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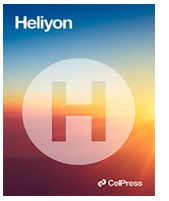

Research article

Cerebellitis following COVID-19 infection: A case-based systematic review and pooled analysis

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ABSTRACT

Background: The COVID-19 pandemic has been linked to neurological complications, including Cerebellitis. This study aims to investigate the clinical features, and consequences of Cerebellitis following COVID-19 infection, informing medical management strategies.
Methods: A systematic search was conducted through PubMed, Web of Science, Embase, ProQuest, and Cochrane databases from January 2018 to September 12, 2023, on cases post-COVID-19. Demographics, clinical characteristics, and diagnostic techniques were analyzed using descriptive statistics. Chi-Square tests assessed associations between diagnoses and treatments, with visualizations including heatmaps and scatter plots.
Results: After the final Screening, the analysis of 18 cases revealed Cerebellitis post-COVID-19 spanned 9 countries, predominantly from the USA (27.8 %), with a mean patient age of 40.1 years (±24.6). Males comprised 94.4 % of cases. Common underlying conditions included hypertension (22.2 %) and diabetes (11.1 %). Neurological symptoms presented on average 15.15 ± 12.7 days post-COVID-19 infection. A moderate negative correlation ($r = -0.358$) was observed between age and symptom onset. Blood and CSF biomarkers showed weak correlations with symptom onset intervals. Treatment efficacy varied, with most cases achieving symptom-free outcomes. The Chi-Square test for diagnosis-treatment associations yielded a p-value of 0.089, and for follow-up outcomes, a p-value of 0.283, indicating no significant statistical associations.
Conclusion: This systematic review highlights increased reports of Cerebellitis in males in their fourth decade of life, with the highest comorbidities being vascular diseases. Marker assessments show a decrease in CSF protein in half of patients, along with complete recovery following combination treatment with antivirals and steroids in acute Cerebellitis.

1. Introduction

Coronavirus disease 2019 (COVID-19) was a global pandemic that spread rapidly since December 2019, with population flow and close human contact playing a significant role in its transmission [1]. The prevalence of COVID-19 varies among countries and is

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List of abbreviations

AIDP	Acute Inflammatory Demyelinating Polyneuropathy
BBB	Blood-Brain Barrier
CNS	Central Nervous System
COVID-19	Coronavirus Disease 2019
CRP	C-Reactive Protein
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CXR	Chest X-Ray
DPP4	Dipeptidyl Peptidase-4
EEG	Electroencephalogram
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
GAD	Glutamic Acid Decarboxylase
GBS	Guillain-Barré Syndrome
GFAP	Glial Fibrillary Acidic Protein
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IL:	Interleukin; IVIg: Intravenous Immunoglobulin
JBI	Joanna Briggs Institute
MMP-9	Matrix Metalloproteinase-9
MIS-C:	Multisystem Inflammatory Syndrome in Children
MRI	Magnetic Resonance Imaging
NfL:	Neurofilament Light Chain Protein
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RICP	Raised Intracranial Pressure
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SPECT	Single-Photon Emission Computed Tomography
TNF-α:	Tumor Necrosis Factor Alpha
TPE	Therapeutic Plasma Exchange

influenced by economic, demographic, geostrategic, and political factors [2]. In addition to non-specific systemic symptoms including disorientation, weakness, and altered taste and smell perception, this virus initially induced respiratory symptoms like fever (83 %), cough (82 %), and shortness of breath (31 %). Later on, it resulted in serious respiratory problems and multi-organ involvement. Approximately 36 % of afflicted patients also had symptoms indicating involvement of the central or peripheral nervous systems [3,4].

Acute cerebellar ataxia and acute cerebellitis denote a phenomenon marked by cerebellar inflammation occurring near infections or vaccinations. This condition is generally benign and manifests as sudden trunk and gait ataxia, sometimes accompanied by appendicular ataxia, nystagmus, dysarthria, and hypotonia. However, it typically resolves completely, carrying a favorable long-term outlook [5]. Neurological manifestations of COVID-19, including Cerebellitis, are associated with marked immune and microglial activation in the central nervous system (CNS) [6]. Studies have shown that SARS-CoV2, the virus causing COVID-19, can infect the cerebellum through hematogenous or transneuronal routes, affecting receptors such as angiotensin-converting enzyme-2 (ACE2), Dipeptidyl peptidase-4 (DPP4), and neuropilin-1(7). The clinical presentation of cerebellitis can vary, with mild forms causing mild ataxic symptoms, while fulminant forms can lead to increased intracranial pressure and herniation of the cerebellar tonsils [8]. Although direct viral invasion of the CNS is not confirmed, neuroinflammation plays a significant role in cerebrovascular disease associated with COVID-19(9).

Post-COVID-19 Cerebellitis can result in various complications such as thrombosis, microbleed, hemorrhage, stroke, autoantibody production, ataxia, and widespread inflammation. These effects can exacerbate the multiorgan impact of the virus and should be considered in disease prognosis [7]. Also, this pathogen manifests as a combination of neurological conditions including cerebellitis, transverse myelitis, and Guillain-Barré syndrome (GBS) [10].

Cerebellitis can be diagnosed using brain MRI, which is the preferred imaging modality for this condition [11]. The imaging findings in acute cerebellitis can vary, but bilateral diffuse hemispheric abnormalities are the most common presentation [12]. In some cases, there may be simultaneous involvement of both hemispheres and the vermis [11]. MRI can also detect transient abnormalities before clinical manifestations of cerebellitis appear. Additionally, MRI findings can help differentiate between infectious and immune-related acute cerebellitis. As T2-FLAIR hyperintense signal in the brainstem and supratentorial brain may indicate immune-related cerebellitis, while downward herniation may indicate infectious cerebellitis [13].

Treatment for cerebellitis depends on the underlying cause and severity of the condition. In cases of cerebellar edema and hydrocephalus, treatment with steroids, such as dexamethasone, is recommended [14]. Neurosurgical intervention, such as decompressive craniectomy, may be necessary to prevent brain herniation in cases of progressive cerebellar swelling [15]. However, other

precise treatment methods such as intravenous immunoglobulin, antiviral agents, and antimicrobial therapy can also be used as alternatives [16].

To our knowledge, this is the first systematic review and pooled analysis written on cerebellitis post-COVID-19 infection with clinical and therapeutic considerations. We comprehensively reviewed the demographic findings of studies in addition to various imaging results and serum and CSF tests, symptoms, and treatment performed on the patients, in addition to the qualitative evaluation of each study, as a conclusion.

2. Methods

This systematic review follows the checklist's Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines design [17].

2.1. Search strategy

We systematically searched five electronic databases (PubMed, Web of Science, Embase, ProQuest and Cochrane) from January 2018 to September 12, 2023. Our search strategy included the: ("COVID-19" OR "COVID 19" OR "COVID19" OR "2019-nCoV" OR "2019 nCoV" OR "SARS-CoV-2" OR "SARS CoV 2" OR "Coronavirus" OR "severe acute respiratory syndrome" OR "SARS") AND ("Cerebell*"). EndNote X9 (Clarivate Analytics) was used to collect, manage, and identify duplicate citations. Additional articles were identified by searching the reference lists of all included studies as well as review articles identified in the screening process. The search query specific to each database is available in the Supplement (Table S1).

2.2. Eligibility criteria

All Case reports and Case series reported.

- Development of Cerebellitis after COVID-19 infection,
- Brain Imaging representing Cerebellitis after COVID-19 infection,
- Cerebellar ataxia, or cerebellar syndrome with Brain imaging representing Cerebellitis,
- Confirmed diagnosis of COVID-19 (e.g., nasopharyngeal swab and RT-PCR) and/or past medical history of confirmed COVID-19 diagnosis, were eligible to include in our study.

All studies which represent.

- Neurological Presentations after COVID-19 Vaccination,
- Non-English language studies,
- in-vivo and in-vitro studies,
- Animal studies,
- Autopsy study,
- Medical history showing Cerebellitis before COVID-19 infection,
- Cerebellar ataxia complication after COVID-19 without Brain imaging representing Cerebellitis,
- Other types of studies (narrative, systematic, meta-analysis, original articles), were excluded.

2.3. Study selection

Title and Abstract screening by two independent reviewers (S.N. and D.N.D.) resulted in the exclusion of papers that weren't relevant. The remaining papers' full texts were then evaluated by the same reviewers to determine if they should be included in our study. Discrepancies that were present were resolved following consultations with a third reviewer (N.E.).

2.4. Data extraction

The same investigators (S.N. and D.N.D.) extracted the following information based on a predesigned datasheet: Study, Country, Type of report, Gender, Age, PMH (Past Medical History), PDH (Past Drug History), COVID-19 Detection, Neurological Signs and Symptoms, COVID-to-Neuro Symptom Interval, Blood/CSF analysis, CXR/chest CT, Brain Imaging, Neurological diagnosis/Dx, Treatment, Follow-up Outcome (Tables 1 and 2). Any disagreement surrounding the screening process or data extraction was resolved by consultation with the third reviewer (N.E.).

2.5. Quality assessments

Two reviewers (S.N. and D.N.D.) independently evaluated the included studies' quality using the Joanna Briggs Institute (JBI) Critical Appraisal tools for Case Report [18]. The answers to the questions include the alternatives "Yes", "No", "Unclear" and "Not Applicable" and are divided into three categories: high quality (Yes answer to more than 70 % of questions), medium (Yes answer to

Table 1
Summary of Patients' Demographic Information and COVID-19 characteristics.

Study	Country	Type of report	Gender	Age	PMH	PDH	COVID-19 Detection	Neurological Signs and Symptoms	COVID-to-Neuro Symptom Interval
Konstantina Yiannopoulou et al., 2023 [1]	Greece	Case report	Male	74	Cardiac surgery	Warfarin	-Blood and tracheobronchial aspirate RT-PCR: Positive -CSF RT-PCR: Negative	Confusion, left side facial numbness, episodic arrhythmic rest tremor of the right hand, persistent paranoid ideation characterized by an extreme feeling of threat, visual and auditory hallucinations → myoclonic jerks of the four limbs, trunk, and face (after admission) → multiple generalized convulsions of prolonged duration nonresponsive to anticonvulsive treatment	14 days
Kenta Osaw et al., 2022 [2]	Japan	Case report	Male	52	-Hypertension -Hyperlipidemia	N.A.	-Nasal swab: Positive -CFS SARS-CoV-2 RT-PCR: negative	mild jerky involuntary movements in all limbs along with difficulty in walking and writing	16 days
Hernan Nicolas Lemus et al., 2022 [3]	USA	Case report	Female	54	-CVID -UTIs -Pneumonia -Breast cancer	Tamoxifen, 40 g IVIg, metoprolol and hydrochlorothiazide	-Nasopharyngeal swab: Positive -CFS SARS-CoV-2 RT-PCR: negative	marked dysmetria and intermittent myoclonus in all of her extremities, prominent truncal unsteadiness, hyperreflexia in the upper extremities, and a wide-based ataxic gait	N.A.
Eric K. H. Chow et al., 2022 [4]	USA	Case report	Male	3	N.A.	N.A.	Rapid at-home antigen test: positive	mild headache	9 weeks
Nihal Akçay et al., 2022 [5]	Turkey	Case report	Male	3	NL	N.A.	-Blood SARS-CoV-2 antibody: Positive -CFS SARS-CoV-2 RT-PCR: negative	unconscious and disoriented, GCS = 11 (E3, V4, M4)	N.A.
Dace Ziemele et al., 2021 [6]	Latvia	Case report	Male	70	-Hypertension -Heart failure -Diabetes -ICH -Ischemic cerebral stroke	N.A	-Nasopharyngeal swab: Positive -CFS SARS-CoV-2 RT-PCR: negative	severe headache, generalized tonic-clonic seizure → GCS = 3/15	N.A.
Sanjiv Sharma et al., 2021 [7]	India	Case report	Male	12	N.A.	N.A.	Nasopharyngeal swab: Positive	headache and altered mental status	15 days
Sanjiv Sharma et al., 2021 [7]	India	Case report	Male	10	N.A.	N.A.	Nasopharyngeal swab: Positive	severe occipital headache, mild left-sided dysmetria, dysdiadochokinesia, and gait ataxia	N.A.
Perrin, P et al., 2021 [8]	France	Case series	Male	64	-Hypertension -Diabetes -Dyslipidemia	N.A.	Nasopharyngeal swab: Positive	Confusion, agitation, tremor, cerebellar ataxia, aphasia, apraxia,	8 days

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Table 1 (*continued*)

Study	Country	Type of report	Gender	Age	PMH	PDH	COVID-19 Detection	Neurological Signs and Symptoms	COVID-to-Neuro Symptom Interval
					-Sleep apnea -Diabetic nephropathy -Peritoneal dialysis -Hypothyroidism			pyramidal syndrome, coma, dysautonomia	
Moreno-Escobar, M. C. et al., 2021 [9]	USA	Case report	Male	24	N.A.	N.A.	-Nasopharyngeal RT-PCR: Positive -CFS SARS-CoV-2 RT-PCR: negative	severe headache, dysarthria, vertigo, photophobia, and mild encephalopathy, moderate bradyphrenia	14 days
Malayala, S. V. et al., 2021 [10]	USA	Case report	Male	63	-Asthma -Hypertension -Atrial fibrillation -Hypothyroidism -Rheumatoid arthritis -Sleep apnea	Apixaban, methotrexate, flecainide, metoprolol	N.A. (just mentioned positive)	Confusion	3 days
Afreen Khan et al., 2021 [11]	India	Case Series	Male	11	N.A.	N.A.	Serum RT-PCR: Positive	generalized tonic-clonic seizures, delirious, horizontal nystagmus, dysarthria, nuchal rigidity, features of raised ICT and shock	3 days
Ahmed Serkan Emekli et al., 2021 [12]	Turkey	Case report	Male	54	Hypertension	Candesartan	Nasopharyngeal RT-PCR: Positive	Disoriented, dysarthria and a convergence spasm in his ophthalmologic examination,	14 days
Dumitru Ciolac et al., 2021 [13]	Moldova	Case report	Male	44	Unremarkable	N.A.	-Naso- and oropharyngeal swabs: Positive -CFS SARS-CoV-2 RT-PCR: negative	severe headache, followed by altered mental status (confusion, disorientation, amnesia), GCS = 13 (E3/V4/M6), nuchal rigidity, and positive bilateral Kernig sign	7 days
Ülkü Türk Börü et al., 2021 [14]	Turkey	Case report	Male	42	Unremarkable	Favipiravir (1200 mg/day for five days)	Serum RT-PCR: Positive	Nausea, vomiting, diplopia, ataxia, headache, urinary retention, excessive sweating, weakness in the legs, inability to walk without help, lethargy, right sixth cranial nerve involvement, symmetrical distal and proximal weakness (4/5) of the lower extremities, mildly decreased deep tendon reflexes, dysmetria, orthostatic hypotension, no sensory deficit	13 days

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Table 1 (*continued*)

Study	Country	Type of report	Gender	Age	PMH	PDH	COVID-19 Detection	Neurological Signs and Symptoms	COVID-to-Neuro Symptom Interval
Stephan Grimaldi et al., 2020 [15]	France	Case report	Male	72	N.A.	N.A.	-Nasopharyngeal swab test: Positive -CFS SARS-CoV-2 RT-PCR: negative	Action tremor, ataxia, dysarthria, upper-limb dysmetria, spontaneous diffuse myoclonus	17 days
Nima Fadakar et al., 2020 [16]	Iran	Case report	Male	47	Unremarkable	N.A.	-Oropharyngeal and nasopharyngeal PCR: Positive -CFS SARS-CoV-2 RT-PCR: Positive	progressive vertigo, headache, and ataxia (7 days before admission), ataxic gait and mild dysarthria, impaired tandem gait, wide-based and ataxic gait, head titubation, mild truncal swaying while sitting on a bed, irregular rapid alternating hand movements, mild dysarthria, and dysmetria in both upper and lower extremities in finger to nose and heel to shin, instability of visual fixation in the primary position, saccadic pursuit (saccade superimposed on a pursuit eye movement), loss of optokinetic nystagmus, impaired vestibular suppression response, and end gaze rotational nystagmus	10 days (on the admission)
Sean Byrnes et al., 2020 [17]	USA	Case report	Male	36	NL	intramuscular midazolam before arrival	Nasopharyngeal RT-PCR: Positive	obtunded, with slurred speech and pinpoint pupils (probably due to midazolam injection before arrival), intermittent rapid, irregular, and non-purposeful movements of the bilateral upper extremities	Unknown

Abbreviations: CSF: Cerebrospinal Fluid; CVID: Common Variable Immunodeficiency; GCS: Glasgow Coma Scale; ICH: Intracranial Hemorrhage; ICT: Intracranial Tension; IVIg: Intravenous Immunoglobulin; NL: Normal; N.A.: Not Available; PCR: Polymerase Chain Reaction; PMH: Past Medical History; PDH: Presenting Diagnosis History; RT-PCR: Reverse Transcription Polymerase Chain Reaction; UTI: Urinary Tract Infection.

Table 2
Summary of serum and CSF markers, Imaging, Diagnosis, treatment, and outcomes.

Study	Gender	Age	Blood/CSF analysis	CXR/chest CT	Brain Imaging	Neurological diagnosis/Dx	Treatment	Follow-up Outcome
Konstantina Yiannopoulou et al., 2023 [1]	Male	74	**Blood**: Lymphocyte: Elevated **CSF:** -Protein: Elevated -Glucose: NL * The CSF of the patient exhibits robust IgG autoreactivity on rat brain sections, determined by indirect immunofluorescence.	**CXR:** reticular and hazy left lower lobe opacities **CT:** small pleural effusions bilaterally, passive or relaxation atelectasis in the dorsal portions of the lower lobes, and ground-glass opacities in areas of both lungs, mainly in the left upper lobe (related to TRALI, During the last days of plasmapheresis)	**CT:** only minor white matter microangiopathy (unremarkable) **MRI:** T2 and fluid-attenuated inversion recovery with hyperintensities on the left hippocampus in coronal sections → bilateral brain hyperintensities on T2-weighted fluid attenuation inversion recovery on the medial temporal lobes. **EEG:** absence of basal rhythm with frequent recording of low-potential bradyarrhythmia, predominantly in the right hemisphere	Autoimmune encephalitis	**During hospitalization:** -Haloperidol -Valproic acid -Lorazepam (2 mg/day IV) -Pulse steroid therapy (1000 mg intravenous methylprednisolone per day) -Cycles of plasmapheresis **After discharge:** -Valproate 500 mg/day -Oral steroid tapering (prednisone per os)	Symptom-free
Kenta Osaw et al., 2022 [2]	Male	52	**CSF:** -WBC: NL -Protein: NL -Glucose: NL	**CT:** bilateral multifocal ground-glass opacities	**MRI:** NL (without contrast) **EEG:** NL **SPECT:** hyper perfusion in the cerebellum and hypoperfusion in the cerebral cortices with frontal lobe predominance	Acute Cerebellitis	-Remdesivir (for 5 days) -Yokukan-san (YKS) extract (7.5 g/day) -Intravenous high-dose methylprednisolone (IVMP, 1 g/day for 3 days) -Benfotiamine (103.74 mg/day) -Pyridoxine hydrochloride (75 mg/day) -Cyanocobalamin (750 μg/day)	Symptom-free
Hernan Nicolas Lemus et al., 2022 [3]	Female	54	**Blood:** -WBC: NL -Lymphocytes: NL -IgG: Decreased -IgA: Decreased -IgM: Decreased	**CT:** NL	**MRI:** symmetric, non-enhancing T2 white matter hyperintensities in the bilateral striatum and inferior cerebellar hemispheres	Acute Cerebellitis	-Methylprednisolone, 1 g IV daily for 5 days -Maintenance IVIg infusion	-Minimal residual spasticity -Walking returned to baseline
Eric K. H. Chow et al., 2022 [4]	Male	3	**Blood:** -WBC: NL -Plt: Decreased **CSF:** -RBC: Elevated -WBC: Elevated	N.A.	**MRI:** vasogenic edema in the left cerebellar hemisphere and vermis with mass effect on the fourth ventricle **CT:** left cerebellar hemorrhagic mass-like lesion with temporal horn dilation indicating early hydrocephalus	Postinfectious hemorrhagic cerebellitis	-Dexamethasone 0.25 mg/kg -External ventricular drain (EVD)	Symptom-free
Nihal Akçay et al., 2022 [5]	Male	3	**Blood:** -BS: Decreased -AST: Elevated -ALT: Elevated -CRP: Elevated	N.A.	**MRI:** NL → symmetrical pathological signal changes in both cerebellar hemispheres **EEG:** NL	MIS-C	**During hospitalization:** -Milrinone (0.5 μg/kg/min) -Adrenaline and noradrenaline	Symptom-free

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Table 2 (*continued*)

				CSF: -Protein: mild Increased -Glucose: Decreased				-Cefotaxime -Vancomycin -Acyclovir -Intravenous immunoglobulin (1 g/kg for 2 days) -High-dose corticosteroids (30 mg/kg for 5 day) followed by a prednisone taper **After discharge:** Prednisone and aspirin (100 mg/day)	
	Dace Ziemele et al., 2021 [6]	Male	70	**Blood:** -WBD: Decreased -RBC: Decreased -Plt: Decreased -IL-6: Elevated -CRP: Elevated -LDH: Elevated -Ferritin = upward trend -LDH = upward trend	**CT:** bilateral pneumonia	**MRI:** edematous changes in both thalami, brain stem, and cerebellar peduncles with microhemorrhages, small auto-necrotic cavities, and restricted diffusion **CT:** NL → edematous changes in the pons **CTA:** NL	Acute necrotizing encephalopathy	-Intubated and referred to the ICU -High-dose glucocorticoids	Died
8	Sanjiv Sharma et al., 2021 [7]	Male	12	**CSF:** -Protein: Decreased -Glucose: NL	N.A.	**MRI:** confluent asymmetric (right > left) hyperintensities involving both cerebellar hemispheres with faint folial enhancement, without restricted diffusion or micro hemorrhages **CT:** ill-defined right cerebellar hemispheric hypodensity with compression of fourth ventricle and resultant obstructive hydrocephalus	Acute cerebellitis	-External ventricular drain (EVD) -Steroids and acyclovir for 14 days	Symptom-free
		Male	10	**CSF:** -Protein: mild Decreased -Glucose: Elevated	N.A.	**MRI:** cerebellar hyperintensities on T2 and fluid-attenuated inversion recovery (FLAIR) without hemorrhages	Acute cerebellitis	-External ventricular drain (EVD) -Steroids and acyclovir for 14 days	Symptom-free
	Perrin, P et al., 2021 [8]	Male	64	**Blood:** -CRP: Elevated -IL-8: NL -LDH: NL	N.A.	**MRI:** FLAIR and DWI white matter hyperintensities in the middle cerebellar peduncles, an acute cytotoxic edema on the posterior left	Acute leukoencephalitis	-Lopinavir-ritonavir -Oxazepam -Corticosteroids -IVIg	Symptom-free

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Table 2 (*continued*)

					frontal lobe **EEG:** global and diffuse signal slowdown → slow bilateral delta elements organized in bursts or predominant opposite bifrontal diversions with bilateral 56 Hz theta band elements			
Moreno-Escobar, M. C. et al., 2021 [9]	Male	24	**Blood:** -BS: Elevated -WBC: Elevated -Lymphocyte: NL -Plt: NL -CRP: NL -Ferritin: NL -LDH: NL -D-dimer: NL **CSF:** -WBC: Elevated -Lymphocyte: Elevated -Protein: Elevated -Glucose: Elevated	**CXR:** unremarkable **CT:** unremarkable	**MRI:** nodular leptomeningeal enhancement along the bilateral cerebellar folia, more pronounced on the left. T2/FLAIR images demonstrated cortical hyperintensity in the areas of leptomeningeal enhancement. Restricted diffusion was seen on diffusion-weighted imaging/apparent diffusion coefficient (DWI/ADC) secondary to cytotoxic edema in these same areas **CT:** NL **CTA:** NL	Acute cerebellitis	-Acyclovir and ceftriaxone (discontinued once the CSF Gram stain, culture, and HSV panel were negative) -Methylprednisolone (1gr/day for 5 days)	Symptom-free
Malayala, S. V. et al., 2021 [10]	Male	63	**Blood:** -CRP: Elevated -Fibrinogen: NL -LDH: NL	**CXR:** NL **CT:** subpleural ground glass infiltrates in the right lower Lobe, and left upper lobes	**MRI:** bilateral cerebellar white matter signal abnormalities extending to bilateral cerebellar peduncles (without contrast) → bilateral brachium pontis lesions implying persistent inflammation in the bilateral anterior inferior cerebellar artery territories (with/without contrast) **CT:** NL	Acute cerebellitis	-Systemic steroids -Intravenous remdesivir -Bronchodilators -*Anti*-pyretics	Symptom-free
Afreen Khan et al., 2021 [11]	Male	11	**Blood:** ESR: Elevated	N.A.	**MRI:** Diffuse cerebellar swelling with T2/FLAIR hyperintensity	MIS-C	-Ceftriaxone and acyclovir -Intravenous fluids and inotropes -Methylprednisolone pulse therapy (30 mg/kg/day for 3 days) -Intravenous immunoglobulin (IVIG) infusion (2 g/kg of body weight single dose) -Mannitol and steroids	Symptom-free

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Table 2 (*continued*)

							(intravenous dexamethasone 0.15 mg/kg/dose six hourly)	
Ahmed Serkan Emekli et al., 2021 [12]	Male	54	**Blood:** Anti-GAD antibody: Elevated **CSF:** -Lymphocytes: NL -Protein: NL -Glucose: NL	**CT:** pneumonic infiltration (asymptomatic pneumonia) → NL	**MRI:** edematous changes and hyperintensities in the cerebellar cortex in T2-weighted and FLAIR images → increasing cerebellar edema	anti-GAD-associated autoimmune cerebellitis	**During Hospitalization:** -Favipiravir with a loading dosage of 1600 mg and maintenance dosage of 600 mg per day -Acetylsalicylic acid 100 mg per day -Paracetamol 1000 mg per day -Methylprednisolone 1 gr/day for 10 days -Intravenous immunoglobulin 0.4 gr/kg/day for 5 days **After discharge:** -Monthly intravenous immunoglobulin and oral methylprednisolone treatment for 3 months -Propranolol (for mild tremor)	-Independent walking -No appendicular/truncal ataxia -Mild upper extremity tremor
Dumitru Ciolac et al., 2021 [13]	Male	44	**Blood:** -WBC: NL -Lymphocyte: Decreased -CRP: Elevated **CSF:** -Lymphocytes = Elevated -Erythrocytes = Elevated	**CXR:** bilateral interstitial pneumonia **CT:** multiple, bilateral ground glass opacities and consolidation with a peripheral and predominantly posterior lung distribution	**MRI:** bilateral, symmetrically distributed lesions within the infra- and supratentorial structures with the predominant involvement of both cerebellar hemispheres and vermis → partial regression of the cerebellar lesions **CT:** NL	Acute necrotizing encephalopathy	-Azithromycin 500 mg once daily -Hydroxychloroquine 400 mg twice daily -Lopinavir/Ritonavir 200 mg/50 mg twice daily -Intravenous methylprednisolone 1000 mg/day, reduced to 500 mg/day after 3 days -Intubated and mechanically ventilated for 3 days -Risperidone 1 mg twice daily	-Discharged with a slight disability -Minor behavioral symptoms
Ülkü Türk Börü et al., 2021 [14]	Male	42	**Blood:** -Lymphocyte: NL -RBC: Elevated -CRP: NL **CSF:**	N.A.	**Brain MRI:** hyperintensities on T2-weighted FLAIR sequences in bilateral middle cerebellar peduncles; no gadolinium enhancement. **Spinal MRI:** short segment	-Cerebellitis -Acute inflammatory demyelinating polyneuropathy	Intravenous methylprednisolone: 500 mg/day for 5 days	Symptom-free

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Table 2 (*continued*)

			-Protein: Elevated -Glucose: NL		patchy transverse myelitis at T11/T12 with mild gadolinium enhancement.	(AIDP) -Transverse myelitis		
Stephan Grimaldi et al., 2020 [15]	Male	72	**Blood:** -Fibrinogen: Elevated -CRP: Elevated -IgG Autoantibody: Elevated **CSF:** -Protein: Elevated -Oligoclonal Banding: Not seen -IgG Autoantibody: Elevated	**CT:** peripheral bilateral ground-glass lesions and consolidative opacities	**MRI:** NL **PET with 18 F-FDG:** putaminal and cerebellum hypermetabolism associated with diffuse cortical hypometabolism, confirmed by whole-brain voxel-based SPM quantification	Autoimmune encephalitis	-Intravenous immunoglobulins: 0.4 g/kg/day for 5 days -Intravenous methylprednisolone: 1 g/day for 5 days -Oral drops of Clonazepam: 0.3 mg three times a day	Symptom-free
Nima Fadakar et al., 2020 [16]	Male	47	**Blood:** -WBC: NL -Lymphocyte: NL -CRP: NL -Ferritin: Elevated **CSF:** -Opening Pressure: 250 mm of H2O - Elevated -WBC: Mild Pleocytosis -Glucose: NL -Protein: Elevated	**CT:** NL	**MRI:** Bilateral cerebellar hemispheres as well as vermis hyperintensities and edema in FLAIR with cortical meningeal enhancement of cerebellum in T1-weighted with gadolinium sequences	Acute Cerebellitis	lopinavir/ritonavir: 400/100 mg twice daily for 14 days	Significant improvement in ataxia and other symptoms
Sean Byrnes et al., 2020 [17]	Male	36	**Blood:** -WBC: NL -Lymphocytes: Decreased -CRP: Mildly Increased -ESR: Mildly Increased -Blood Culture: Negative **CSF:** -WBC: Elevated -Lymphocyte Predominance -Myelin Basic Protein: Increased	**CXR:** NL → hazy opacity in the left lung base	**MRI:** multiple focal enhancing lesions primarily affecting the bilateral medial putamen and left cerebellum **CT:** NL	Encephalopathy	-Vancomycin and ceftriaxone -IVIG 2 g/kg -Solu-Medrol 500 mg IV (for four additional days)	Undergoing therapy

Abbreviations: AIDP: Acute Inflammatory Demyelinating Polyneuropathy; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BS: Blood Sugar; CRP: C-Reactive Protein; CSF: Cerebrospinal Fluid; CT: Computed Tomography; CXR: Chest X-Ray; DWI: Diffusion-Weighted Imaging; EEG: Electroencephalography; ESR: Erythrocyte Sedimentation Rate; FLAIR: Fluid-Attenuated Inversion Recovery; GAD: Glutamic Acid Decarboxylase; HSV: Herpes Simplex Virus; ICU: Intensive Care Unit; IgA: Immunoglobulin A; IgG: Immunoglobulin G; IgM: Immunoglobulin M; IL-6: Interleukin 6; IL-8: Interleukin 8; IV: Intravenous; IVIG: Intravenous Immunoglobulin; LDH: Lactate Dehydrogenase; MRI: Magnetic Resonance Imaging; N.A.: Not Available; NL: Normal; PET: Positron Emission Tomography; Plt: Platelets; RBC: Red Blood Cells; SPM: Statistical Parametric Mapping; SPECT: Single Photon Emission Computed Tomography; TRALI: Transfusion-Related Acute Lung Injury; WBC: White Blood Cells.

50–69 % questions) and low (answer Yes to less than 50 % of questions). The total rank of each study based on the number of "Yes's" has also been calculated (Table S2).

2.6. Outcome definition

The primary objective of this study is to evaluate the range of neurological manifestations in COVID-19 patients with Cerebellitis and identify the most effective treatment modalities that lead to favorable outcomes. The secondary objectives aim to analyze the effectiveness of different treatment strategies in managing patients' conditions, determine the clinical outcomes of patients' post-treatment, and explore any significant associations between specific treatment modalities and patient outcomes using statistical tests such as the Chi-Square test.

2.7. Data analysis

In this study, comprehensive statistical methods were employed to analyze the cases' data effectively. We summarized the patients' basic demographic and clinical characteristics, such as age, gender, and underlying conditions, using measures of central tendency (mean, median) and dispersion (standard deviation, range). The Chi-Square Test assessed the association between categorical variables, specifically neurological diagnosis categories and treatment types. The test results, including the Chi-Square statistic (χ^2), degrees of freedom (dof), and p-value, were reported to determine the significance of these associations. Additionally, heatmaps were generated to visually represent the frequency distribution of treatments across different diagnosis categories, aiding in the identification of patterns and correlations within the data. All statistical analyses were conducted using Python (Version 3.10.12).

3. Results

The initial search yielded 889 articles. After the removal of duplicates, 479 articles remained. Title and abstract screening narrowed this to 77 articles. A full-text review, applying exclusion criteria, reduced this number to 14. Citation reviews of these articles identified 5 additional titles, and 3 of these were included after full-text review. One article reported two cases [19], resulting in 18 cases being selected for final analysis [10,19–34](Fig. 1). The demographic and clinical characteristics of these studies are detailed in Tables 1 and 2

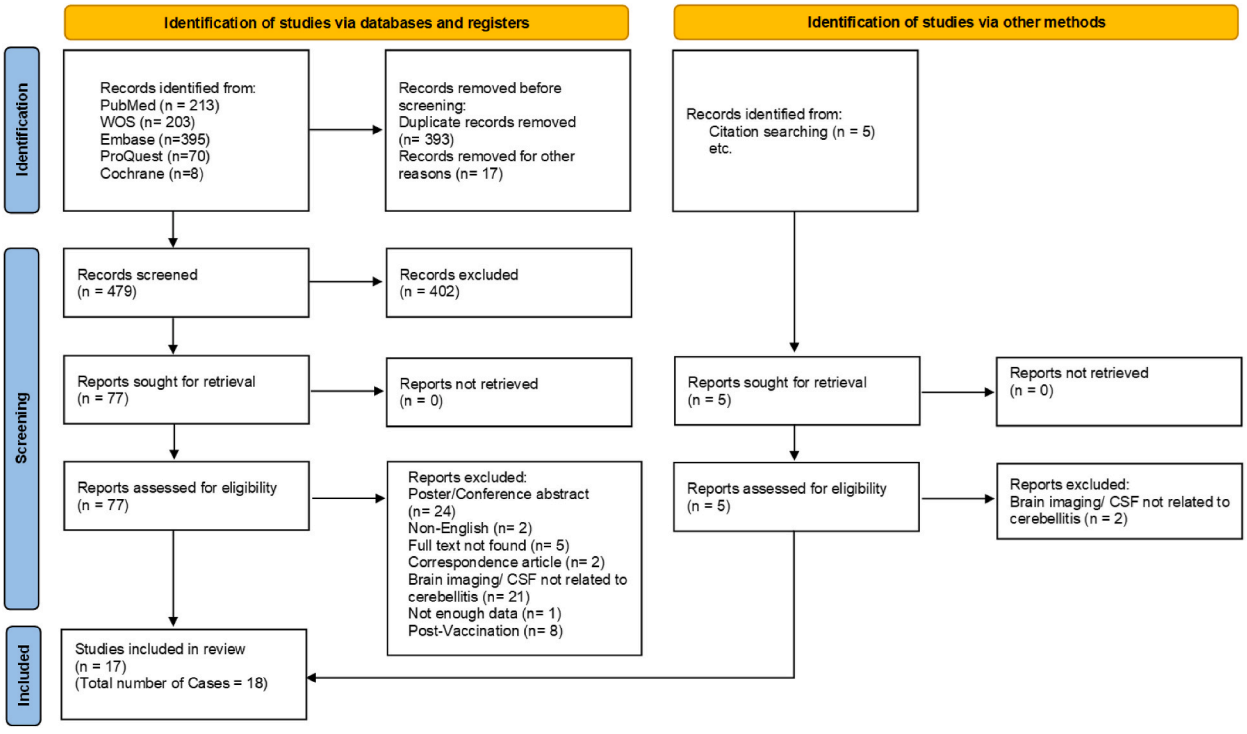

Fig. 1. PRISMA flow diagram depicting the flow of information through the different phases of a systematic review and meta-analysis.

3.1. Demographics, global distribution, and patient profile

The repository of neurological case reports encompasses data from 9 countries. The highest representation comes from the USA, accounting for 5 cases (27.8 %), followed by India and Turkey with 3 cases each (16.7 %), and France with 2 cases (11.1 %). Collectively, these four countries contribute 72.2 % of the total case reports (Fig. 2A). The mean age of the patients is 40.1 years (±24.6), with an age range of 3–74 years (Fig. 2B). There is a predominant representation of male patients, with 17 cases (94.4 %) compared to a single case involving a female patient (5.56 %) (Fig. 2C).

Analysis of patient medical histories reveals that 4 cases (22.22 %) involved a history of vascular disease (hypertension), 2 cases (11.11 %) had underlying heart conditions (cardiac surgery, heart failure), 2 cases (11.11 %) had diabetes, 1 case (5.56 %) involved cancer (breast cancer), and 2 cases (11.11 %) had autoimmune diseases (CVID, rheumatoid arthritis), which progressed to post-COVID-19 cerebritis. Furthermore, previous medications in 3 cases included immunosuppressive drugs (e.g., IVIg, steroids), and 2 cases involved anticoagulants (e.g., Warfarin, Apixaban).

3.2. Diagnostic techniques and neurological symptom onset in COVID-19 patients

Diagnostic methods for COVID-19 in the analyzed patients include Nasopharyngeal swab, tracheobronchial aspirates, bladder tests (antibodies), and CSF RT-PCR. Swab or blood tests yielded positive results in all patients tested; however, CSF RT-PCR was positive in only one patient [33].

Clinical presentations of neurological symptoms were diverse, with many patients exhibiting multiple symptoms. The most prevalent manifestations were confusion and altered mental status, as well as ataxia and coordination issues, each reported in 5 cases (27.8 %). Headache was reported in 4 cases (22.2 %), while seizures and convulsions, along with myoclonus and jerky movements, were noted in 3 cases each (16.7 %). Additionally, the interval between the onset of COVID-19 symptoms and the manifestation of neurological symptoms averaged 15.15 ± 12.7 days, ranging from 3 to 63 days.

In Fig. 3, three visualizations are presented, each offering distinct insights into the onset of neurological symptoms in the context of COVID-19.

A) **Histogram of Days Until Onset of Neurological Symptoms:** This histogram provides a visual representation of the distribution of days elapsed between COVID-19 infection and the onset of neurological symptoms. By showcasing the frequency of occurrences within different time intervals, it offers a comprehensive view of the temporal pattern of symptom onset within the studied population (Fig. 3A).

B) **Scatter Plot of Age versus Days to Neurological Symptoms:** The scatter plot illustrates the relationship between age and the number of days until the onset of neurological symptoms. The Pearson correlation coefficient of −0.358 indicates a moderate negative correlation between age and the time elapsed before neurological symptoms manifest. This suggests that, on average, younger individuals tend to experience neurological symptoms sooner after contracting COVID-19 compared to older individuals (Fig. 3B).

C) **Box Plot Comparing Days to Neurological Symptoms Across Various Neurological Diagnoses:** The box plot allows for a comparison of the distribution of days until the onset of neurological symptoms across different neurological diagnoses. The Kruskal-Wallis test result of 3.0569 and a p-value of 0.5483 suggest that there are no significant differences in the time taken for neurological symptoms to appear among the various neurological diagnoses studied. This indicates that the onset of neurological symptoms does not significantly vary across different types of neurological conditions in the context of COVID-19 infection (Fig. 3C).

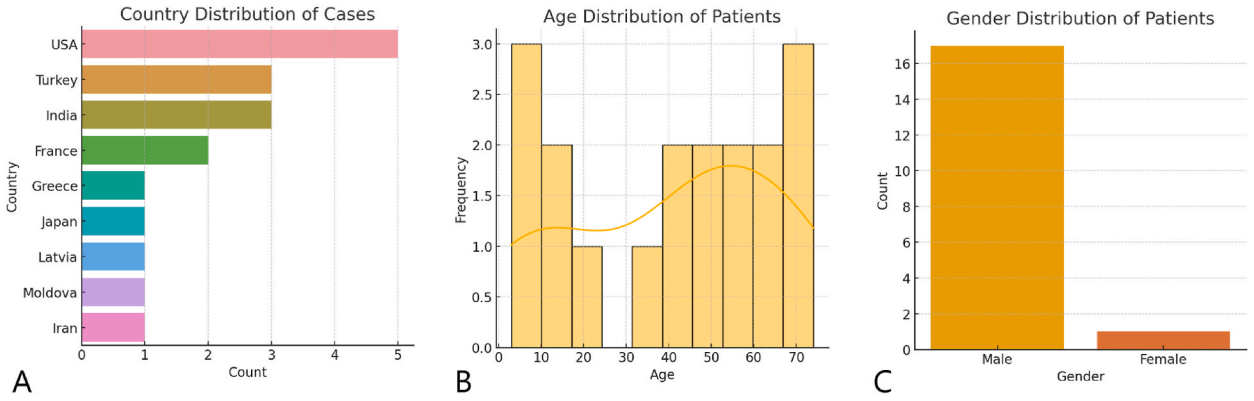

Fig. 2. Patient demographics. **(A)** Country distribution; **(B)** age distribution; **(C)** gender distribution of patients.

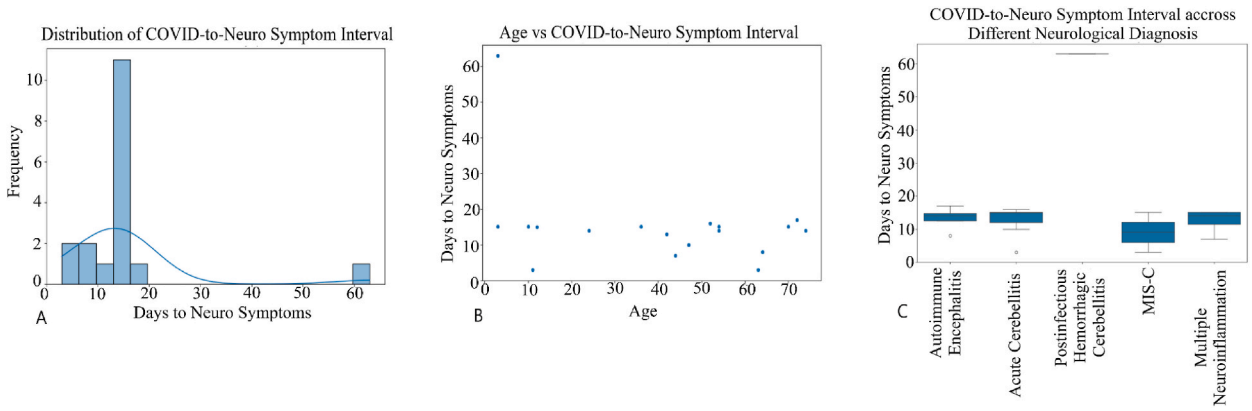

Fig. 3. Distribution and relationship of COVID-19 onset across age groups and different neurological diagnoses. (A): Histogram showing the distribution of days from COVID-19 onset to the appearance of neurological symptoms; **(B)**: Scatter plot illustrating the relationship between age and the interval from COVID-19 onset to neurological symptoms; **(C)**: Box plots comparing the COVID-to-neurological symptom interval across various neurological diagnoses.
MIS-C: Multisystem Inflammatory Syndrome in Children.

3.3. Analysis of blood and CSF markers in COVID-19 patients with neurological symptoms

This analysis focuses on the relationship between elevated lymphocyte levels in blood, elevated protein levels in CSF, and the interval from COVID-19 diagnosis to the manifestation of neurological symptoms. Additionally, we examined the variation of these markers across different neurological diagnoses.

Distribution of Blood and CSF biomarkers in patients represents that blood lymphocyte count was normal in most cases (72.22 %), elevated in 3 cases (16.67 %), and decreased in just 2 cases (11.11 %). Blood CRP was increased in 6 cases (33.3 %) and measured in the normal range in 3 cases (16.7 %). Moreover, CSF protein count represents degrees of elevation in nearly 50 % of cases, which indicates blood-brain barrier disruption or inflammation. Additionally, its glucose state was mostly in the normal range (61.11 %), besides minor fluctuation in a few cases (Fig. 4 A – D).

3.3.1. Correlation and comparative analysis

To quantify the blood and CSF analysis results, we numerically encoded the categorical variables for lymphocyte levels in blood (Elevated = 1, Normal = 0, Decreased = −1) and protein levels in CSF (Elevated = 1, Normal = 0, Decreased = −1, Increased = 1). The

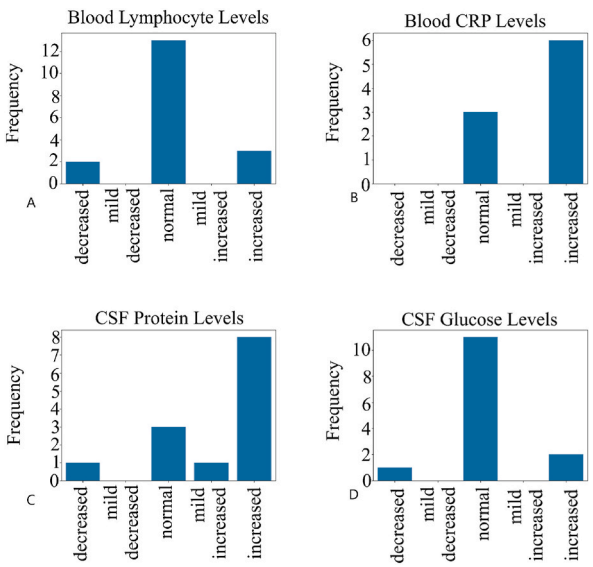

Fig. 4. Summary of blood and cerebrospinal fluid (CSF) biomarker levels in patients with neurological symptoms post-COVID-19. (A): Blood lymphocyte levels among patients; **(B)**: Blood CRP levels in the studied population; **(C)**: CSF protein levels among patients; **(D)**: CSF glucose levels in the cohort.
CSF: Cerebrospinal Fluid; NL: Normal.

COVID-to-neuro symptom interval was calculated for each patient, and missing values were imputed with the mean interval.

A Pearson correlation coefficient of 0.31 was observed between age and the COVID-to-neuro symptom interval, indicating a moderate positive correlation. This suggests that as age increases, the duration between COVID-19 infection and the onset of neurological symptoms tends to increase moderately.

Furthermore, correlations between blood lymphocyte levels and the COVID-to-neuro symptom interval, as well as between CSF protein levels and the same interval, were both found to be weak ($r = 0.11$ and $r = 0.14$ respectively). These weak correlations suggest that variations in blood lymphocyte and CSF protein levels have limited predictive value in determining the duration between COVID-19 infection and the onset of neurological symptoms (Fig. 5A and B).

Subsequently, the Kruskal-Wallis test was employed to compare blood lymphocyte and CSF protein levels across different neurological diagnoses. The results revealed no significant differences in lymphocyte levels ($p = 0.42$) or CSF protein levels ($p = 0.23$) among the diagnostic categories. This indicates that the variations in these biomarkers are not strongly associated with specific neurological diagnoses in the context of COVID-19-related neurological symptoms.

These findings suggest that while age demonstrates a moderate positive correlation with the COVID-to-neuro symptom interval, blood lymphocyte and CSF protein levels exhibit weak correlations. Additionally, these biomarkers do not significantly differ across various neurological diagnoses, as evidenced by the Kruskal-Wallis test results. These insights contribute to our understanding of the temporal dynamics and biomarker associations in COVID-19-related neurological manifestations.

3.4. Imaging findings

The diagnostic imaging findings revealed COVID-19-associated pulmonary changes, The most common finding is “bilateral multifocal ground-glass opacities”, some cases show “reticular and hazy left lower lobe opacities” or “subpleural ground glass infiltrates” and others may not be available or with a normal view.

Regarding quantity, Ground-Glass Opacities were present in 6 cases (33.3 %), and Consolidations/Other Opacities in 2 cases (11.11 %), indicating the manifestations of pneumonia (Fig. 6A).

Neurological imaging indicates brain imaging findings are diverse, with some cases showing “symmetric non-enhancing T2 white matter hyperintensities” or “vasogenic edema”, many reports highlight various forms of cerebellar hyperintensities or edema.

The frequency analysis of image classifications indicates the diagnosis of 6 cases (33.3 %) with Cerebellar Hyperintensities/Edema, 3 cases (16.7 %) with White Matter Hyperintensities, 2 cases (11.11 %) with Edematous Changes, and 1 case (5.5 %) with Hemorrhagic Lesions (Fig. 6B).

3.5. Treatment protocols

In the context of the clinical and imaging manifestations of the presented cases, the final diagnosis of neurological disease and the treatment strategies can be categorized as follows.

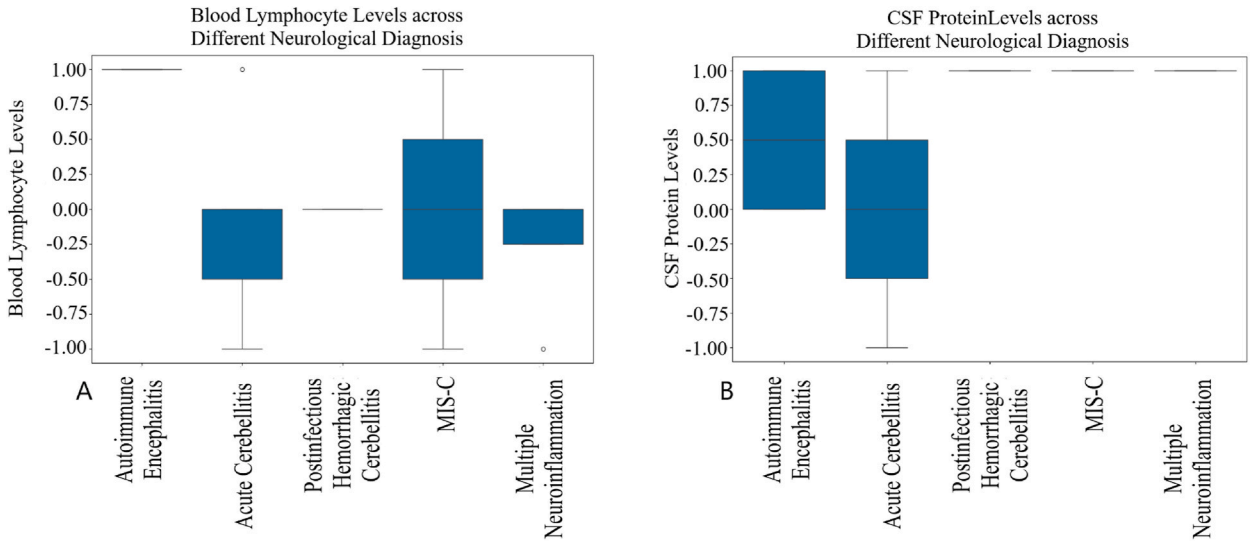

Fig. 5. Biomarker Levels Across Different Neurological Diagnoses. (A) Blood Lymphocyte Levels: This box plot compares blood lymphocyte levels, showing variability across different neurological conditions, with notable consistency in autoimmune encephalitis; **(B)** CSF Protein Levels: This box plot illustrates the distribution of CSF protein levels, indicating higher levels in autoimmune encephalitis and MIS-C compared to other conditions.
CSF: Cerebrospinal Fluid; MIS-C: Multisystem Inflammatory Syndrome in Children.

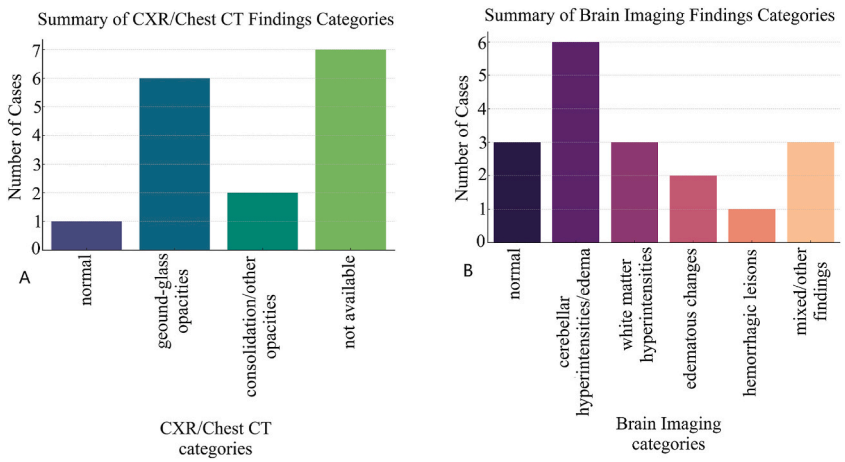

Fig. 6. Summary of imaging findings from chest X-rays/CTs and brain scans in patients with neurological symptoms post-COVID-19. **(A)**: Bar chart summarizing CXR/Chest CT findings in different categories among patients; **(B)**: Bar chart summarizing brain imaging findings across various categories in the studied cases.

A) **Autoimmune Encephalitis** (including patients with this diagnosis and anti-GAD-associated autoimmune cerebellitis): The treatment strategy focuses on aggressive immunosuppression to control the overactive immune response. Steroids and IVIg are the cornerstone therapies, often supplemented by other medications to manage specific symptoms or complications [20,26,30,32].
B) **Acute Cerebellitis**: Treatment addresses the underlying infection (often viral) and the inflammatory response. Antivirals and steroids are primary treatments, with IVIg and supportive measures used as needed [19,21,22,27,28,33].
C) **Postinfectious Hemorrhagic Cerebellitis**: The treatment is focused on reducing inflammation and managing complications from hemorrhage. Steroids are key, with supportive care measures to handle raised intracranial pressure [23].
D) **MIS-C** (Multisystem Inflammatory Syndrome in Children): Treatment is multifaceted, targeting the widespread inflammation with steroids and IVIg. Additional supportive treatments are tailored to manage the diverse systemic manifestations of the syndrome [24,29].
E) **Multiple Neuro-Inflammations** (Including Acute Inflammatory Demyelinating Polyneuropathy (AIDP), Transverse Myelitis, and Acute necrotizing Encephalopathy): The treatment strategy emphasizes immunosuppression with steroids and IVIg, supported by antivirals if needed. This approach aims to address the inflammation and manage the multifocal neurological damage [10,25,31,34].

we employed a Chi-Square test to assess the relationship between the reclassified diagnosis categories and the treatments administered. Additionally, we utilized a heatmap to visually illustrate how treatments are distributed across various diagnosis categories (Fig. 7A). The statistical analysis yielded the following results: Chi-Square value of 28.95, associated with a p-value of 0.089, and with 20 degrees of freedom. These findings provide insights into the potential associations between diagnosis categories and treatments in our dataset, although the p-value suggests that the association may not be statistically significant at conventional levels.

3.6. Post-treatment and follow-up outcomes

Considering the diverse treatments applied in the management of patients, the post-treatment outcomes and follow-up of the patients fall into one of the following categories.

A) **Symptom-free**: Most cases treated with steroids, antivirals, or IVIg resulted in symptom-free outcomes, indicating the effectiveness of these treatments in achieving full recovery [10,19–21,23,24,26–29,32].
B) **Minimal Residual Symptoms:** Some cases treated with IVIg still had minimal residual symptoms, suggesting that while IVIg is generally effective, there may be instances where complete recovery is not achieved. Additionally, cases treated with IVIg and antivirals resulting in slight disability underscores the long-term impacts of Cerebellitis and the need for prolonged rehabilitation [22,30,31].
C) **Significant Improvement**: Cases treated with antivirals showed significant improvement, indicating the role of antiviral therapy in facilitating substantial recovery in certain conditions [33].
D) **Died:** A case with multiple neurological inflammations treated with steroids resulted in death, highlighting the severity of the condition and the need for aggressive treatment [25].
E) **Undergoing Therapy:** Cases with ongoing therapy indicate the complexity of treatment and the necessity for prolonged medical intervention [34].

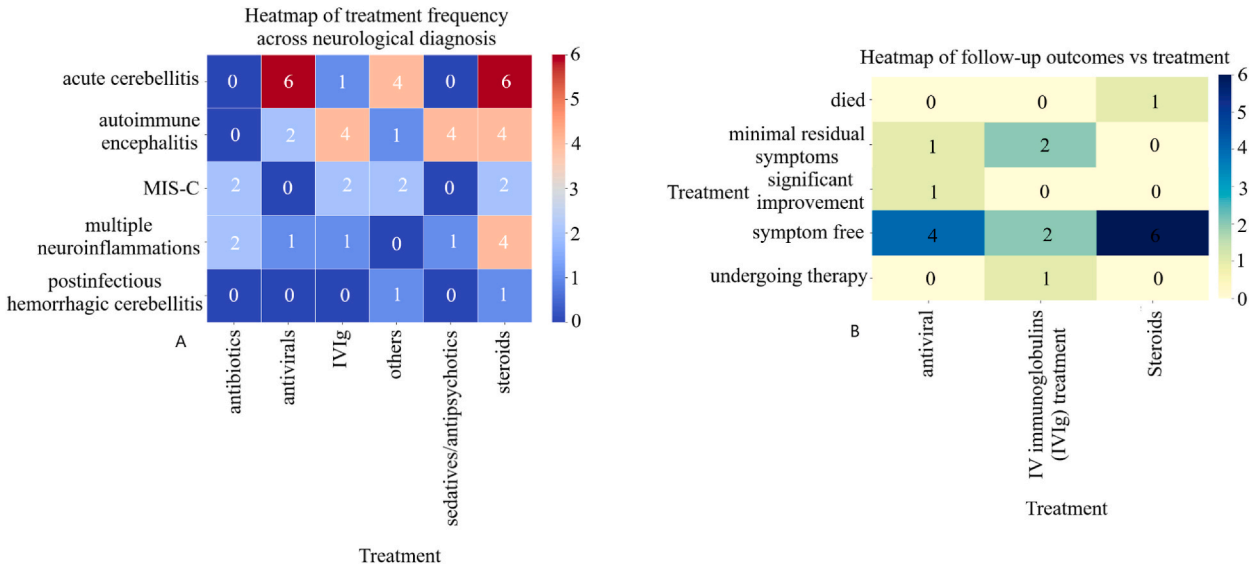

Fig. 7. Treatment Frequencies and Outcomes. (A) Heatmap of Treatment Frequency across Neurological Diagnoses: This heatmap visualizes the frequency of various treatments used across neurological diagnoses, with IVIg and steroids being notably prevalent in specific conditions; (**B**) Heatmap of Follow-up Outcomes vs Treatment: This heatmap correlates follow-up outcomes with treatments, showing that IVIg and antibiotics are associated with symptom-free statuses, while steroids are linked to minimal residual symptoms.
MIS-C: Multisystem Inflammatory Syndrome in Children.

we employed a Chi-Square test to examine the potential association between follow-up outcomes and distinct treatment modalities. Our statistical analysis yielded a Chi-squared value of 14.29, accompanied by 8 degrees of freedom, resulting in a p-value of 0.283. These findings suggest a lack of statistically significant association between the follow-up outcomes and the administered treatments. Consequently, it can be inferred that the treatments under investigation exerted no discernible influence on the observed follow-up outcomes (Fig. 7B).

3.7. Quality assessment

The results of the JBI quality assessment [18] demonstrated that all studies were of high quality, with an average score of 6.944 (based on the number of "yes" responses). This comprised 5 cases with a score of 6 (27.8 %), 7 cases with a score of 7 (38.9 %), and 6 cases with a score of 8 (33.3 %). In this assessment, two articles were published as case series [26,29]; however, considering the individual descriptions of their cases within the articles, only cases diagnosed with cerebellitis were considered, and therefore, the evaluation utilized the JBI Case Report criteria (Table S2).

4. Discussion

This systematic review stands at the forefront of discerning cerebellitis as a post-infectious consequence of SARS-CoV-2, an uncommon but significant neurological event. A methodical evaluation of data from 17 selected articles (18 cases) surfaces a notable incidence in males (94.4 %), predominantly in their early forties, hinting at a possible sex-linked susceptibility.

A recent meta-analysis of 229 studies covering over 10 M patients, demonstrated that men have a higher risk for COVID-19 infection, hospitalization, disease severity, ICU admission, and death, with temporal trends showing lower risks at the beginning of the pandemic and higher risks for death later [35]. This may be since male COVID-19 patients have higher levels of innate immune cytokines and more non-classical monocytes, while female patients have more robust T-cell activation, along with higher expression of ACE2, which may explain the sex differences in disease outcomes [36,37].

4.1. Diagnostic approaches to post-COVID cerebellitis

A multidisciplinary approach is crucial to managing COVID-19, correlating clinical features with laboratory and imaging findings to establish the right timing for each treatment. In March 2020, a multidisciplinary guideline panel was established by the Infectious Diseases Society of America (IDSA) to systematically review evidence and provide expert recommendations for the treatment and management of individuals with COVID-19 [38]. However, to date, there is no unique therapeutic strategy for managing neurological complications, especially Cerebellitis. Nevertheless, here we discuss diagnostic imaging methods, serum/CSF biomarkers, and the main treatment approaches mentioned in various cases.

4.1.1. Imaging modalities

Non-contrast head CT, the initial imaging choice, distinguishes acute infarctions and neoplasms and reveals cerebellar edema's potential complications. MRI, the gold standard, categorizes findings into bi-hemispheric cerebellitis, hemi-cerebellitis, and cerebellitis with encephalitic features. Abnormal cortical hyperintensity and constrained diffusion patterns aid this stratification, reflecting cytotoxic edema and inflammation [11,39–42]. Imaging may also uncover rare but significant cerebellar hemorrhage, termed pseudotumor cerebellitis with hemorrhage [42].

In the study reported by Stephan Grimaldi et al. [32], a case with neurological manifestations consistent with encephalitis post-COVID-19 infection presented with normal MRI imaging; however, findings from PET with 18F-FDG revealed putaminal and cerebellum hypermetabolism associated with diffuse cortical hypometabolism. This indicates that the changes might be too subtle to be detected by standard imaging techniques such as MRI. Functional or metabolic imaging (e.g., FDG-PET) might show abnormalities that structural imaging does not.

Contrarily, in the study by Jana Werner et al. [43], subacute cerebellitis manifestations in a post-COVID-19 patient showed no changes in various brain imaging modalities (Brain-MRI and FDG-PET). The justification for this occurrence has possible reasons [43]:

A) COVID-19 can trigger immune-mediated reactions in the central nervous system, leading to neurological symptoms without visible changes in imaging. This is supported by the improvement seen with immunosuppressive treatments like high-dose methylprednisolone; B) Any initial inflammation or edema could have resolved by the time imaging was performed, especially if there was a delay between symptom onset and imaging; and C) Standard imaging methods might not always detect early or mild forms of neurological damage. Advanced imaging (e.g. SPECT) techniques or more sensitive modalities might be required to detect such changes. As indicated in a case by Kenta Osaw et al. [21] in a patient diagnosed with post-COVID-19 Cerebellitis, although all CSF biomarkers and Brain EEG and MRI were normal, a SPECT modality imaging detect perfusion abnormality within the Cerebellum, as a result.

To be added, Cerebellar inflammation-induced brainstem compression can obscure initial signs, possibly manifesting as raised intracranial pressure (RICP) symptoms like autonomic dysregulation and coma. Fulminant acute cerebellitis, a clinical syndrome associated with sudden-onset RICP symptoms, must be considered in the differential diagnosis. This condition poses serious, sometimes irreversible sequelae and a risk of mortality [44].

4.1.2. Blood biomarkers in post-acute COVID-19

Elevated levels of blood biomarkers such as neurofilament light chain protein (NfL), glial fibrillary acidic protein (GFAP), and matrix metalloproteinase-9 (MMP-9) are associated with severe COVID-19 and neurological symptoms [45]. Additionally, increased levels of NSE in CSF, along with elevated white blood cell count and protein, indicate neuroinflammation [46]. According to our results, blood CRP was increased in 33.33 % of cases, while the correlation between the lymphocyte levels and the COVID-to-neuro symptom interval as well as its levels across different neurological diagnoses, were considered weak in correlation. Hence, the evaluation of CRP is therefore recommended to be considered alongside unique post-COVID inflammatory factors (NfL, GFAP, MMP-9) in the assessment of blood biomarkers.

Additionally, disruption of the blood-brain barrier (BBB) is evidenced by increased levels of albumin ratio and markers of inflammation in CSF [47]. While the persistent elevation of BBB disruption markers like MMP-9 in COVID-19 patients with neurological manifestations suggests ongoing CNS involvement [48]. Similarly, our surveys indicate to the elevation of CSF protein level in nearly 50 % of cases, as a prognostic marker of BBB disruption.

4.1.3. CSF findings in post-acute COVID-19

Studies show consistent absence of SARS-CoV-2 antigens in CSF, indicating that neurological symptoms in long COVID are not due to persistent viral presence in the CNS [49]. Markers like IL-6, IL-8, and MCP-1 were elevated in the CSF of COVID-19 patients, indicating ongoing inflammation [50].

The results are in line with a study by Nina-Maria Wilpert et al. [51], who evaluated pediatric ataxia and movement disorder, indicated a tendency towards more favorable outcomes in lacking signs of inflammatory CSF (broadly defined as pleocytosis or elevated protein level or positive oligoclonal bands or CSF anti-neuronal/-glial antibodies or positive immunofluorescence on murine brain sections) compared to those exhibiting such markers.

4.2. Therapeutic approaches to post-COVID cerebellitis

The treatment regimen for post-COVID cerebellitis, a novel and complex pathology, lacks a formalized guideline. Current therapeutic responses are extrapolated from isolated clinical encounters and observational studies. Here, we address the treatments reported, ranging from pharmacological interventions to invasive procedures.

4.2.1. Antiviral and steroid therapy

Remdesivir, repurposed from Ebola for COVID-19, shows promise in early cases, potentially reducing recovery time and hospital stays [52]. The standard regimen, per Zhenchao Wu et al., is an initial 200 mg dose followed by 100 mg daily for 9 days. While generally safe, continuous liver and kidney monitoring is essential [53]. However, studies suggest remdesivir alone may be insufficient, prompting subsequent steroid treatment, indicating potential therapeutic inadequacy or the disease's severity [21,28]. Other antiviral agents such as Lopinavir/Ritonavir and Acyclovir have also successfully treated several cases of post-COVID-19 Cerebellitis [24,27,29,33].

Corticosteroid therapy's impact on neurological complications post-COVID-19 is underexplored, but emerging evidence shows a positive trajectory. Corticosteroids may attenuate dysregulated cerebrospinal fluid cytokine levels linked to observed neurologic sequelae [54–56]. Case studies, like one by Takuya Watanabe et al., demonstrate significant symptomatic relief and neurological recovery with intravenous methylprednisolone in post-COVID cerebellitis [57].

Research by Alexander Grundmann et al. [58] suggests COVID-19-associated neurological manifestations, when treated with regimens including Dexamethasone and/or Remdesivir, minimize complications, hinting at a potential cumulative or synergistic therapeutic effect.

Along with it, a few cases of our results were treated with a combination of Steroids and Antiviral and hence, significant improvement in Neurological and Serum/CSF markers [19,21,24,27–29,31].

4.2.2. Immunotherapy insights

Immunotherapy, particularly Intravenous Immunoglobulin (IVIg), derived from pooled immunoglobulin G of healthy donors, is integrated into COVID-19 treatment for its effects on innate and adaptive immunity [59,60]. Clinical observations show a substantial reduction in IL-6 post-IVIg therapy, with successful treatment of a post-COVID anti-GAD antibody-associated cerebellar syndrome case [30,61].

Despite IVIg's recognized anti-inflammatory and immunomodulatory properties, its efficacy against post-COVID cerebellitis remains unconfirmed, considering the inadequacy of antiviral agents [62]. However, the treatment is prescribed in all cases of cerebellitis that didn't respond to corticosteroid therapy, and all show improved results [22,26,29,34].

4.2.3. The role of plasmapheresis

Plasmapheresis, also known as therapeutic plasma exchange (TPE), is being explored as a treatment for severe COVID-19. It involves removing pathogenic plasma components like autoantibodies and cytokines using centrifugation or hemofiltration [63,64]. This process depletes plasma proteins, particularly immunoglobulins and coagulation factors. Studies show some improvements in lab markers and reduced mortality rates due to decreased inflammatory factors [65]. However, compared to standard treatments, its impact on reducing inflammation and death rates isn't significant [66].

Similarly, according to one of the included cases that showed an increase in blood lymphocytes and elevated levels of CSF IgG, ultimately diagnosed with autoimmune encephalitis and treated with pulse steroid therapy, eventually achieved a favorable clinical response after undergoing cycles of plasmapheresis [20].

4.3. Limitations

Limitations in our study include reliance on few case reports, and potentially introducing selection bias towards unusual or severe presentations. This may skew perceptions of cerebellitis prevalence and spectrum. Moreover, variability in clinical management across healthcare settings complicates diagnosis and treatment standardization. Retrospective data collection poses challenges in capturing crucial nuances, impacting conclusion accuracy. Additionally, some cases of Cerebellitis have been reported following COVID-19 vaccine administration, but due to different search strategies in Databases and biases in their inclusion, they have been excluded.

5. Conclusion

The comprehensive examination of post-COVID cerebellitis highlights a male predilection in individuals in their early forties, indicating a possible gender-related susceptibility. The intricate relationship between COVID-19 and cerebellar inflammation underscores the necessity for a multidisciplinary diagnostic and therapeutic approach. Treatment modalities, incorporating antiviral, steroid, and immunomodulatory agents, exhibit the potential to mitigate symptoms and promote recovery. Continued research is imperative to enhance diagnostic precision and refine treatment strategies for enhanced clinical outcomes.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

The datasets analyzed during the current study are available upon request with no restriction.

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CRediT authorship contribution statement

Soroush Najdaghi: Writing – review & editing, Writing – original draft, Validation, Project administration, Data curation. **Delaram Narimani Davani:** Software, Project administration, Data curation, Conceptualization. **Mohammadreza Hashemian:**

Writing – original draft, Visualization, Software, Data curation. **Narges Ebrahimi:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of competing interest

All authors have no declaration of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34497.

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