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REVIEW

Systematic review and evidence gap mapping of biomarkers associated with neurological manifestations in patients with COVID-19

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Abstract

Objective This study aimed to synthesize the existing evidence on biomarkers related to coronavirus disease 2019 (COVID-19) patients who presented neurological events.

Methods A systematic review of observational studies (any design) following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and the Cochrane Collaboration recommendations was performed (PROSPERO: CRD42021266995). Searches were conducted in PubMed and Scopus (updated April 2023). The methodological quality of nonrandomized studies was assessed using the Newcastle−Ottawa Scale (NOS). An evidence gap map was built considering the reported biomarkers and NOS results.

Results Nine specific markers of glial activation and neuronal injury were mapped from 35 studies published between 2020 and 2023. A total of 2,237 adult patients were evaluated in the included studies, especially during the acute phase of COVID-19. Neurofilament light chain (NfL) and glial fibrillary acidic protein (GFAP) biomarkers were the most frequently assessed ($n=27$ studies, 77%, and $n=14$ studies, 40%, respectively). Although these biomarkers were found to be correlated with disease severity and worse outcomes in the acute phase in several studies ($p<0.05$), they were not necessarily associated with neurological events. Overall, 12 studies (34%) were judged as having low methodological quality, 9 (26%) had moderate quality, and 9 (26%) had high quality.

Conclusions Different neurological biomarkers in neurosymptomatic COVID-19 patients were identified in observational studies. Although the evidence is still scarce and conflicting for some biomarkers, well-designed longitudinal studies should further explore the pathophysiological role of NfL, GFAP, and tau protein and their potential use for COVID-19 diagnosis and management.

Keywords SARS-CoV-2 · Neurological · Biomarker · Neurofilament light chain · Tau protein

Abbreviations

Aβ	Amyloid beta
BBB	Blood−brain barrier
CNS	Central nervous system
GFAP	Glial fibrillary acidic protein
NfH	Neurofilament heavy chain
NfL	Neurofilament light chain
NSE	Neuron-specific enolase
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PNS	Peripheral nervous system
S100B	S100 calcium-binding protein B
sTREM2	Soluble triggering receptor expressed on myeloid cells 2
UCH-L1	Ubiquitin C-terminal hydrolase L1

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Introduction

SARS-CoV-2, the virus responsible for causing COVID-19, can invade human cells through the interaction between the Spike (S) protein and the angiotensin-converting enzyme 2 receptor, which is expressed in different organs, including

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the lungs, brain, and nervous tissues [1–3]. The virus also has neurotropism and can cross the blood−brain barrier (BBB), resulting in damage to the central and peripheral nervous system (CNS, PNS) tissues due to thromboembolic events, hypoxia, the excitability of glutamatergic neurotransmitters, generation of reactive oxygen species, and activation of innate immunity and systemic inflammatory response. These processes lead to the activation of astrocytes and microglia, resulting in increased cytokines, chemokines, and other biomarkers of damage [1–4].

Neurological manifestations associated with COVID-19 can vary from nonspecific symptoms, such as headache, fatigue, and myalgia, to more severe complications, such as seizures, cerebral ischemia, worsening of neurodegenerative conditions, and cause neurological disorders related to the immune system, such as encephalopathies, meningoencephalitis, acute encephalomyelitis, and Guillain−Barré syndrome [5–7]. Patients with severe COVID-19 also have a high incidence of cerebrovascular disorders, which are associated with severity and mortality [8, 9]. Long-COVID patients often report persistent neurological symptoms, such as worsened migraine, sensory dysfunction of smell and taste, fatigue, and neuropsychiatric disorders (e.g., anxiety, depression, memory impairment, and cognitive decline) [10–12].

Nonspecific biomarkers of systemic inflammation and cytokine storm, such as C-reactive protein (CRP), ferritin, D-dimer, and circulating proinflammatory cytokines, have already been associated with COVID-19 severity and mortality [13–15]. Some of these cytokines (e.g., interleukin 6—IL-6, interleukin 8—IL-8, and tumor necrosis factor alpha—TNF-α) are also involved in neuroinflammation processes [16]. In addition, specific biomarkers of neurological damage have been identified in samples from COVID-19 patients [17, 18]. These biomarkers may be associated with microglial activation in response to inflammation, as evidenced by the elevation of serum and CSF biomarkers of glial and astrocytic function (e.g., glial fibrillary acidic protein—GFAP, and soluble triggering receptor expressed on myeloid cells 2—sTREM2). Biomarkers of axonal integrity (e.g., neurofilament chains and ubiquitin C-terminal hydrolase L1—UCH-L1), neuronal glycolysis (e.g., neuron-specific enolase—NSE), and intracellular calcium regulation (e.g., S100 calcium-binding protein B—S100B) were also identified [13, 17, 19–22]. Additionally, alterations in the levels of proteins related to neurodegenerative disorders, such as tau and amyloid β (Aβ), are also observed in COVID-19 patients. These biomarkers are measured in differential diagnoses of Alzheimer's disease and other dementias, which are determined based on the levels of total tau protein and phosphorylated tau (p-tau), as well as the ratio between their concentrations and the levels of Aβ protein in the cerebrospinal fluid. [18, 23–25].

In this scenario, tracking certain biomarkers in patient samples enables a better understanding of the profile and progression of the viral infection, the measurement of damage caused, and potential sequelae. This is also important for prognostic factors, enabling differential diagnosis and more efficient interventions by identifying potential therapeutic targets for managing related symptoms, especially considering patients still experiencing long COVID, and individuals with neurological comorbidities and neurodegenerative disorders (e.g., Alzheimer's disease, dementia, and persistent cognitive deficits). [26–28]. However, there is a lack of updated literature on all structural markers that could be linked to CNS and PNS damage from COVID-19 in cerebrospinal fluid (CSF) and blood. Thus, this study aims to synthesize the available evidence on neurological biomarkers that may act as indicators or therapeutic targets of COVID-19 through a broad systematic review and evidence gap analysis.

Methods

Protocol and registration

This study was performed and reported in accordance with the Cochrane Collaboration recommendations [29] and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting [30]. The study protocol (CRD42021266995) is registered in the International Prospective Register of Systematic Reviews (PROSPERO). Two authors independently conducted all the study selection and data extraction steps. A third author was consulted in case of discrepancies.

Search strategy

A comprehensive literature search without language limits was conducted to identify relevant studies published since January 2020 (the beginning of the pandemic) in PubMed and Scopus (last updated in April 2023). Keywords related to COVID-19, biomarkers, neurological events, and observational studies were combined using the Boolean operators AND and OR (e.g., complete strategy in Online Resource 1).

Study selection

Registers retrieved from the databases were allocated to reference manager Endnote X9®, where duplicate records were removed. Two reviewers independently performed the screening (title/abstract reading) and full-text evaluation using Microsoft Excel® 2019 sheets.

Eligibility criteria

This systematic review included articles meeting the following criteria: (i) observational studies of any design (cohort cross-sectional studies, case−control, case series, case reports), (ii) published since the pandemic began in 2020, and (iii) identifying any neurological biomarker in blood or CSF samples of adult patients (≥ 18 years old) diagnosed with COVID-19 (by real-time polymerase chain reaction [RT−PCR] or other diagnostic method used in a hospital setting, such as antigen testing and imaging chest X-ray exams) and presenting neurological signs and symptoms. Studies without data for extraction (unavailable information) and those in non-Roman characters were excluded.

Data extraction

A standardized form (Microsoft Excel®, Redmond, WA) was used to extract information on the articles' general data (authors name, year of publication, study design, country, and sample size); population characteristics (age, sex, neurological events, and comorbidities); and biomarkers found in blood and CSF.

Data synthesis

Individual results of the studies were summarized as reported by the authors, including the type of measures and units (narrative synthesis). Additionally, an evidence gap map was built around the methodological quality of the included studies and the biomarkers identified. This approach provides a visual overview of the breadth and availability of information in a given area. It highlights the gaps in current evidence, which may ground further research and decision-making. No meta-analyses were possible, given the high heterogeneity among studies regarding design, population, and reported biomarkers.

Quality assessment

For the assessment of methodological quality, the Newcastle−Ottawa Scale (NOS) was used for nonrandomized studies (cohort and case−control), and the same scale was adapted for cross-sectional studies [31]. Regardless of their methodological quality, all studies were included in this review. This tool classifies study quality as 'poor/low', 'fair/moderate', or 'good/high' by incorporating the evaluation of the following major domains: selection, comparability, and outcomes.

Results

A total of 3058 articles were retrieved after removing duplicates, of which 2605 were excluded during screening titles and abstracts. From the 448 reads in full text, 35 observational studies that met the eligibility criteria were included for synthesis (Fig. 1). The majority of excluded studies focused on mapping other nonspecific disease biomarkers, such as cytokines and other systemic markers of inflammation (e.g., table of excluded studies in Online Resource 2).

The included studies were published in Italy ($n=7$; 20%), Sweden ($n=5$; 14%), the USA ($n=5$; 14%), Germany ($n=3$; 9%), Spain ($n=3$; 9%), England ($n=2$; 6%), France ($n=2$; 6%), and Turkey ($n=2$; 6%). Norway, Brazil, Egypt, Iran, Canada, and Switzerland published one paper each evaluating neurological markers in CSF and blood samples of patients with COVID-19. Most articles ($n=23$; 66%) were cohorts, with some ($n=5$; 14%) being multicenter. Only one case−control study was included in this review [32]; other registers ($n=5$; 14%) refer to descriptive case reports [33] and series [21, 34–36].

A total of 2237 COVID-19 patients were evaluated in the selected papers (Table 1). According to the severity scale proposed by the National Institutes of Health (NIH) guidelines, 23 studies (66%) predominantly included severe patients, while 14 articles (40%) also included individuals with mild severity; eight articles (23%) did not explicitly specify the subdivision of patients based on their respiratory symptoms.

The main non-neurological comorbidities reported in the studies were hypertension ($n=452$ patients; 20%) and diabetes mellitus ($n=246$; 11%). Regarding neurological comorbidities, fourteen studies (40%) did not report pre-existing conditions, while 6 studies (17%) only included patients without neurological diseases.

Only five studies (14%)—Fleischer et al. (2021) [44], Perrin et al. (2020) [21], Virhammar et al. (2021) [62], Guasp et al. (2022) [47], and Ziff et al. (2022) [25]—analyzed both plasma and CSF. Most studies ($n=23$; 66%) were restricted to blood samples, while seven (20%) solely evaluated CSF samples from hospitalized patients. Eight cohort studies (23%) predominantly focused on the acute phase of COVID-19 (up to one month of follow-up), with most of them ($n=6$) measuring biomarkers only once during patients' hospitalization and after disease onset.

Headache ($n=311$ patients; 14%), olfactory disorders (e.g., anosmia, hyposmia) ($n=282$ patients; 13%), taste disorders (e.g., ageusia, hypogeusia) ($n=264$ patients; 12%), myalgia ($n=168$; 7%), encephalopathy ($n=120$; 5%), and cognitive and memory impairments ($n=113$; 5%) were the most reported neurological symptoms. Stroke and cerebrovascular events, movement disorders, and Guillain−Barré syndrome were less prevalent symptoms (<2% of patients)

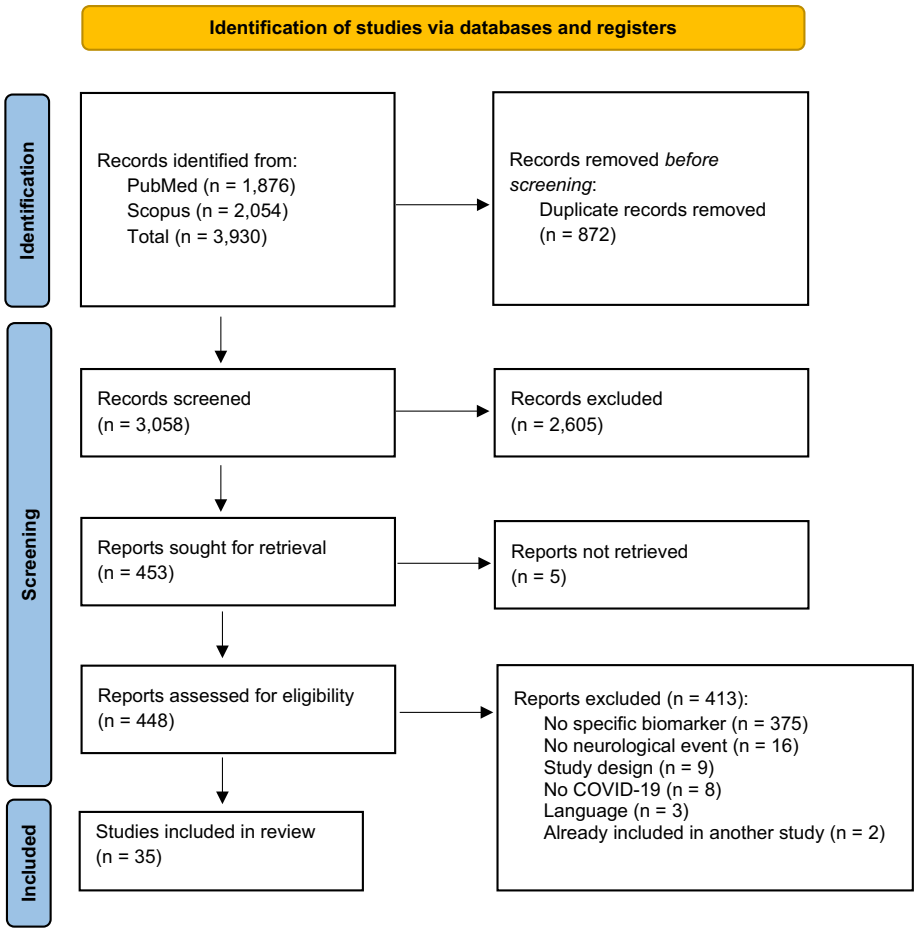


Fig. 1 PRISMA flowchart of the study selection

and were mainly associated with patients with a higher severity level. Regarding neurological sequelae, the most persistent ones were headaches in 69 patients (3%), ageusia in 75 patients (3%), anosmia in 29 patients (1%), and cognitive and memory impairments in 96 patients (4%).

As shown in Table 2, nine biomarkers were mapped in this systematic review: neurofilament light chain (NfL), neurofilament heavy chain (NfH), glial fibrillary acidic protein (GFAP), tau protein (tau; phospho-tau; total tau), amyloid beta (Aβ), S100 calcium-binding protein B (S100B), neuron-specific enolase (NSE), ubiquitin C-terminal hydrolase L1 (UCH-L1) and soluble triggering receptor expressed on myeloid cells 2 (sTREM2). NfL was the most frequently evaluated biomarker ($n = 27$ studies, 77%), with one-third of these studies ($n = 12$) restricted to assessing this specific biomarker. The second most identified biomarker was GFAP ($n = 14$; 40%); 13 studies (37%) assessed both NfL and GFAP.

Increased levels of NfL and GFAP were frequently associated with worse outcomes in COVID-19 in the acute phase (including mild neurological symptoms to severe events and mortality), and this trend was similarly observed for less commonly assessed biomarkers such as S100B and NSE (9% papers, each). Conversely, Fleischer et al. (2021) [44], the only study to date that measured neurofilament heavy chain (NfH), found no significant differences in the level of this biomarker among mild-to-severe COVID-19 patients, who presented different degrees of neurological involvement.

Cooper et al. (2021) [18] reported a correlation between the elevation of UCH-L1 and delirium in COVID-19 patients compared to ICU controls ($p < 0.05$), despite respiratory function or cytokine levels. This biomarker was also significantly associated with prolonged sedation time in ICU patients ($p = 0.0075$).

In the study by Pilotto et al. (2021) [22], in addition to NfL and GFAP, the increase in tau protein and (unprecedentedly) sTREM2 concentrations were also associated with encephalopathies caused by SARS-CoV-2. Tau protein and Aβ are usually monitored together in the clinical setting for the differential diagnosis of AD; we found that most studies assessed these biomarkers in CSF (12%), yet two studies performed blood analyses. One patient presented with an AD prodromal stage after COVID-19 infection [27].

Magdy et al. (2022) [32], the only case−control study assessing post-COVID neuropathic pain, reported correlations between increased NfL levels in COVID-19 patients

Table 1 Characteristics of the included studies ($n=35$)

References	Study design	Country	*n*, COVID-19	Age, years	Sex, *n* (%) m*asculine*	Control group, (*n*)	Follow-up time, *days*	Month/year of hospitalization	Sample time	Neurologic comorbidities (% COVID-19 patients)
Aamodt et al. (2021) [37]	Prospective multicenter cohort	Norway	47	60.3 (SD 16.3, 27–93)	34 (72%)	2000 healthy controls (no published data)	≈ 30 days	Mar–May/2020	During the disease onset (acute phase, admission) and after the follow-up time	Dementia (6%)
Ameres et al. (2020) [38]	Prospective single-center cohort	Germany	28	range 18–65	3 (11%)	Healthy controls ($n=72$)	≈ 36 days	Mar/2020	≈ 23 days (IQR 21–26) and 35 days (range 29 –36) after onset of disease	No
Bonetto et al. (2022) [39]	Prospective multicenter cohort	Italy	157	63 (IQR 53–71)	118 (75.2%)	ALS group ($n=51$) Healthy controls ($n=20$)	Long-term (15 – 90 days) in ICUCovid (50%) and NeuroCOVID samples (20%)	Feb/2020–Feb/2021	During the disease onset (acute phase, admission) (0 –14 days) and in the long-term phase (15 –90 days)	–
Bozzetti et al. (2021) [40]	Prospective single-center cohort	Italy	107	median 63 (range 32–90)	70 (65.4%)	Healthy controls ($n=60$)	≈ 124 days	Mar–Jun/2020	During the disease onset (acute phase, admission) and after follow-up time	No
Chaumont et al. (2023) [41]	Prospective single-center cohort	France	24	62 (IQR 56–70)	15 (62.5%)	Non-COVID-19 with psychiatric illness ($n=20$)	≈ 33 days (ICU hospitalization)	Mar/2020–Jun/2021	During the disease onset (acute phase, admission)	No
Cooper et al. (2020) [18]	Prospective multicenter cohort	Canada	27	70 (IQR 54–76)	18 (67%)	ICU pneumonia non-COVID-19 ($n=17$)	≈ 21 days	Mar–May/2020	1–10, 14, and 21 days after admission to ICU	Dementia (19%)
Edén et al. (2021) [34]	Case series	Sweden	6	40– 80	5 (83%)	–	≈ 22 days in five patients 36 days in one patient	Mar–Apr/2020	During the disease onset (acute phase, admission)	Schizophrenia (17%)

Table 1 (continued)

References	Study design	Country	*n*, COVID-19	Age, years	Sex, *n* (%) *masculine*	Control group, (*n*)	Follow-up time, *days*	Month/year of hospitalization	Sample time	Neurologic comorbidities (% COVID-19 patients)
Edén et al. (2022) [42]	Cross-sectional	Sweden	44	57 (IQR 48–69)	30 (68%)	Healthy controls ($n=10$) COVID-19 negative group ($n=41$)	≈ 21 days	Mar/2020–Jun/2021	During the disease onset (acute phase, admission)	–
Ermis et al. (2021) [43]	Cross-sectional	Germany	53	61 (IQR 56–68)	32 (60%)	Without ARDS $n=28$	–	Mar–Sep/2020	During the disease onset (acute phase, admission)	Depression (13%) History of stroke (8%) History of brain damage (6%)
Fleishcher et al. (2021) [44]	Prospective single-center cohort	Germany	102	median 61 (21–90)	71 (70%)	Comparisons only between severity groups	≈ 20 days	Apr–Jul/2020	During the disease onset (acute phase, admission)	40% (nonspecified)
Frithiof et al. (2021) [45]	Prospective single-center cohort	Sweden	100	64 (IQR 55–70)	11 (11%)	ICU controls ($n=10$)	≈ 41 days	Mar–Jun/2020	≈ 9 days on ICU admission and 11 days	6% (nonspecified)
Garcia et al. (2021) [46]	Cross-sectional	USA	18	range 20–79	10 (56%)	Healthy controls (n = 14) non-COVID-19 neurological diseases ($n=68$)	≈ 30 days	Apr–Jul/2020	During the disease onset (acute phase, admission)	Dementia (17%) Parkinson's disease (6%) Epilepsy (6%) History of stroke (11%)
Guasp et al. (2022) [47]	Prospective single-center cohort	Spain	60	66 (IQR 56–75)	36 (60%)	Healthy controls ($n=60$)	≈ 18 months	Mar–Aug/2020	During the disease onset and follow-up	–
Hay et al. (2021) [48]	Prospective single-center cohort	USA	89	The average range of 60.8	26 (52%)	Healthy controls ($n=8$) COVID-19 negative ICU controls ($n=11$)	≈ 37 days	Apr–Aug/2020	During the disease onset (acute phase, admission)	–
Hirzel et al. (2022) [49]	Prospective single-center cohort	Switzerland	53	51 (IQR 33–65)	33 (62%)	-	≈ 35 days	Mar–Jul/2020	During the disease onset (acute phase, admission) and follow-up	Cerebrovascular disease (7%)

Table 1 (continued)

References	Study design	Country	*n*, COVID-19	Age, years	Sex, *n* (%) *masculine*	Control group, (*n*)	Follow-up time, *days*	Month/year of hospitalization	Sample time	Neurologic comorbidities (% COVID-19 patients)
Kanberg et al. (2021) [50]	Prospective single-center cohort	Sweden	151	55 (IQR 48–65)	57 (57%)	Healthy controls ($n=51$)	≈ 262 days	Feb–Nov/2020	During the disease onset (acute phase, admission) and follow-up (4 time points)	Previous stroke (2%)
Lennol et al. (2023) [51]	Prospective biobank cohort	Spain	45	mean ± SEM (range) 64 ± 3 (21–89)	27 (45%)	Healthy controls ($n=14$)	≈ 70 days	Mar–Jun/2020	During the disease onset (acute phase, admission) and after follow-up	–
Magdy et al. (2022) [32]	Case−control	Egypt	90	43 (SD 16)	31 (34%)	Recovered ($n=34$) Depression ($n=12$)	≈ 90 days	Sep–Nov/2020	During the disease onset (acute phase, admission) and after recovery time	No (73%) Depression (18%)
Matias-Guiu et al. (2021) [33]	Case report	Spain	1	67	0 (0%)	-	1 year	Mar/2020	Seven months after the disease onset	No
Morassi et al. (2021) [35]	Case series	Italy	2	range 70–73	0 (0%)	-	≈ 9 months	Feb–May/2020	One month after the disease onset	Anxiety (100%) Depression (100%)
Needham et al. (2022) [52]	Prospective multicenter cohort	England	175	51 (IQR 35–21)	93 (53%)	Healthy controls ($n=21$)	≈ 136 days	Feb/2020–Feb/2021	During the disease onset (acute phase, admission) subacute and convalescent at outpatient follow-up	–
Pellitteri (et al. 2022) [53]	Prospective and retrospective single-center cohort	Italy	47	60 (IQR 51–68)	39 (83%)	-	≈ 10 months	Mar/2020–May/2021	After 2 months of discharge and during follow-up (2-time points)	Insomnia (11%) Obstructive sleep apnea (4%) Anxiety 4 (8%)

Table 1 (continued)

References	Study design	Country	*n*, COVID-19	Age, years	Sex, *n* (%) *masculine*	Control group, (*n*)	Follow-up time, *days*	Month/year of hospitalization	Sample time	Neurologic comorbidities (% COVID-19 patients)
Peluso et al. (2022) [54]	Prospective single-center cohort	USA	121	44 (IQR 37–57)	55 (45%)	Patients without PASC (included, *n* = 69)	≈ 90 days (late recovery)	Apr–Aug/2020	In early recovery (subacute/subchro-c phase) and late recovery	–
Perrin et al. (2020) [21]	Case series	France	5	range 51–71	3 (60%)	-	≈ 39 days	Mar–Apr/2020	During the disease onset (acute phase)	Sleep apnea (40%)
Pilotto et al. (2021) [22]	Cross-sectional	Italy	13	range 50–78	7 (54%)	Healthy controls (*n* = 19) Encephalitis (n = 21)	-	Feb–Jun/2020	During the disease onset (acute phase)	–
Plantone et al. (2022) [55]	Prospective single-center cohort	Italy	148	71 (IQR 58–82)	92 (62%)	IPF (n = 53) Healthy controls (*n* = 108)	-	Oct/202–Apr/2022	During the disease onset (acute phase, admission)	No
Prudencio et al. (2021) [56]	Prospective single-center cohort	USA	142	median 62 (range 22–99)	85 (60%)	Healthy controls (*n* = 55)	≈ 119 days	–	During the disease onset (acute phase, admission) and after follow-up	–
Sahin et al. (2022) [57]	Prospective single-center cohort	Turkiye	59	range 26–58	27 (46%)	Healthy controls (*n* = 20)	≈ 13 days	Apr–Oct/2021	During the disease onset (acute phase, admission)	–
Sahin et al. (2023) [58]	Cross-sectional	Turkiye	58	range 26–54	28 (48%)	Healthy controls (*n* = 20)	≈ 13 days	Feb–Nov/2021	During the disease onset (acute phase, admission)	–
Shafiee et al. (2022) [36]	Case series	Iran	3	range 3–45	0 (0%)	NI	≈ 8 months	1st semester/2021	10 months after the disease onset	Chronic migraine (33%) Seizures (33%)
Silva et al. (2023) [59]	Prospective multicenter cohort	Brazil	141	Mild 37 (IQR 22–73) Severe 51 (IQR 21–81)	79 (56%)	Healthy controls (*n* = 36)	21 days	2nd semester/2020–1st semester/2021	During the disease onset (acute phase, admission) (2-time points)	–

Table 1 (continued)

References	Study design	Country	*n*, COVID-19	Age, years	Sex, *n* (%) m*asculine*	Control group, (*n*)	Follow-up time, *days*	Month/year of hospitalization	Sample time	Neurologic comorbidities (% COVID-19 patients)
Sun et al. (2021) [60]	Cross-sectional	USA	24	range 33–58	6 (25%)	COVID-19 negative with historic infection samples	Days till visit ≈ 103 At least ≈ 21	–	At admission	–
Verde et al. (2022) [61]	Prospective single-center cohort	Italy	57	64 (IQR 54–62)	41 (72%)	Healthy controls neurological and non-COVID-19 ($n=30$)	≈ 29 days	Mar–Apr/2020	During the disease onset (acute phase) and after follow-up (2-time points)	No
Virhammar et al. (2021) [62]	Prospective single-center cohort	Sweden	19	median 64 (range 34–76)	-	Used listed reference values	≈ 78 days	Apr–Jul/2020	23 days (IQR = 6–43) between the onset of symptoms and LP	Cerebrovascular disease (5%)
Ziff et al. (2022) [25]	Cross-sectional	England	21	57 (SD 15)	13 (62%)	Healthy controls (n$n=21$)	≈ 40 days of symptoms	Mar–Jun/2020	During the disease onset (acute phase) ≈ 40 days of symptoms	–

ARDS acute respiratory distress syndrome, *PASC* postacute sequelae of severe SARS-CoV-2 infection, *IPF* interstitial pulmonary fibrosis

Table 2 Main findings in the included studies regarding the neurological manifestation of COVID-19 ($n=35$)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Aamodt et al. (2021) [37]	Blood	NfL GFAP	Myalgia (55%) Headache (30%) Fatigue (17%) Confusion (13%) Ageusia (6%) Anosmia (6%) Encephalitis (2%)	NI	↑ [NfL] (admission) in nonsurvivors ($p<0.001$) ↑ [GFAP] (admission) in nonsurvivors and unfavorable outcomes ($p=0.02$) Correlation between [NfL] and [GFAP] ($p=2.2\times10^{-7}$) ↑ [NfL] in myalgia, adjusted for age and creatinine ($p=8.7\times10^{-4}$) No significant correlation between [NfL] and [GFAP] with events, such as confusion, headache, and sense disorders
Ameres et al. (2020) [38]	Blood	NfL	Mild—headache and anosmia (75%)	No (100%)	[NfL] correlated with COVID-19 status ($p=0.005$)
Bonetto et al. (2022) [39]	Blood	NfL GFAP	n = 78 neuroCOVID patients Cerebrovascular disorders (11%) Guillain−Barré (17%) Encephalitis/encephalopathies (17%) Epilepsy (2%) Myelopathy (1%) Syncope (1%) Movement disorders (1%) Headache (1%)	Mild cognitive impairment (n = 11, 7%)	↑[NfL] and [GFAP] in NeuroCOVID compared to control groups ($p<0.05$) No difference in ↑ [NfL] and [GFAP] between ICU and Neuro-COVID groups in the acute phase ($p=0.7054$) ↑[GFAP] in the NeuroCOVID group in the acute phase (tendency) compared to the ICU group ($p=0.0088$) between alive and dead Persistent high levels dependent on disease severity, with a long-term difference for [NfL] ($p<0.001$)
Bozzetti et al. (2021) [40]	Blood	NfL	Hypogeusia (51%) Fatigue (44%) Hyposmia (35%) Myalgia (24%) Headache (19%) Vertigo (10%) Syncope (9%) Impaired consciousness (6%) Impaired memory (6%)	Fatigue (7%) Myalgia (4%) Impaired memory (4%) Hyposmia (2%) Hypogeusia (2%) Vertigo (2%)	↓ [NfL] postfollow-up compared to [NfL] on admission ($p<0.001$) At least one neurological symptom at admission correlated with prolonged symptoms ($p<0.01$)

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Chaumont et al. (2023) [41]	CSF	NfL tau protein Aβ	Encephalopathy (71%) Meningoencephalitis (29%) Movement disorders (33%) Stroke (21%)	NI	↑[NfL] in neuroCOVID patients compared with the control group (p =0.005) Positive correlation between [NfL] e [tau] (p=0.036) No CSF profile indicating AD
Cooper et al. (2020) [18]	Blood	NfL GFAP tau protein UCH-L1	Delirium (41%) Headache (27%)	NI	↑[NfL] (p=0.0005) ↑[GFAP] (p=0.0064) and [UCH-L1] (p=0.0358) in delirium COVID-19 patients compared to ICU controls ↑ [NfL] in COVID-19 patients with dementia compared to individuals without dementia (p =0.023) ↑ [NfL] (p=0.0098) in the acute phase ↑ [GFAP] e [tau] correlated with delirium at admission (p=0.0009 e p =0.0012, respectively) ↑ [UCH-L1] correlated with time of sedation (p=0.0075) ↑ Levels of biomarkers despite levels of cytokines and respiratory function
Edén et al. (2021) [34]	CSF	NfL	Encephalopathy (67%) Fatigue (33%) Dysgeusia (17%) Memory loss (17%) Suspected meningitis (17%)	NI	↑[NfL] in 2 patients
Edén et al. (2022) [42]	CSF	NfL GFAP	Encephalopathy (22%) Encephalitis (1%) Guillain−Barré (1%)	NI	No difference between symptomatic and asymptomatic patients for [NfL] (p=0.12) and GFAP (p =0.28) Differences between HC and neuro-symptomatic patients (p =0.002)
Ermis et al. (2021) [43]	Blood	NSE	Cognitive decline (62%) Paresis (47%) Weakness (32%) Hyposmia/anosmia (26%) Headache (21%) Ageusia (15%) Delirium (13%) Encephalopathy (4%)	NI	Nine patients (17%) who assessed NSE levels ↑[NSE] compared to the reference value

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Fleishcher et al. (2021) [44]	Blood CSF	NfH	Ischemia (20%) Anosmia (15%) Delirium (10%) Cognitive impairment (9%) Seizure (5%) Encephalitis (3%) Headache (2%)	Worsening of preexisting neurological deficit in 5 patients (8.5%)	No differences in [NfH] between groups separated according to the severity of neurological symptoms 83% of patients with severe neurological symptoms already had neurological comorbidity ($p=0.009$)
Frithiof et al. (2021) [45]	Blood	NfL GFAP tau protein	CIM and CIN (n = 11, 11%) ICU-acquired weakness (8%)	NI	↑[NfL] and [GFAP] in CIN/CIM group compared with non-CIN/CIM patients ($p=0.001$ both) ↑[NfL] correlated with an increase in ICU stay in CIN/CIM group ($p=0.02$) and without CIN/CIM ($p=0.005$) [GFAP] not correlated with ICU stay ↑ [tau] in CIN/CIM ($p=0.04$) but with no difference in the timepoints
Garcia et al. (2021) [46]	CSF	NfL	Ischemia (39%) Encephalopathy (33%) Headache (28%) Anosmia (28%) Ageusia (17%) Seizure (6%) Cognitive decline (6%)	NI	↑[NfL] COVID-19/ischemia compared to healthy controls ($p \leq 0.001$) ↑[NfL] COVID-19/headache compared to healthy controls ($p \leq 0.01$) ↑[NfL] COVID-19/stroke compared to healthy controls ($p \leq 0.001$) and COVID-19/headache group ($p \leq 0.01$) Difference not significant in COVID-19/encephalopathy group compared to healthy controls
Guasp et al. (2022) [47]	Blood CSF	NfL	Cognitive impairment (100%) Encephalopathy (42%) Encephalitis (23%) Status epilepticus (11%) Movement disorders (6%) Ischemia (2%)	15 patients (31%) with mild-moderate neurological disability and two (4%) with severe functional dependence	↑[NfL] correlated with COVID-19 severity ($p<0.001$) ↑[NfL] in COVID-19/encephalopathy and COVID-19/encephalitis patients compared to healthy controls ($p<0.001$ and $p=0.012$, respectively) [NfL] correlated with neurological status after 18 months follow-up ($p=0.006$)

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Hay et al. (2021) [48]	Blood	NfL	Encephalopathy (10%) Delirium (10%) Seizure (4%) Stroke (3%)	Depression (15%) Sleep apnea (8%) Dementia (2%)	↑[NfL] of patients with neurological complications post-COVID-19 compared to those without neurological persistent symptoms ($p = 0.01$) Correlation of [NfL] with some level of CVD ($p < 0.001$) ↑[NfL] in ICU patients with COVID-19 compared to NfL in non-COVID-19 patients ($p = 0.01$) and healthy controls ($p = 0.005$)
Hirzel et al. (2022) [49]	Blood	NfL	Confusion (13%) Brain hemorrhage (2%) Critical polyneuropathy (2%)	NI	↑[NfL] in severe cases on admission ($p = 0.037$) and after follow-up ($p < 0.001$) ↑[NfL] in severe disease compared with mild-moderate COVID-19 ($p < 0.001$) [NfL] not changed in mild-moderate COVID-19 ($p = 0.317$), just in severe cases ($p < 0.001$)
Kanberg et al. (2021) [50]	Blood	NfL GFAP	Myalgia (54%) Dysgeusia (43%) Headache (41%) Hyposmia (38%) Cognitive impairment (7%)	Fatigue (40%) Brain fog (29%) Cognitive impairment (25%)	↑[NfL] and fatigue—OR 0.195 ($p = 0.034$, 95%CI-043—881) ↑[NfL] compared to all groups ($p < 0.001$) in the acute phase and severe cases after follow-up ↑[GFAP] compared to the control group ($p < 0.001$) in moderate disease ↑[NfL] 70 days after symptom onset ($p < 0.001$) and ↓[GFAP] after this period ($p < 0.001$) No significant correlation between biomarkers and persistent symptoms ($p > 0.05$) NfL and GFAP normalized after 6 months in the patients involved in the study

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Lennol et al. (2023) [51]	Blood	NfL, GFAP tau protein	Headache (27%) Myalgia/arthralgia (27%) Anosmia/ageusia (27%) Memory loss (23%) Vision impairment (4%)	Headache, myalgia, sensorial disorders, memory impairment (nonspecified)	↑[[NfL], [GFAP] and [tau] in COVID-19 compared to healthy controls ($p < 0.001$, $p = 0.015$ and $p = 0.001$, respectively) ↓[[NfL], [GFAP] and [tau] in post-COVID syndrome ($p < 0.005$, $p = 0.032$, $p = 0.053$, respectively)
Magdy et al. (2022) [32]	Blood	NfL	Neuropathic pain (100%) Allodynia (38%) Depression (27%)	Persistent neuropathic pain (50%) Allodynia (19%)	↑[NfL] in COVID-19/neuropathic pain compared to control groups ($p = 0.029$) ↑[NfL] in COVID-19/allodynia compared to control groups ($p = 0.05$) [NfL] correlated with VAS ($p = 0.001$)
Matias-Guiu et al. (2021) [33]	CSF	tau/p-tau protein Aβ protein	Myalgia, memory loss, cognitive impairment, difficulty concentrating, fatigue, anxiety, and insomnia	"Brain fog"—cognitive impairment, prodromal AD, neuropsychiatric disorders	↓[Aβ-42] ↑ [tau] ↑[p-tau] Early signs of the prodromal phase of AD
Morassi et al. (2021) [35]	CSF	tau protein Aβ protein	Dysgeusia (50%) Confusion (50%) Sleep disorders (50%) Tonic−clonic seizure (50%)	Parkinsonism, cognitive impairment, and late-day confusion (50%)	↓[Aβ42] ↑[tau] above reference (pathological levels) in 1 patient (50%) Parkinsonism in 2 patients after encephalopathy related to COVID-19
Needham et al. (2022) [52]	Blood	NfL, GFAP tau protein	NI	NI	[NfL] and [GFAP] in convalescent phase correlated with paired samples taken at the 15–42 day time point ($p = 0.0008$ e $p < 0.0001$) but tau did not ($p = 0.02$) ↑ [tau] in COVID-19 convalescent patients ($p = 0.003$) [UCH-L1] predominantly below the functional lower level of quantification
Pellitteri et al. (2022) [53]	Blood	NfL	Ageusia (53%) Myalgia (53%) Anosmia (44%) Headache (38%) Poor sleep quality (36%) Delirium/confusion (25%) Syncope (8%)	Insomnia and poor sleep quality (36%)	↑[NfL] at first timepoint on COVID-19/poor sleepers ($p < 0.001$) No significant difference in [NfL] was found at the second time point between good and poor sleepers

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Peluso et al. (2022) [54]	Blood	NfL, GFAP	NI	Cognitive impairment (35%) Sleep disorders (26%) Sensorial disorders (22%) Myalgia (16%) Headache (15%) Neuralgia (14%)	↑[GFAP] ($p=0.02$), but no [NfL] ($p=0.50$) in the COVID-19 group that reported persistent neurological symptoms Significant differences in trends of [NfL] (p = 0.041) between neuro-COVID and COVID-19 patients without persistent neurological symptoms
Perrin et al. (2020) [21]	Blood CSF	S100B	Confusion (80%) Agitation (80%) Tremor (80%) Headache (60%) Extrapyramidal syndrome (60%) Cognitive impairment (40%) Confusion (40%) Coma (40%) Anosmia/dysgeusia (20%)	Temporary cognitive deficit (40%)	↑[S100B] in the acute phase compared to reference values in all patients Persistent S100B levels above reference after 1 month in 1 patient (20%)
Pilotto et al. (2021) [22]	CSF	NfL GFAP tau protein sTREM2	Encephalitis (100%) Altered mental status (100%) Aphasia (38%) Seizure (31%) Motor deficits (31%) Behavioral changes (31%)	NI	[GFAP] and [sTREM2] were abnormal in 12 (92%) and 10 (77%) COVID-19/encephalopathy patients, respectively ↑[NfL], [GFAP], [tau], and [sTREM2] levels correlated with COVID-19/encephalopathy, when compared to healthy controls ($p=0.001$ for all)
Plantone et al. (2022) [55]	Blood	NfL GFAP	None or minor symptoms, like ageusia and anosmia (no specified)	No (100%)	↑[NfL] in COVID-19 patients without clinical neurological manifestations compared to healthy controls and IPF ($p<0.001$, both) ↑[NfL] ↑[GFAP] in subgroups of patients with COVID-19 (moderate, severe) compared to control patients with IPF ($p<0.001$)
Prudencio et al. (2021) [56]	Blood	NfL	Headache, seizure, encephalopathy, hemorrhagic lesions (nonspecified)	NI	↑[NfL] on COVID-19 patients compared with controls ($p<0.0001$) ↓[NfL] with remdesivir administration ($p=0.008$) ↑[NfL] higher than the cutoff on 8 patients with COVID-19 (34%) ↑[NfL] on worst outcomes ($p<0.001$)

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Sahin et al. (2022) [57]	Blood	GFAP S100B	Headache (81%) Anosmia (62%) Ageusia (55%) Vertigo (19%) Peripheral neuropathy (2%) Cranial nerve damage (2%) Memory/cognitive decline (2%)	NI	↑[GFAP] in COVID-19 severe group compared to controls regardless of neurological symptoms ($p=0.007$) ↑[S100B] in COVID-19 patients with multiple neurological symptoms compared with COVID-19 patients with one ($p=0.044$) [S100B] similar between control and COVID-19 groups ($p>0.05$)
Sahin et al. (2023) [58]	Blood	NfL NSE	Headache (78%) Ageusia (54%) Anosmia (52%) Vertigo (20%) Peripheral neuropathy (20%) Memory/cognitive decline (8%) Cranial nerve damage (5%)	NI	↑[NfL] after 5 days in the mild group ($p=0.019$) than < 5 days [NfL] similar between COVID-19 and controls ($p>0.05$) No significant difference between [NfL] and [NSE] across the groups ($p>0.05$)
Shafiee et al. (2022) [36]	Blood	Aβ protein	Insomnia (33%) Confusion (33%) Myalgia (33%)	Cognitive impairment (33%) Myalgia (33%) Worsened migraine (33%)	↑[Aβ] 10 months after the disease onset in one patient (25%)
Silva et al. (2023) [59]	Blood	NSE S100B	Headache (49%) Anosmia (32%) Myalgia (31%) Ageusia (27%)	Headache (35%) Myalgia (32%)	[S100B] and [NSE] did not differ from mild COVID-19 and control groups ($p=0.4123$ and 0.2136, respectively) Difference between [S100B] in COVID-19 severe group and control group ($p=0.04$) Difference between [NSE] in the control group compared to the severe group and mild-to-severe group ($p<0.0001$, both)
Sun et al. (2021) [60]	Blood	NfL	Cognitive impairment (24%) Double vision (4%) Hallucination (4%)	NI	No difference between [NfL] in COVID-19 patients and neuro-COVID patients compared to healthy controls [NfL] correlated with increasing age in neuroCOVID patients but not in control or COVID-19 nonneurological groups

Table 2 (continued)

Article	Sample type	Biomarker(s)	Neurological events in the acute phase (% COVID-19 patients)	Neurological sequelae (% COVID-19 patients)	Main findings
Verde et al. (2022) [61]	Blood	NfL	Mild symptoms	NI	↑[NfL] in COVID-19 patients compared to healthy non-COVID-19 control groups ($p < 0.0001$) Strong positive correlation between baseline and longitudinal [NfL] ($p < 0.0001$) Longitudinal [NfL] did not significantly differ between the 3 categories of COVID-19 severity ($p = 0.477$)
Virhammar et al. (2021) [62]	Blood CSF	NfL GFAP tau protein	Encephalopathy (74%) Headache (42%) Anosmia (26%) Central weakness (21%)	NI	[NfL], [GFAP], and [tau] above adjusted reference in 63, 37, and 16% of patients ↑[NfL] correlated to a decrease in conscience level and time in ICU ($p < 0.05$ and $p < 0.0001$) ↑[GFAP], not [tau], correlated with worse ECG ($p < 0.05$) ↑[NfL] correlated with CNS symptoms (coma, weakness) and severity ($p < 0.05$) Levels of NfL and GFAP correlated both in CSF and blood ($p < 0.001$)
Ziff et al. (2022) [25]	Blood CSF	NfL GFAP Tau (t, p) Aβ (protein and precursors)	Guillain−Barre syndrome (43%) Encephalopathy (29%) Encephalitis (14%) Acute Disseminated Encephalomyelitis (ADEM) (9%) Intracranial hypertension (5%) Central pain syndrome (5%)	NI	↑[NfL], serum and CSF, neuroCOVID patients compared to control ($p = 0.001$ and $p = 0.047$) ↓[GFAP] in CSF of neuroCOVID patients compared to control ($p = 0.0001$) ↓[sAPP] and [sAPPß] in COVID-19 neurological patients compared to non-COVID controls ($p = 0.004$ e $p = 0.03$) ↓[Aβ42] in patients with neurological syndromes ($p < 0.0001$) Tau/t-tau not correlated with sAPPα or sAPPβ in either neuroCOVID patients or the control group

Aβ Amyloid beta, *ECG* Electroencephalogram, *GFAP* Glial fibrillary acidic protein, *IPF* Idiopathic pulmonary fibrosis, *NfH* Neurofilament heavy chain, *NfL* Neurofilament light chain, *NSE* Neuron-specific enolase, *S100B* S100 calcium-binding protein B, *sTREM2* Soluble triggering receptor expressed on myeloid cells 2, *UCH-L1* Ubiquitin C-terminal hydrolase L1, *CIN* Critical illness neuropathy, *CIM* Critical illness myopathy, *NI* not informed

and pain ($p = 0.029$), as well as between COVID-19 patients and allodynia ($p < 0.05$), compared to control groups.

No consistent results regarding the alteration in the levels of the biomarkers mentioned above were found across longer-term follow-up studies, with some studies demonstrating significant changes (either higher or lower values compared to controls) and others revealing no meaningful differences among comparisons [34, 35, 42, 45–48, 52].

The overall methodological quality of the studies was judged as low to moderate, with 12 (34%) studies presenting at least one poorly conducted and reported domain and nine (26%) with some methodological concerns. Nine papers (26%) were judged as high quality. The factors that most influenced the decrease in score refer to patient selection (including a low number of samples of patients, lack of detailed information on neurological comorbidities, or eventual recurrence of COVID-19). Some studies did not include patients without COVID-19 in the control group or were not compared with groups with similar exposure to COVID-19 or other neurological disorders. Studies with follow-up shorter than 28 days (acute phase) and with single sample collection per patient were also classified as low quality considering the range of time for SARS-CoV-2 negative results, postviral clinical scenario, and reduction of the inflammatory response that occurs in the acute phase, which involves increased cytokines and other circulating markers that also trigger damage to the CNS and PNS (complete assessment is available in Online Resource 3).

Figure 2 illustrates the neurochemical findings in the blood and CSF of neuroCOVID patients, with the appearance of markers involved in the structure, support, and maintenance of neurons and other cells in the CNS and PNS. The evidence gap map summarizing the study's results and methodological quality is shown in Table 3**.**

Discussion

This updated systematic review with evidence gap mapping synthesized the data from 35 observational studies on neurological complications from COVID-19. It highlighted nine specific biomarkers of BBB disruption and neuronal damage, whose increase may be associated with disease severity in the acute phase.

With advancements in laboratory testing technology, there has been a corresponding improvement in identifying and monitoring specific biomarkers. These biomarkers, measurable changes in biological samples, such as cells, biochemistry, or molecules, indicate the presence, progression, and response to COVID-19 or treatment. This information is especially useful in managing patients with neurological sequelae or accelerated progression of neurodegenerative disorders since specific brain regions show a particular susceptibility to SARS-CoV-2 infection [63–67].

Although most of the studies included in this review (over 60%) are prospective cohort studies and some were multicenter, methodological flaws, including scarce information on patients and lack of a control group or comparator, in addition to the between-studies heterogeneity (e.g., sample size, different populations [country, disease characteristic]), require caution when translating findings to practice and may not reflect all groups of individuals exposed to COVID-19. Prudencio et al. (2021) also highlighted the need to track biomarkers longitudinally and measure the neurological impact of COVID-19 and possible risk factors in long-term studies [56]. Most studies have a short follow-up period and a limited methodological design. While this is understandable, given the urgency of the COVID-19 pandemic context, it may affect the ability of these studies to accurately predict the risks and events associated with increased neurological

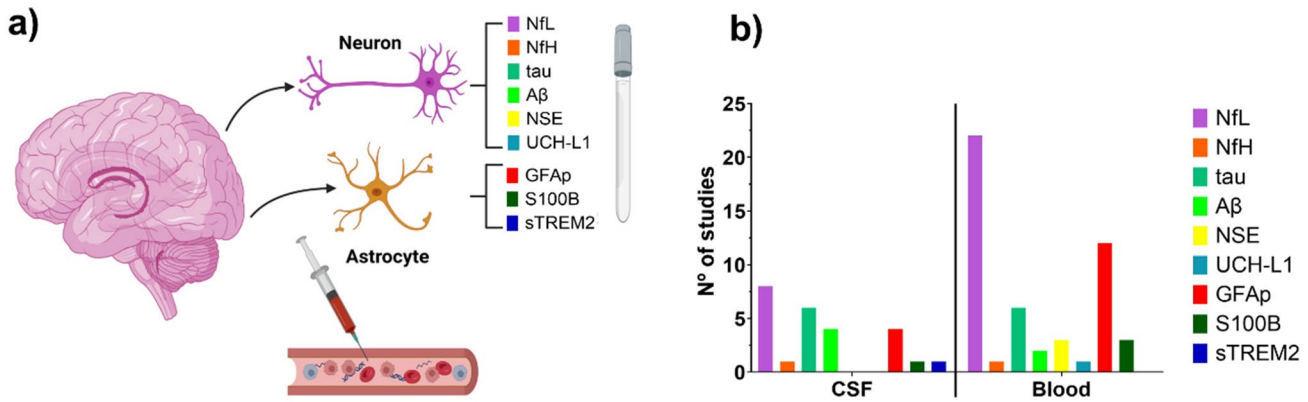
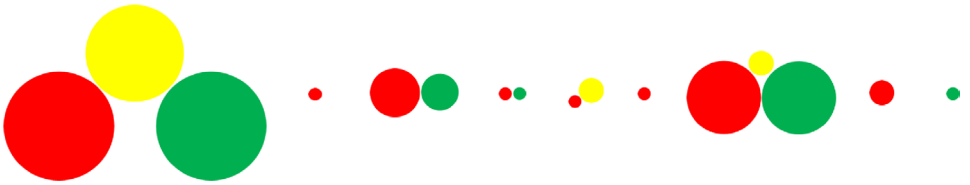


Fig. 2 Graphical summary of findings. **a** Illustration of neurological biomarkers identified**; b** number of included studies per biomarker, according to the sample type. *NfL* neurofilament light chain, *NfH* neurofilament heavy chain, *Aβ* amyloid beta, *NSE* neuron-specific enolase, *UCH-L1* ubiquitin C-terminal hydrolase L1, *GFAP* glial fibrillary acidic protein, *S100B* S100 calcium-binding protein B, *sTREM2* soluble triggering receptor expressed on myeloid cells 2

Table 3 Evidence gap map of the included observational studies (case−control, cohort, cross-sectional, n = 30)

Biomarker	NfL	NfH	Tau	Aβ	NSE	UCH-L1	GFAP	S100B	sTREM2
Correlations with any neurological event ($p<0.05$)	↑↑↑↑↑↑↑↑ ↑↑↑↑↑↑↑↑	–	↑↑↑	–	↑	↑	↑	↑↑	↑
Methodological quality									

The size of each circle is proportional to the number of papers that identified each biomarker (large circle = 9; small = 1). Green circle: high methodological quality; yellow, moderate; red, low/poor quality.; ↑ represents each study included that presents significant correlations ($p < 0.05$).

NfL neurofilament light chain, *NfH* neurofilament heavy chain, *Aβ* amyloid beta, *NSE* neuron-specific enolase, *UCH-L1* ubiquitin C-terminal hydrolase L1, *GFAP* glial fibrillary acidic protein, *S100B* S100 calcium-binding protein B, *sTREM2* soluble triggering receptor expressed on myeloid cells 2.

damage over time. This is particularly important during the subacute to chronic phases of the disease, as the acute phase already has a higher level of overall inflammation (typically occurring in the first few weeks after infection). Nonetheless, neurological biomarkers of CNS immune activation and neuroaxonal injury appear without signs of cytokine storm and direct viral invasion [42, 46].

Among the nine specific neurological biomarkers mapped in our review, NfL has previously been related to demyelination processes resulting from axonal damage and tracked in other CNS and PNS pathologies, such as multiple sclerosis and AD. Similar to tau protein, it can also be increased in other damage situations, such as cerebral ischemia, anesthesia, and surgical procedures [68–70]. Similarly, GFAP proteins are usually released in the dysregulation of microglial homeostasis, in the case of neuroinflammation and neurodegeneration, related to tissue healing processes [71, 72]. Some studies have not found a link between particular biomarkers and neurological symptoms in COVID-19, suggesting that this may be age-related, where older patients are more likely to have comorbidities and experience more severe symptoms. However, most authors have noted a significant increase in NfL and GFAP, and the levels of these biomarkers have been found to correspond with the severity of COVID-19, particularly during the acute phase when systemic inflammation is at its worst.

A previous systematic review performed in 2022 on biomarkers for long COVID (i.e., postacute sequelae of COVID-19; persistent symptoms for one or more months after infection) similarly demonstrated that in addition to cytokines and other biochemical markers, such as Il-6, CRP, and TNF-α (usually associated with severe systemic inflammation, leukocyte trafficking, cytokine storm, and tissue necroptosis), neurological factors, especially NfL and GFAP, are directly associated with COVID-19 neurological manifestations, including headaches and persistent neuropathic pain [27]. Peluso et al. (2022) [54] additionally reported that serum levels of these biomarkers are correlated with cytokines, which may indirectly induce immune cells and activate detrimental neuroinflammation. Another systematic review of CSF analysis found nonspecific inflammatory abnormalities frequently reported in patients (> 85% of cases) with COVID-19 CNS syndromes (stroke, encephalitis, encephalopathy, headache, inflammatory syndromes, seizure) as well as increased neurodegeneration CSF biomarkers, especially NfL, GFAP, and tau protein (71, 18, and 36%, respectively) [73]. Our study also highlights evidence of increased tau and Aβ protein levels in CSF patients with consistent signs of the prodromal phase of AD and parkinsonism after encephalitis [27, 29]. Furthermore, other less-known biomarkers found in our review, such as S100B and NSE, related to rapid neuronal injury extent, may play a complementary role in neurological manifestations that should be further investigated [20, 74–76]. Although the functions of UCH-L1 are not yet well elucidated, the absence of this marker is associated with the induction of neurodegenerative processes, as its enzymatic activity as a hydrolase and ligase can interact with proteins such as Aβ, promoting their accumulation and synaptic dysfunction [77].

Patients with severe cases who require ICU hospitalization in the acute phase of COVID-19 are more likely to experience long-term neurological impairments and neuropsychological issues. However, beyond the response to viral invasion and the associated damage, other conditions can lead to these events, such as (i) cerebral hypoxemia following prolonged hypoxia during episodes of acute respiratory

distress, (ii) complications related to disseminated intravascular coagulation (DIC) that can result in stroke, and (iii) critical illness neuropathy (CIN) and critical illness myopathy (CIM) acquired in the ICU, associated with prolonged ventilation, muscular weakness, systemic inflammation and organ failure during extended hospital stays. Moreover, alterations in mental state, such as delirium and encephalopathy, can occur independently of the cause of admission and may be linked to other factors, such as sedation and adverse events related to medications administered during hospitalization [45, 78, 79]. Nonetheless, in a systematic review conducted by Antony and Haneef [80], a distinctive pattern of involvement in the frontal region of the brain was observed in COVID-19 patients, as evidenced by electroencephalogram (EEG) findings, and it was considered a potential biomarker for encephalopathy resulting from SARS-CoV-2 infection.

The development and the implementation in routine practice of a panel of biomarkers, including a core set of cytokines/biochemical markers (e.g., interferons, CRP, TNF-α) and other specific markers, such as NfL, GFAP, and tau protein, may effectively detect neurological manifestations early in COVID-19 patients. Moreover, it may serve to assess the risk of developing other neurodegenerative CNS and PNS disorders, including AD and Parkinson's disease. This may change clinical practices toward a further differential diagnosis of neurological diseases, which should be integrated with patient-centered care (including the patient's clinical history and tailored treatments). Previous attempts in this field were related to developing cytokines (of immune paralysis degree, inflammatory response, and endothelial dysfunction), biochemical parameters, and N protein peptide panels for early-stage COVID-19 patients at hospital admission or predicting fatal infections [81–83].

Although we were able to provide a map of neurological biomarkers potentially associated with COVID-19, which could guide clinicians during the development of a core set of both serum and CSF diagnostic and prognostic markers to monitor COVID-19 in practice, our study has some limitations. No quantitative analyses were possible, given the heterogeneity of data from different study designs and the lack of enough studies properly reporting biomarker measurements. Moreover, studies were not sufficiently robust due to the relatively small number of participants. This may contribute to selective bias, loss of information, and impaired evidence gathering on the impact of biomarkers in different populations. It is important to note that other confounding factors, such as patient comorbidities, SARS-CoV-2 variants, and vaccination, also share similar mechanisms involving inflammation and could influence biomarker levels [12, 84, 85]. Nevertheless, although the results are only exploratory, a systematic and critical review process was followed in this study. The data synthesized using an evidence map may support the development of further research in this field—especially regarding the most common biomarkers. We used the NOS tool to assess the studies' methodological quality, as this is a validated and reliable tool. Nonetheless, other approaches may produce similar results. It should be noted that the studies' findings and conclusions were considered as presented by the authors, meaning that evidence may not be immediately transposed to different scenarios/settings and geographical regions. For these reasons, further well-designed and well-reported longitudinal studies (with at least one month of follow-up) on neurological biomarker expression (a minimum set including NfL, GFAP, and tau protein) among COVID-19 patients should be performed to enable understanding of the causal relationship between disease symptoms (both in acute and in long-term phases) and neuroinflammation pathways.

Conclusions

This systematic review mapped nine specific biomarkers, NfL, NfH, GFAP, tau, Aβ, S100B, NSE, UCH-L1, and sTREM2, potentially related to neurological damage in COVID-19 patients. Further well-designed longitudinal studies investigating these biological markers (especially NfL, GFAP, and tau) as prognostic and therapeutic targets should be performed to enable their use as neuroaxonal damage and neuroinflammation trackers in clinical practice for both COVID-19 and other CNS and PNS disorders.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00415-023-12090-6.

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Data availability Search strategy, quality assessment, and the list of excluded articles data, are available in supplementary material. Additional data will be made available upon request.

Declarations

Conflicts of interest The authors declare no conflicts of interest.

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