected by SARS-CoV-2, cytokine storm, or immune-mediated endotheliocyte damage (Méndez *et al.* 2022; Savarraj *et al.* 2021).

Out of 13 studies, only three tested for the presence of SARS-CoV-2 in the CSF. No evidence of viral RNA in the CSF was reported (M.A. Garcia *et al.* 2021). Likewise, all tested negative among four out of 29 patients who underwent lumbar puncture (Hosp *et al.* 2021). On the other hand, one out of 19 patients tested positive for SARS-CoV-2 in CSF findings (Virhammar *et al.* 2021). The lack of studies reporting the presence of viral RNA in the CSF leads to inadequate evidence of SARS-CoV-2 neuroinvasion, suggesting that it is not the primary pathogenic mechanism in most cases. The NfL protein is an indicator of neuroaxonal damage. Recent research of 544 Mexican Americans found that NfL had a detrimental influence on processing speed, attention, executive skills, and delayed recognition memory in normal and mild cognitive impairment groups, suggesting its significance as a marker of cognitive impairment and early cognitive impairment changes (Hall *et al.* 2020). In a previous study that used a community-based population of non-cognitive impairment participants, CSF NfL is a better predictor

of cognitive deterioration than other CSF markers of neurodegeneration (Mielke *et al.* 2021). Another study elaborates on the association of biomarkers such as t-tau with cognitive decline (Chen *et al.* 2021). The findings showed that higher levels of plasma biomarkers (*i.e.* Aβ42, t-tau, and Aβ42 × t-tau) were found in participants who showed a cognitive decline (the declined group) compared to those who did not (the stable group) and were associated with lower episodic verbal memory performance at baseline and a more significant annual decrease in MMSE score (Chen *et al.* 2021).

Instead of the classic post-viral syndrome, cognitive impairment may be a distinct post-COVID-19 manifestation caused by altered neuronal signaling in the brain due to the immune response triggered by the virus. However, there is no evidence of a link between inflammatory responses during acute infection (Woo *et al.* 2020). The presence of oligoclonal bands in one patient might be similar to the association of these bands with cognitive decline in other inflammatory and neurodegenerative diseases of the central nervous system like multiple sclerosis (Giedraitiene *et al.* 2021).

This study is limited by the number of studies available with the appropriate parameters. Most studies available were systematic and meta-analysis studies and observational studies that were inconclusive or unrelated to the topic of interest. Moreover, the majority of the excluded studies focused on neurological manifestations in general and did not necessarily mention cognitive dysfunction. Additionally, there is a possibility of a false negative result among the tests conducted by the studies that included HCs. Another limitation is the possibility that some relevant studies were not taken into account because they have been published in languages other than English (*e.g.* Chinese). We also did not have access to some other databases that may store some articles on COVID-19 and cognitive dysfunctions. And lastly, there could be some other studies on this theme in the literature that skipped our attention and analyses. However, a comprehensive search strategy that covers a broad range of evidence was implemented.

This systematic review gathered evidence that could provide clarity on the association between brain fog and COVID-19 infection. The information acquired in this study may help re-evaluate the impact of the virus. Furthermore, the use of the data gleaned from this analysis may assist in earlier treatment, allowing physicians and clinicians to manage the neurological manifestation effectively. Additionally, this will aid in the development of various therapeutic strategies to support COVID-19 patients in recovering from impaired cognitive capacity. Finally, the analysis of such data could provide an insight into the challenges that this virus could cause people in their prime years, particularly those in the workforce.

CONCLUSION

Attention, memory, and executive function were the most frequently affected cognitive domains in COVID-19 patients. There was also a significant difference in the neuropsychological assessment scores between COVID-19 patients and HC. Interestingly, results from the included studies showed no correlation between cognitive dysfunction and depression. Increasing evidence suggests that cognitive dysfunction due to COVID-19 is manifested across disease severity ranging from asymptomatic to critical illness. The interplay of physical and cognitive impairments may lead to functional problems inhibiting health-related standards of life. The knowledge gained from this study may be used to improve the implementation of comprehensive treatment modalities and rehabilitation throughout the COVID-19 care continuum to remove such barriers and restore the meaningful lives of patients brought about by brain fog. The findings from this systematic review indicate multiple potential pathophysiological mechanisms related to cognitive dysfunction in COVID-positive individuals. Neuroinflammation is one of the mechanisms that have led to cognitive dysfunction based on the studies obtained. Neuroinflammation in the NFL protein and inflammatory levels indicated by CRP provide further insight into the pathophysiology that could lead to cognitive dysfunction. The evidence appears to be contrasting; however, from what was gathered, the CNS invasion is not the primary pathological mechanism due to the lack of studies that portray the presence of SARS-COV-2 concerning said mechanism. It is also suggested that neuroinflammation is not substantial enough even with the rising levels of pro-inflammatory markers due to the lack of value in numbers. Therefore, more studies are needed to substantiate these pathophysiological mechanisms further.

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AUTHORS' CONTRIBUTIONS

ADL conceptualized the study following discussions with JCD. MFDC, TRFM, OKSD, NDB, and AMOD designed the protocol, with feedback from ADL, ESB, ZGR, and JCD. MFDC, TRFM, OKSD, NDB, and AMOD ran the database search and oversaw the search, screening, full-text review, and data extraction process. ZGR, ESB, and ADL drafted the manuscript. All authors reviewed the

draft, provided critical review, and read and approved the final manuscript. The corresponding author, as guarantor, accepts full responsibility for the finished article has access to any data, and controlled the decision to publish. The corresponding author attests that all listed authors meet the authorship criteria, and that no others meeting the criteria have been omitted.

AUTHORS' STATEMENTS

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Data availability: data are available on reasonable request; extracted data are available on request to the corresponding author.

Registration: this study is registered in PROSPERO (International Prospective Register for Systematic Reviews) as CRD42022325669.

Note: if there is a need to amend the study protocol or results, the date of each amendment and the reason for the change will be described.

Ethics: patient consent for publication is not applicable; ethical approval was not required for this systematic review, since all data came from information freely available in the public domain (*i.e.* published articles or conference abstracts); this study does not involve human participants.

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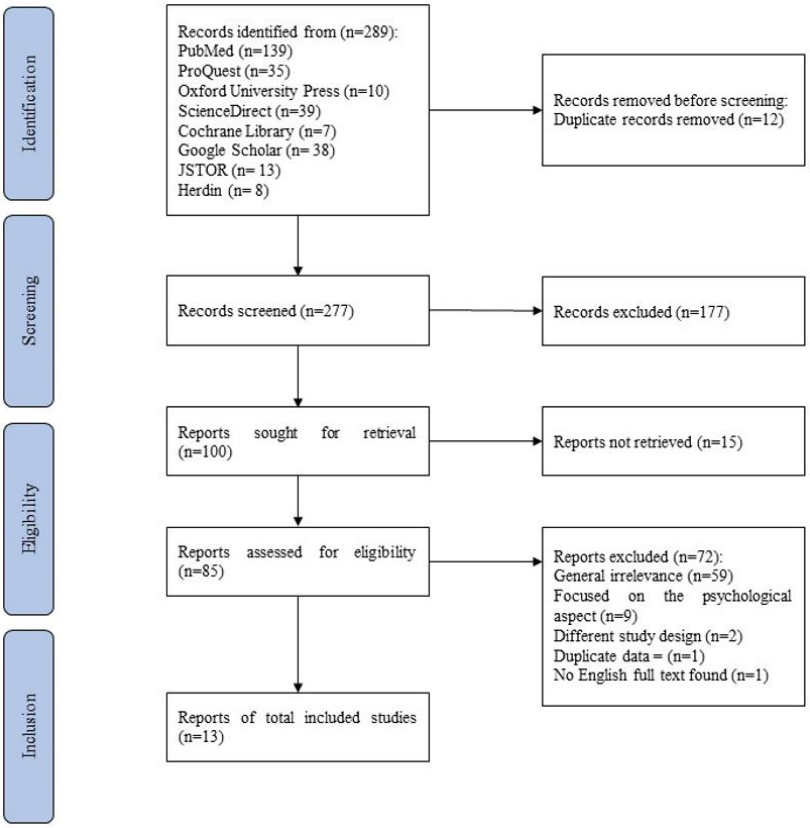
APPENDICES

Appendix Table I. Summary of domain-specific and non-domain-specific test results of included studies (n = 7).

Author	Sample size	MoCA global score (> 26)		Cognitive domains*					
		1st exam	2nd exam	O	A	L	VSF	M	EF
Blazhenets *et al.* (2021)	8	19.13	23.38	x	x	✓	✓	✓	✓
Graham *et al.* (2021)	50	n/a		n/a	✓	n/a	n/a	✓	✓
Hosp *et al.* (2021)	26	21.77		x	✓	x	✓	✓	✓
Ortelli *et al.* (2020)	12	17.80		n/a	✓	n/a	n/a	n/a	✓
Vannorsdall *et al.* (2021)	82	n/a		n/a	x	✓	n/a	✓	✓
Woo *et al.* (2020)	18	n/a		✓	✓	✓	n/a	✓	n/a
Zhou *et al.* (2020)	29	n/a		n/a	✓	n/a	x	x	x

Appendix Table II. Summary of occurrence of cognitive dysfunction across illness severity from included studies (n = 5).

Author (year)	Clinical spectrum of SARS-CoV-2 infection					Cognitive dysfunction
	Asymptomatic or presymptomatic infection	Mild illness	Moderate illness	Severe illness	Critical illness	
Garcia MA *et al.* (2021)	X	✓	✓	✓	✓	✓
Garcia MHC *et al.* (2021)	X	✓	✓	X	X	✓
Vannorsdall *et al.* (2022)	X	X	X	X	✓	✓
Virhammar *et al.* (2021)	X	✓	✓	✓	✓	✓
Woo *et al.* (2020)	X	✓	✓	✓	✓	✓



Appendix Figure I. PRISMA flow diagram.

SUPPLEMENTAL FILE A: SEARCH STRATEGY

PubMed

"COVID-19 and neurocognitive dysfunction" OR "brain fog"

Oxford University Press

"COVID-19 and neurocognitive impairment" OR "COVID-19 and brain fog" OR "COVID-19 and cognitive dysfunction" OR "COVID-19 and memory problems"

ProQuest Health and Medical Complete

"COVID-19 and brain fog" "COVID-19 and neurological mechanism"

ScienceDirect

"COVID-19 and neurocognitive impairment" OR "brain fog" OR "COVID-19 and confusion" OR "COVID-19 and memory problems" OR "COVID-19 and brain fog" OR "COVID-19 and pathophysiology" OR "COVID-19 and neurological mechanism" OR "COVID-19 and cognitive dysfunction"

Jstor

"COVID-19 and brain [public health]" OR "COVID and neurological impairment"

HERDIN

"COVID and brain fog"

Google Scholar

"Brain fog Covid-19" OR "brain fog covid-19" "Cognitive dysfunction Covid-19" OR "cognitive dysfunction covid-19" OR "Cognitive deficit Covid-19" OR "cognitive deficit covid-19" OR "neurocognitive dysfunction and Covid-19" OR "cognitive impairment Covid-19" OR "cognitive impairment COVID19"

Cochrane Library

"SARS-CoV-2 and neurocognitive impairment" OR "SARS-CoV-2 and brain fog" OR "COVID-19 and cognitive dysfunction"