ARTICLE REVIEW

Mild Cognitive Impairment Modelling of Disease due to Inflammation: A Bottom-Up & Longitudinal Overview of Infection Exposure Induced Inflammation in Older Adults

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ABSTRACT

Introduction: Global population aging has increased the burden of age-related cognitive disorders, with mild cognitive impairment representing a critical transitional stage between normal aging and dementia. Although conventional models of Mild Cognitive Impairment pathogenesis emphasize neurodegenerative processes such as amyloid-β and tau pathology, accumulating evidence highlights the central role of systemic and neuroinflammation in early cognitive decline. This review conceptualizes Mild Cognitive Impairment as an inflammation-mediated condition using a bottom-up and longitudinal framework, with particular emphasis on infection exposure, especially SARS-CoV-2 as a trigger of sustained inflammatory responses in older adults. **Methods:** A structured review of PubMed and ScienceDirect (2021–2026) synthesized observational studies in adults ≥60 linking inflammatory biomarkers to Mild Cognitive Impairment outcomes. **Results:** Elevated systemic inflammatory markers, particularly C-reactive protein, interleukin-6, tumor necrosis factor-α, D-dimer, and lactate dehydrogenase, were consistently associated with impairments in executive function, processing speed, and global cognition. Longitudinal findings revealed heterogeneous cognitive trajectories, with partial recovery in some domains but persistent deficits lasting up to 42 months post-infection. Neuroimaging and biomarker evidence supported inflammation-mediated mechanisms, including microstructural brain alterations and neuroaxonal injury indicated by increased plasma neurofilament light chain, in the absence of direct viral neuroinvasion. Psychological stress and mental health symptoms further interacted with immune dysregulation, amplifying cognitive vulnerability. **Conclusions:** Overall, findings support a multifactorial, inflammation-driven model of Mild Cognitive Impairment, where infection-induced immune activation interacts with aging vulnerability, neurobiological injury, and psychosocial factors, highlighting the value of longitudinal inflammatory frameworks for earlier risk stratification and development of targeted preventive and disease-modifying interventions.

Keywords: Mild Cognitive Impairment, COVID-19, Inflammation, Older Adults, Pathophysiology

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INTRODUCTION

The rapid global demographic transition toward an aging population has substantially increased the prevalence and clinical burden of age-related cognitive disorders, particularly mild cognitive impairment (MCI). MCI, which is classified as Mild Neurocognitive Disorder (mild NCD) in DSM-5-TR, is a clinical condition characterized by objective evidence of cognitive decline greater than expected for age and educational level, while functional independence is largely preserved and diagnostic criteria for dementia are not met.[1] This transitional state is clinically significant, as individuals with MCI are at increased risk of progression to dementia, yet the condition remains potentially modifiable during its early stages.

The etiopathogenesis of MCI has traditionally focused on neurodegenerative mechanisms associated with amyloid-β deposition and tau pathology, but emerging evidence highlights an increasingly important role for systemic and central inflammatory processes in the pathophysiology of cognitive decline. Elevated levels of pro-inflammatory biomarkers, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor-α (TNF-α), have been consistently documented in blood samples of individuals with MCI when compared to cognitively normal controls, suggesting a robust inflammatory response associated with early cognitive dysfunction.[2] These pro-inflammatory profiles are not only associated with cognitive status cross-sectionally but may also reflect underlying mechanisms of neuroinflammation that disrupt neuronal homeostasis, compromise synaptic integrity, and accelerate neurodegenerative cascades.

The coronavirus disease 2019 (COVID-19) pandemic has further underscored the importance of infection-induced inflammation as a trigger for cognitive dysfunction in older adults. Studies have demonstrated that SARS-CoV-2 infection is associated with sustained neuroinflammatory responses, structural brain abnormalities, and accelerated cognitive aging, even in individuals with mild disease.[3,4] The combination of chronic inflammation and neuroimmune dysregulation due to COVID-19 in older adults may accelerate processes linked to neurodegenerative diseases, resulting in more pronounced cognitive deficits, including memory loss, executive dysfunction, and impaired attention. Long COVID, characterized by persistent symptoms that persist for months after acute infection, has been associated with declines in multiple cognitive functions, including memory, executive function, and working memory.[5]

Given the multifactorial nature of MCI pathogenesis and the emerging role of inflammation as a central mechanism, there is a compelling need to synthesize the available evidence within a comprehensive framework. This review aims to model MCI as an inflammation-mediated condition using a bottom-up and longitudinal framework, with particular attention to infection exposure—most notably SARS-CoV-2—as a trigger of sustained inflammatory responses in older adults.

METHODS

The literature search was conducted up to 26 January 2026 in two databases, PubMed and ScienceDirect. The search screened articles published between 1 January 2021 and 26 January 2026. The search strategy used the following keywords: (((COVID-19) AND (Inflammation)) AND (Older adults)) AND (Mild cognitive impairment). Articles included in the literature review were those written in English and available in full-text.

Relevant articles were screened by applying predefined eligibility criteria. Studies were included if they involved older

adults aged ≥60 years with a history of infection exposure, assessed systemic inflammation using inflammatory biomarkers, and reported cognitive outcomes related to mild cognitive impairment (MCI), including cognitive trajectories or functional outcomes. Observational cross-sectional or longitudinal cohort studies published in English, available in full text, and published between 1 January 2021 and 26 January 2026 were considered. Studies were excluded if participants were younger than 60 years, lacked inflammatory or cognitive assessments, non-English, unavailable in full text, or duplicates.

REVIEWS

Search Results

The literature search was conducted up to 26 January 2026 using two databases, PubMed and ScienceDirect. The search yielded a total of 52 articles from PubMed and 500 articles from ScienceDirect, all of which were published in English, available in full-text format, and published between 1 January 2021 and 26 January 2026. An initial screening was performed to remove duplicate records. Subsequent screening involved rapid review (skimming) of article titles followed by abstracts. The final selection was conducted by identifying articles that met the predefined eligibility criteria. The flow of the search and selection process is presented in the following figure.

Characteristics of the Study

Table 1. summarizes the main characteristics of the studies included in this review. The table presents key information regarding study design, population characteristics, sample size, setting, outcome measures, and main findings relevant to the research question. This overview is intended to facilitate comparison across studies and to provide a structured synthesis of the existing evidence on the association between COVID-19, inflammation, and cognitive outcomes.

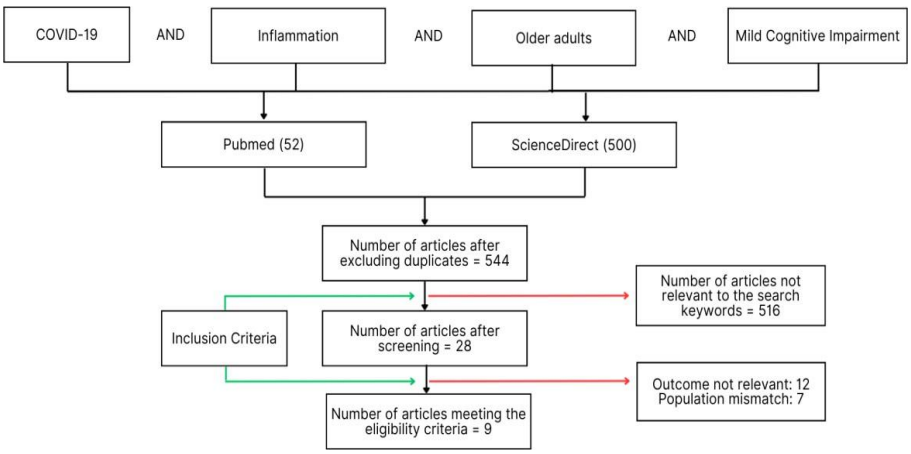


Figure 1. Flow chart of the search strategy

Cognitive Manifestations and Trajectories in Post–COVID-19 Conditions

Cognitive impairment in older adults manifests as multidomain deficits involving episodic memory, processing speed, executive function, attention, language fluency, visuospatial abilities, and reasoning, with preserved basic knowledge and relative independence in early stages.[15] COVID-19 is associated with persistent cognitive disturbances extending beyond the acute phase of infection, particularly in individuals with post–COVID-19 conditions and long COVID.[6,11,12] Previous study found that SARS-CoV-2 infection commonly affected domains include executive function,

processing speed, attention, and global cognition, even among individuals considered clinically recovered.[6,8,10] Executive function impairment in COVID-19 survivors is primarily reflected in reduced cognitive flexibility, task switching, and attentional control, as evidenced by poorer performance on Trails-based tasks.[2,6] The Trail Making Test (TMT) is a brief neuropsychological instrument assessing processing speed, visual attention, and executive function, with Part A measuring psychomotor speed and attention and Part B evaluating cognitive flexibility and set-shifting ability.[16]

Long COVID patients' impaired cognitive function may partially improve. However, cognitive impairments, especially in executive functioning and processing speed, often persist for months to years, reflecting heterogeneous recovery trajectories.[11,13] Notably, cognitive impairments have been documented up to 11 months post-infection, highlighting the long-term neurocognitive burden of SARS-CoV-2 infection.[13] Multiple studies emphasize the role of systemic and neuroinflammation in post-COVID cognitive outcomes. Elevated inflammatory markers such as CRP, IL-6, TNF-α, D-dimer, and LDH have been associated with poorer cognitive performance, particularly in executive domains.[8,10,12,14] In critically ill patients, increased plasma neurofilament light chain (NfL) during ICU admission reflects neuroaxonal damage and is strongly associated with cognitive impairment at six-month follow-up.[14]

Neuroimaging findings further support a biological basis for cognitive symptoms. Multimodal MRI studies reveal persistent microstructural and myelin-related brain alterations in both long COVID and recovered individuals compared with healthy controls, with imaging abnormalities correlating with physical and cognitive functioning.[6,9] Importantly, these alterations are frequently observed without evidence of direct viral invasion of the CNS, suggesting inflammation-mediated mechanisms rather than neurotropism.[9]

Age appears to amplify vulnerability to post-COVID cognitive decline. In older adults, inflammatory biomarkers are associated not only with cognitive impairment but also with functional

dependence, indicating overlapping cognitive and functional trajectories.[7,10] Among the "oldest old," CRP and leukocyte indices are linked to deficits in executive tasks and instrumental activities of daily living, underscoring the clinical relevance of inflammation-related cognitive decline for independence.[7]

Systemic Inflammatory Markers Linked to Cognitive Deterioration

Furthermore, systemic inflammation is a key biological mechanism underlying cognitive deterioration, particularly in the context of post–COVID-19 conditions and aging-related vulnerability.[6,8,11,12] Across multiple observational and longitudinal studies, elevated peripheral inflammatory markers have been consistently associated with impairments in executive function, processing speed, attention, and global cognition.[10,11,14]

Low-grade chronic inflammation is a persistent, subclinical inflammatory state marked by sustained elevation of mediators such as IL-6, CRP, and TNF-α, which contributes to tissue dysfunction and the development of chronic diseases.[17] In line with this mechanism, elevated CRP levels are linked to poorer performance on executive and visuospatial tasks, as well as functional dependence in older adults, suggesting that low-grade systemic inflammation contributes to both cognitive and functional decline.[7,10] Similar associations have been observed in post-COVID populations, where higher CRP levels correlate with worse cognitive trajectories during recovery.[10]

Table 1. Characteristics of the Study

First Author, Year of publication.	Study design	Subject group	Outcome	Key Results	LoE*
Thapaliya K., 2025 [6]	An observational cross-sectional case–control study	Long COVID patients, COVID-recovered healthy controls (COVID-RHC), and non-COVID healthy controls (Non-COVID-HC).	Changes in tissue microstructural and brain neurochemical levels in long COVID and recovered COVID-19 patients compared to healthy controls	1. Long COVID individuals exhibited significantly altered T1w/T2w signal intensities compared with both recovered COVID-19 individuals and healthy controls, indicating changes in myelin-related brain tissue properties. 2. Diffusion-weighted MRI showed distinct microstructural alterations in brain tissue across all group comparisons, suggesting persistent changes in white matter integrity after SARS-CoV-2 infection. 3. Brain neurochemical profiles differed significantly between long COVID and recovered participants, highlighting neurochemical disruptions associated with prolonged post-infection symptoms. 4. T1w/T2w signal intensity correlated with clinical measures of physical and cognitive function in long COVID patients, linking imaging biomarkers to symptom severity. 5. Even individuals considered fully recovered showed measurable brain signal and structural differences relative to never-infected controls, indicating potential long-term central nervous system effects of COVID-19.	3
Aguiar M., 2023 [7]	Observational analytical cross-sectional study	244 elderly individuals aged 80 years and older from the Longevous Project cohort at the Discipline of Geriatrics and Gerontology of UNIFESP	To investigate the role of inflammation in longevity and its potential contribution to unfavorable outcomes, including functional dependence and dementia	1. No statistically significant associations were found between CBC markers (neutrophils, lymphocytes, NLR) and cognitive test scores on the MMSE. 2. CRP levels showed a significant association with performance on the Clock Drawing Test (CDT), with higher CRP linked to poorer CDT performance (P = 0.003). 3. There were no significant associations between CBC markers or CRP and basic activities of daily living (BADLs). 4. A significant association was observed between IADL scores and absolute neutrophil and lymphocyte counts	3

First Author, Year of publication.	Study design	Subject group	Outcome	Key Results	LoE*
				(P = 0.0379 and P = 0.0190, respectively), with higher counts related to lower functional independence. 5. The findings suggest that common inflammatory biomarkers (CRP and leukocyte counts) may be useful in monitoring aspects of cognition and functional capacity in very elderly individuals.	
He D., 2022 [8]	Observational analytical cross-sectional study	66 COVID-19 survivors assessed at ~15 months after hospital discharge and 79 healthy controls matched by age, sex, and education level	Primary outcomes: Objective cognitive function (performance on a digital cognitive test, especially executive function) and associations with inflammatory biomarkers (e.g., TNF-α). Secondary outcomes: Relationship between clinical severity (ICU experience/self-perceived disease severity) and cognitive outcomes	1. COVID-19 survivors performed significantly worse on executive function (Trails test) compared to healthy controls (p = 0.047). 2. Intensive care unit experience and greater self-perceived disease severity were both significantly associated with poorer cognitive performance (β = -2.247, p < 0.0001; β = -1.522, p = 0.007, respectively). 3. Higher years of education were associated with better cognitive outcomes (β = 0.088, p = 0.013). 4. Elevated serum TNF-α levels were significantly negatively correlated with executive function performance in the COVID-19 group (r = -0.19, p = 0.040). 5. Most COVID-19 survivors did not self-report neuropsychiatric symptoms despite objective evidence of cognitive impairment.	3
Barros-Aragao F., 2024 [9]	Retrospective observational cohort study	35 adult hospitalized individuals with confirmed COVID-19 infection and clinically indicated cerebrospinal fluid sampling who presented neurological complications.	Primary outcomes: Correlations between levels of CSF pro-inflammatory biomarkers (especially interleukin-6 [IL-6] and tumor necrosis factor-alpha [TNF-α]) and disease severity as well as neuroimaging alterations. Secondary outcomes: Pattern of systemic hyper-inflammation and CSF proteomic changes in	1. Hospitalized COVID-19 patients with neurological symptoms exhibited elevated systemic hyper-inflammation and broad CSF proteomic alterations related to inflammation and innate immunity regardless of respiratory disease burden. 2. Higher CSF IL-6 concentrations were significantly associated with greater COVID-19 disease severity, even after adjusting for sex, age, and comorbidities. 3. CSF TNF-α and IL-6 levels were significantly higher in patients with pronounced neuroimaging abnormalities compared with patients lacking such findings. 4. SARS-CoV-2 spike protein was not detected in the CSF, suggesting that neurological manifestations may	3

First Author, Year of publication.	Study design	Subject group	Outcome	Key Results	LoE*
			relation to neurological symptom heterogeneity.	be driven more by inflammatory processes than direct viral invasion. 5. Neurological symptoms were heterogeneous and not directly correlated with the extent of pulmonary disease, reinforcing a possible central role of neuroinflammation in COVID-19 neurological complications.	
Mortazavi S., 2024 [10]	Descriptive analytical (observational) cohort study	177 hospitalized COVID-19 patients aged ≥60 years who survived infection and completed follow-up assessments at discharge, 1 month, and 3 months.	Primary outcomes: Changes in cognitive function over time, assessed with General Practitioner Assessment of Cognition (GPCOG), and its relationship with inflammatory biomarkers (e.g., CRP, D-dimer, LDH). Secondary outcomes: Associations between anxiety/depression symptoms and cognitive performance, and trajectory of activities of daily living.	1. Higher levels of C-reactive protein (CRP), D-dimer, and lactate dehydrogenase (LDH) were significantly correlated with lower cognitive performance across follow-up time points. 2. Erythrocyte sedimentation rate (ESR) and creatine phosphokinase (CPK) were not significantly associated with cognitive scores. 3. Global cognitive scores (GPCOG) showed gradual improvement over the three months, suggesting partial recovery of cognition in older COVID-19 survivors. 4. Lower anxiety and depression scores were positively correlated with better cognitive function, indicating emotional health was linked to cognitive outcomes. 5. Instrumental activities of daily living (IADL) improved over time, though basic ADLs remained relatively stable, reflecting functional gains accompanying cognitive recovery.	3
Becker J., 2025 [11]	Longitudinal observational cohort study	Subjects were patients previously infected with COVID-19 followed longitudinally for up to 42 months post-infection to assess long-term cognitive outcomes.	Primary outcomes: Trajectories of cognitive function across multiple domains (e.g., processing speed, executive function) up to 42 months after acute COVID-19 infection. Secondary outcomes: Associations between patient characteristics (e.g.,	1. Cognitive function improved over time in several domains during the 42-month follow-up period. 2. Despite overall improvements, processing speed and executive functioning remained below normal limits at 42 months post-COVID. 3. Lower body mass index was the only factor significantly associated with greater cognitive improvement over time. 4. Persistent deficits in specific cognitive domains suggest long-lasting neurocognitive effects of SARS-CoV-2 infection.	3

First Author, Year of publication.	Study design	Subject group	Outcome	Key Results	LoE*
			body mass index) and cognitive change over time.	5. The results indicate that long COVID patients may experience heterogeneous recovery trajectories, with some cognitive functions recovering more fully than others.	
Bower J., 2022 [12]	Review article	Not applicable	The review aims to elucidate how interactions between the nervous system and the immune system (psychoneuroimmunology) influence mental and physical health in the context of COVID-19, including how psychological states affect immune responses and how immune processes affect cognition, emotion, and behavior	1. There are dynamic bi-directional interactions between the brain and immune system, such that changes in one system can directly influence the other. 2. Both negative psychological states (e.g., stress, anxiety) and positive psychological states (e.g., positive affect, well-being) modulate immune function and antiviral immunity. 3. Immune activation related to COVID-19 infection or associated stressors can impact the brain, influencing cognitive, emotional, and behavioral outcomes. 4. Psychoneuroimmune pathways may help explain why mental health symptoms emerge or persist during the COVID-19 pandemic, including “long-haul” effects. 5. The review highlights interventions (e.g., psychosocial or lifestyle approaches) that may improve immune function and the neuro-immune axis, potentially benefitting both mental and physical health.	5
Damiano R.F., 2023 [13]	Prospective observational cohort study	710 adult COVID-19 survivors (mean age ~55 ± 14 years; ~48.3% female) evaluated 6–11 months after hospital discharge from a tertiary medical center following moderate or severe SARS-CoV-2 infection.	Primary outcomes: Long-term cognitive performance measured by a comprehensive cognitive test battery. Associations of cognitive impairment with sociodemographic factors, clinical features, and a panel of 28 inflammatory markers/cytokines.	1. A substantial proportion of participants reported worsened subjective cognition, with 36.1% reporting slight decline and 14.6% reporting severe impact compared with pre-COVID status. 2. Sociodemographic and clinical variables including sex, age, ethnicity, education, comorbidity, frailty, and physical activity were significantly associated with general cognitive outcomes in multivariate analysis. 3. Bivariate analysis identified several inflammatory markers (e.g., G-CSF, IFN-alpha2, IL-6, IL-7, TNF-beta, VEGF, CRP, D-Dimer) significantly associated with general cognition. 4. However, LASSO regression incorporating all clinical, demographic, and biomarker variables did not support	3

First Author, Year of publication.	Study design	Subject group	Outcome	Key Results	LoE*
				inflammatory markers as independent predictors of long-term cognitive impairment. 5. Overall, cognitive impairment was common among survivors of moderate to severe COVID-19, but its persistence was more strongly linked to contextual sociodemographic and health factors than to specific inflammatory biomarkers	
Duindam H.B., 2024 [14]	Prospective longitudinal cohort study	96 adult patients (median age 61 years, interquartile range 55–69) who survived severe COVID-19 and were admitted to the intensive care unit (ICU); participants were further divided based on whether they received COVID-related immunotherapy.	Long-term cognitive function evaluated by comprehensive neuropsychological testing at 6 months after ICU discharge. Association between systemic inflammatory markers and neuroaxonal damage biomarkers (plasma neurofilament light chain [NfL]) during ICU stay, and later cognitive outcomes	1. Plasma NfL concentrations increased markedly in 95 % of patients over the course of the ICU stay, indicating progressive neuroaxonal damage during critical illness ($p < 0.001$). 2. Higher systemic inflammation markers (including IL-8, tumor necrosis factor, and IL-1 receptor antagonist at day 14) were significant predictors of elevated NfL levels at day 14 of ICU admission ($R^2 = 44$ %, $p < 0.001$). 3. Twenty-seven percent (26/96) of patients exhibited cognitive impairment at six months post-ICU discharge. 4. Patients who developed cognitive impairment showed a more pronounced increase in NfL during ICU stay compared with those without impairment ($p = 0.03$). 5. Higher NfL levels during ICU admission were significantly associated with poorer information processing speed at follow-up (Trail Making Test A: $r = -0.28$, $p = 0.01$; Letter Digit Substitution Test: $r = -0.24$, $p = 0.02$).	3

Pro-inflammatory cytokines, particularly interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have also been implicated in inflammation-related cognitive deterioration. These cytokines are known to influence blood–brain barrier permeability and microglial activation, providing a mechanistic link between systemic immune activation and central nervous system dysfunction.[12] Markers reflecting coagulation and tissue injury, such as D-dimer and lactate dehydrogenase (LDH), have additionally been associated with poorer cognitive outcomes, particularly in older COVID-19 survivors.[10] These findings suggest that inflammatory–vascular interactions may exacerbate neurocognitive vulnerability, potentially through microvascular injury or impaired cerebral perfusion.[10,14]

Compared with pathogenic pathways unrelated to COVID-19, mild cognitive impairment (MCI) has been shown to involve neuroinflammatory and oxidative stress mechanisms, characterized by elevated levels of interleukin-6 (IL-6), C-reactive protein (CRP), and other inflammatory proteins, along with dysregulation of antioxidant defense systems such as glutathione, catalase, and superoxide dismutase, which collectively contribute to neuronal dysfunction and cognitive decline.[18]

In patients with severe COVID-19 requiring intensive care, heightened systemic inflammation during acute illness predicts increased levels of plasma neurofilament light chain (NfL).[14] Neurofilament light (NfL) is a neuron-specific cytoskeletal protein released into extracellular fluids and blood following axonal injury, and it has emerged as a sensitive biomarker of neuroaxonal damage, including in conditions such as chemotherapy-induced peripheral neuropathy and other neurological disorders.[19] This temporal relationship supports a model in which systemic inflammation contributes indirectly to cognitive deterioration via neuronal injury rather than direct viral neuroinvasion.[9,14]

However, not all studies identify inflammatory markers as independent predictors of long-term cognitive impairment. Multivariable models incorporating demographic, clinical, and biological factors suggest that while inflammatory markers correlate with cognitive outcomes in univariate analyses, their predictive value may diminish when broader contextual factors (age, education, frailty, and mental health) are considered.[8] This highlights the multifactorial nature of cognitive deterioration, wherein systemic inflammation interacts with pre-existing vulnerability and psychosocial determinants.[8,11,13]

Bidirectional Links Between Psychological Stress and Immune Responses

Therefore, psychological stress and immune responses are interconnected through bidirectional pathways, whereby psychological states influence immune activity and immune dysregulation, in turn, affects brain function and behavior.[8,10,12] This reciprocal interaction is particularly salient in the context of COVID-19 and post-infectious conditions, where sustained stress and immune activation frequently coexist.[11,12]

Psychological stress has been shown to activate systemic inflammatory responses through neuroendocrine mechanisms involving the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system.[12] Chronic stress exposure is associated with elevated circulating inflammatory markers, including C-reactive protein (CRP), IL-6, and TNF-α, which have been repeatedly linked to adverse cognitive and mental health outcomes.[1,4,6,8,10,12] In post-COVID populations, heightened stress related to illness severity, ICU admission, and prolonged recovery may therefore amplify immune dysregulation and contribute to sustained inflammation.[8,11]

Conversely, immune activation can exert direct effects on the central nervous system, shaping psychological and cognitive outcomes. Pro-inflammatory cytokines are capable of crossing or signaling across the blood–brain barrier, modulating neurotransmitter systems, synaptic plasticity, and neural network functioning.[12] This immune-to-brain signaling has been associated with depressive symptoms, anxiety, fatigue, and cognitive impairment, particularly in individuals with prolonged inflammatory responses following COVID-19 infection.[8,13,14] Compared to non-related COVID-19, CNS inflammation occurs when systemic or local inflammatory stimuli disrupt Blood Brain Barrier (BBB) integrity and activate glial cells, including microglia and astrocytes, leading to the release of pro-inflammatory cytokines, chemokines, reactive oxygen species, and other mediators that promote neuroinflammation, neuronal dysfunction, structural damage, and progression toward neurodegeneration.[20]

Empirical evidence from observational and longitudinal studies supports this bidirectional model. Elevated inflammatory markers are associated not only with cognitive decline but also with worsening psychological symptoms, including anxiety and depression, which themselves predict poorer cognitive recovery trajectories.[8,10]. Among older adults and long COVID patients, psychological distress has been linked to both impaired cognition and functional dependence, suggesting that mental health acts as both a mediator and amplifier of inflammation-related outcomes.[7,10]

In critically ill COVID-19 patients, systemic inflammation during acute illness is associated with biomarkers of neuroaxonal injury, such as plasma neurofilament light chain (NfL), which subsequently predict long-term cognitive impairment.[14] Psychological stressors related to critical illness—such as delirium, social isolation, and perceived threat—may further potentiate immune activation, reinforcing a vicious cycle of stress, inflammation, and neural injury.[12,14]

Importantly, not all individuals exposed to high inflammatory burden develop persistent psychological or cognitive symptoms, underscoring the role of individual vulnerability and resilience factors. Educational attainment, frailty status, pre-existing mental health conditions, and social support appear to modulate the strength of stress–immune interactions and influence recovery trajectories.[8,11,13] These findings emphasize that psychological stress and immune responses operate within a broader biopsychosocial framework rather than as isolated processes.

Summary of Major Findings and a Proposed Pathological Pathway

Post–COVID-19 conditions are associated with persistent cognitive impairments, particularly in executive function, processing speed, and attention, which may endure months to years after infection despite partial recovery.[6,8,11,13,14] These deficits occur across disease severities, indicating a substantial and lasting neurocognitive burden.[6,8]

Systemic inflammation plays a central role in cognitive deterioration, with elevated CRP, IL-6, TNF-α, D-dimer, and LDH linked to poorer cognitive outcomes.[7,8,10,13] In severe cases, inflammation-related neuroaxonal injury predicts long-term impairment, while psychological stress interacts bidirectionally with immune dysregulation, amplifying cognitive vulnerability.[8,10,12] Overall, evidence from predominantly Level 3 observational studies supports a multifactorial inflammatory–neurobiological model of post–COVID-19 cognitive dysfunction.[21] The illustration below presents a proposed pathological pathway linking COVID-19, inflammation, and mild cognitive impairment (MCI).

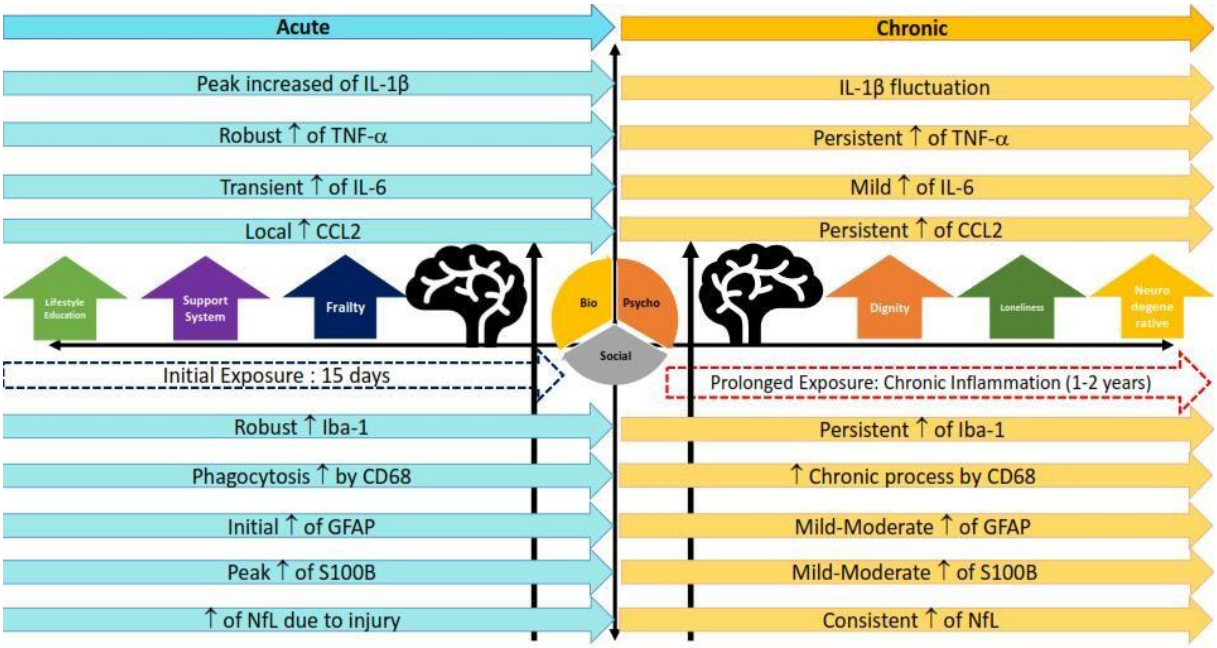


Figure 2. Schematic illustration of the propose pathological pathway linking COVID-19, inflammation, and MCI. *Created by the authors*.

CONCLUSION

COVID-19 has been increasingly recognized as a condition capable of inducing prolonged systemic inflammation, which may contribute to cognitive decline through complex neuroimmune mechanisms. Persistent inflammatory activity, interacting with psychological stress and central nervous system vulnerability, plays a critical role in shaping long-term cognitive outcomes among COVID-19 survivors. However, the precise biological pathways underlying inflammation-related cognitive impairment remain incompletely understood, highlighting an important gap in current knowledge. Future research employing longitudinal designs, comprehensive inflammatory and neurobiological biomarkers, and integrative biopsychosocial frameworks is warranted to clarify causal relationships and identify individuals at greatest risk. Such advances are essential for informing the development of targeted preventive and therapeutic strategies aimed at mitigating cognitive sequelae and improving long-term functional outcomes following COVID-19 infection.

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CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest related to this article.

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