Neurological Involvement of Coronavirus Disease 2019: A Systematic Review

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Abstract

Background: In December 2019, unexplained cases of pneumonia emerged in Wuhan, China, which were found to be secondary to the novel coronavirus SARS-CoV-2. On March 11, 2020, the WHO declared the Coronavirus Disease 2019 (COVID-2019) outbreak, a pandemic. Although the most common presentations of COVID-19 are fever, cough and shortness of breath, several clinical observations indicate that COVID-19 does affect the central and peripheral nervous system.

Methods: We conducted a systematic literature search from December 01, 2019 to May 14, 2020 using multiple combinations of keywords from PubMed and Ovid Medline databases according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We included articles with cases of COVID-19 that were evident for neurological involvement.

Results: We were able to identify 82 cases of COVID-19 with neurological complications. The mean age was 62.28 years. 37.8% of the patients were women (n = 31). 48.8% of the patients (n=40) had cerebrovascular insults, 28% (n=23) had neuromuscular disorders, 18.3% of the patients (n=15) had encephalitis or encephalopathy, and 2.4% (n=2) presented with status epilepticus.

Conclusions: Neurological manifestations of COVID-19 infection are not rare, especially large vessel stroke, Guillain barre syndrome and meningoencephalitis. Moving forward, further studies are needed to clarify the prevalence of the neurological complications of COVID-19, investigate their biological backgrounds, and test treatment options. Physicians should be cautious not to overlook other neurological diagnoses that can mimic COVID-19 during the pandemic.

Introduction

Coronaviruses (CoV) are a family of enveloped, positive-sense, single-stranded RNA viruses that have been described for more than 50 years. Some strains are found to be zoonotic, whereas others may infect humans and transmit from human-to-human (HCoV). [1] Multiple strains of Coronavirus are associated with human disease, causing mainly respiratory infections. [2] Of these, SARS-CoV-1, MERS-CoV, HCoV-OC43, and HCoV-229E are associated with neurological complications. [3] Large territory stroke, polyneuropathy, myopathy, seizures and status epilepticus were reported in patients with SARS CoV-1 outbreak in 2002/2003. [4, 5] In-vivo, intranasal inoculation of the SARS-CoV-1 led to severe neuronal loss at the brainstem and specifically the respiratory center at the medulla. This was postulated to contribute to the respiratory failure seen in the most severe cases of coronavirus infections, in addition to the primary lung pathology. [6] The full spectrum of COVID-19 infection is not fully described yet. Some patients may have no clinical symptoms, [7, 8] while others might suffer from severe disease and die. The most commonly recognized symptoms are cough, fever, fatigue, shortness of breath, myalgia, anosmia, and sputum production. Other less-reported symptoms include diarrhea, hemoptysis, and nasal congestion. [7, 9] During the current uncertain times, growing evidence suggests that SARS-CoV-2 virus has neuroinvasive potential, like other coronaviruses. Hence, it was only a matter of time before neurological complications were reported, especially stroke, neuromuscular disorders and meningoencephalitis. The goal of this review is to outline the broad spectrum of the neurological consequences of COVID-19 infection.

Methods

We conducted a systematic literature search from December 01, 2019 to May 14, 2020 from PubMed and Ovid Medline databases according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search strategy was implemented and these keywords and their synonyms (in the all fields) were combined in each database as follows: (“COVID 19" OR "coronavirus") AND ("brain" OR "CNS" OR “spinal cord” OR “nerve” OR "neurologic” OR “stroke” OR “cerebrovascular” OR “cerebral vein thrombosis” OR “sinus thrombosis” OR “Intracerebral hemorrhage” OR “hemorrhage” OR “myelitis” OR “GBS” OR “Guillain barre syndrome” OR “neuropathy” OR “radiculopathy” OR “cranial neuropathy” OR “myopathy” OR “myositis” OR “rhabdomyolysis” OR “encephalitis” OR “encephalopathy” OR

"meningitis" OR "meningoencephalitis" OR "seizure" OR "convulsion" OR "epilepsy") **[Figure 1]**. We included case series and case reports of COVID-19 that were evident for neurological involvement. After exclusion of duplicates, all articles were evaluated through title and abstract screening by three independent reviewers (M.G., QA., GM.). The same three reviewers performed an accurate reading of all full-text articles assessed for eligibility and performed a collection of data to minimize the risk of bias. In case of disagreement among the investigators regarding the inclusion and exclusion criteria, the senior investigator (GM.) made the final decision. Articles were included if they met the following inclusion criteria: (i) described patients with neurological signs or symptoms attributed to COVID-19 (e.g.focal neurological deficit or impairment of consciousness); (ii) written in English language; and (iii) published in a peer-reviewed journal. The exclusion criteria were: (i) studies conducted in animals or in vitro models or basic science studies; (ii) patients age less than 18-year old; and (iii) conference proceedings, pooled analysis, clinical trials, case control studies, case reports or case series of anosmia or mental health problems in COVID-19 patients, reviews and books.

For each study, the following descriptive, microbiological, and clinical information were extracted: patient demographic data, SARS-CoV-2 testing from nasal swab and CSF, neurological symptoms and signs and their onset in relation to respiratory or gastrointestinal (GI) symptoms or anosmia or dysgeusia, any neurological investigations and CSF or any other relevant laboratory testing (such as CK, LDH, CRP, D-dimer, lupus anticoagulant, fibrinogen, ganglioside antibodies), neurological diagnosis, occurrence of respiratory failure (defined as need for intubation, abnormal PO2 in blood gas, or Glasgow Coma Scale score less than or equal 8), treatments administered for the neurological diagnosis, and final outcome. We studied the following outcomes: good, recovering, poor, and deceased. Good outcome was defined as discharge of the patient to home or a quarantine facility, or the use of the following descriptive terms in the study: "no morbidity", "no worsening" or "discharged well" or "good recovery". Recovering outcome was defined as discharge of the patient to a rehabilitation facility or use of the following descriptive terms: "began to improve", "recovering", or "stayed in the floor". Poor outcome was defined as continuing deterioration of the patient's clinical status, need for ICU admission, continued intubation, or use of the following descriptive terms: "poor" or "no improvement after certain time of treatment", at the time of submitting the manuscript. Deceased was defined as reported death within 30 days of COVID-19 diagnosis.

Results

Through the search strategy, we could identify 42 articles about neurological involvement by COVID-19. We were able to identify 82 cases of COVID-19 with neurological complications. The mean age was 62.28 years (22-91). 37.8% of the patients were women (n = 31). All patients except 2 had positive nasopharyngeal (NP) or oropharyngeal (OP) SARS-CoV-2 RT-PCR swabs. Only 2 patients had positive CSF SARS-CoV-2 RT-PCR, one of which showed negative NP swab testing. 48.8 % of patients (n=40) had cerebrovascular insults (CVIs), 28% (n=23) had neuromuscular disorders (NMDs), 18.3 % (n=15) developed CNS complications related to infection or inflammation, 2.4% (n=2) presented with status epilepticus and 1.2 % (n=1) had CNS demyelinating lesions. 32.9% of patients (n=27) were recovering, 18.3% (n=15) had good outcome, 25.6 % (n=21) had poor outcome and 18.3% (n=15) died. One patient showed postmortem evidence of the presence of viral particles in the neurons and capillary endothelial cells in the frontal lobe **(Table 1)**. In 23.2 % of patients (n=19), the neurologic syndrome was the initial presentation of COVID-19. Four of which, they developed respiratory symptoms 2-8 days after the onset of neurologic syndrome. In 2 patients the neurologic syndrome proceeded by 2-3 days of GI symptoms, while in 2 other patients, it was proceeded only by anosmia and dysgeusia. **[Figure 2]**.

5% (n=2) of the CVIs were cerebral vein thrombosis (CVT), 5% (n=2) were intracerebral hemorrhage (ICH), 2.5% (n=1) were aneurysmal subarachnoid hemorrhage & ICH, and 87.5% (n=35) were ischemic stroke. 3 out of the 35 patients were cardioembolic stroke, 5 were small vessel disease stroke, and 27 were large vessel occlusion (LVO) stroke. 25.7% (n=9) of the ischemic stroke patients had significant elevation of D-dimer level (>7000 ng/ml), 28.6 % (n=10) had significant

Author, Year	Age(y), Sex	SARS-CoV-2		Neurological Presentation	Neurological Investigations (Images, EMG, EEG, autopsy)	Neurological Diagnosis	CSF & Others
		Nasal Swab	CSF				
Poyiadji et al. 2020 [10]c	58, F	Pos	NA	Altered mental status (AMS)	MRI: Hemorrhagic rim enhancing lesions within the bilateral thalami, medial temporal lobes, and subinsular regions	Acute Hemorrhagic Necrotizing Encephalopathy	CSF was negative for HSV 1 & 2, VZV and West Nile PCRs
Moriguchi et al. 2020 [11] #	24, M	Neg	Pos	Headache then unconsciousness, generalized convulsions and neck rigidity	T2WI/FLAIR: hyperintensity in the right mesial temporal lobe and hippocampus	Meningitis/Encephalitis Ventriculitis	CSF: OP >32 cmH_2O, 12 mononuclear cells, 2 PMNs, CSF HSV1 PCR was not tested
*Duong et al & Haung et al. 2020 [12&13] **	41, F	Pos	Pos	Headache, new onset seizure, neck stiffness, fever and photophobia	CT head was normal EEG: Generalized slowing with no epileptic discharges	Meningoencephalitis	CSF: protein 100 mg/dl. WBCs 70 cells/µL 100% lymphocyte. Glucose 120
*Ye et al. 2020 [14] ***	No age, M	Pos	Neg	Myalgia and confusion. Nuchal rigidity, positive Kernig sign and Brudzinski sign	CT head was normal	Encephalitis	CSF: OP 220 mmHg. Normal WBC, protein and glucose
Yin et al. 2020 [15]	64, M	Pos	Neg	AMS, neck stiffness. Positive clonus, Babinski, Chaddock and Brudzinski signs	CT head was normal	Encephalitis	CSF: OP 200 cmH_2O. protein, WBCs and glucose were normal
Filatov et al. 2020 [16] R	74, M	Pos	NA	Headache and AMS	EEG: bilateral slowing and focal slowing in the left temporal region with sharply contoured waves	Encephalopathy	CSF: protein 68 mg/dl. WBCs 4 cells/µL.
*Wong et al. 2020 [17] ****	40, M	Pos	NA	Ataxia, diplopia, oscillopsia, hiccups, right arm paresthesia	MRI: T2 hyperintensity of the right inferior cerebellar peduncle and upper cord associated with microhemorrhages	Rhombencephalitis	CSF: normal WBC, protein and glucose
Zhao et al. 2020 [18]	61, F	Pos	NA	Legs & arms weakness. Areflexia	Day 5 EMG/NCS revealed demyelinating pattern	GBS	CSF: protein 124 mg/dl. Cell counts 5 cells/µL
Sedaghat et al. 2020 [19]	65, M	Pos	NA	Ascending quadriparesis. Bifacial nerve palsy. Areflexia	Day 9 EMG/NCS revealed axonal pattern	GBS variant - AMSAN	CSF was not performed
Virani et al. 2020 [20]	54, M	Pos	NA	Ascending weakness and Paresthesia. Areflexia	T& L spine MRI was normal. EMG/NCS were not performed	GBS	CSF was not performed
El-Otmani et al.	70, F	Pos	Neg	Quadriplegia.	Day 10 EMG/NCS	GBS variant - AMSAN	CSF: protein 100

2020 [21]				Hypotonia. Areflexia	revealed axonal pattern		mg/dl. Normal WBC
Alberti et al. 2020 [22]	71, M	Pos	Neg	Ascending weakness and paresthesia. Areflexia	EMG/NCS revealed mixed axonal and demyelinating patterns	GBS - mixed damage	CSF: protein 54 mg/dL. WBCs 9 cells/µL
Camdessanche et al. 2020 [23]Q	64, M	Pos	NA	Flaccid tetraparesia and paresthesia. Areflexia	Day 5 EMG/NCS revealed demyelinating pattern	GBS	CSF: protein 166 mg/dl. Normal WBCs.
Padroni et al. 2020 [24]	70, F	Pos	NA	Gait difficulty and paresthesia. Areflexia	EMG/NCS revealed demyelinating pattern	GBS	CSF: protein 48 mg/dl. WBCs 1 cells/µL
Scheidl et al. 2020 [25]	54, F	Pos	NA	Paraparesis. Areflexia	Admission EMG/NCS revealed demyelinating pattern	GBS	CSF: protein 140 mg/dl. Normal WBCs
Ottaviani et al. 2020 [26]	66, F	Pos	Neg	Difficulty walking, paraparesis. Areflexia then quadriparesis and facial weakness	Day 10 EMG/NCS revealed mixed axonal and demyelinating patterns	GBS - mixed damage.	CSF: protein 108 mg/dl. Normal WBCs. Serum anti-glycolipid antibodies were absent
Abdelnour et al. 2020 [27]	69, M	Pos	NA	Bilateral lower limb weakness. Areflexia	Brain and spine MRIs were normal. EMG/NCS were not performed	GBS	CSF was not performed
Caamaño DS et al. 2020 [28]	61, M	Pos	Neg	Bilateral facial weakness. Unresponsive blink reflex on both eyes	Brain MRI and CT were normal. EMG/NCS were not performed	Atypical GBS variant - Facial diplegia	CSF: protein 44 mg/dl. WBCs 0 cells
Wei et al. 2020 [29]	62, M	Pos	NA	Binocular diplopia and left ptosis. Left eye was down and out at rest. No anisocoria. No areflexia	Brain MRI and MRA were negative	Left oculomotor nerve palsy	CSF was not performed. CRP 142.21 mg/L
Jin et al. 2020 [30]	61, F	Pos	NA	Muscle tenderness & weakness of lower extremities	EMG/NCS were not performed	Rhabdomyolysis	Myoglobin >12,000.0 µg/L. CK 11,842 U/L. LDH 2,347 U/L. CRP 111 mg/L
Suwanwongse et al. 2020 [31]	88, M	Pos	NA	Bilateral thighs weakness and pain	EMG/NCS were not performed	Rhabdomyolysis	CK 13,581 U/L. LDH 364 U/L
*Vollono et al. 2020 [32]^*	78, F	Pos	NA	Myoclonic jerks of the right face and right limbs. Fever	EEG: semi-rhythmic, irregular, high amplitude delta activity, predominantly over the left fronto-centro-temporal regions	Focal status epilepticus	CSF was not performed
Sohal et al. 2020 [33]	72, M	Pos	NA	AMS, episodes of tonic colonic movements	CT head: no acute findings EEG: Six left temporal seizures	Status epilepticus	CSF was not performed

				and left temporal sharp waves			
Zanin et al. 2020 [34]T	54, F	Pos	Neg	AMS	MRI: Periventricular confluent white matter hyperintensity EEG: Two focal frontotemporal seizures	Demyelinating lesions	CSF: normal WBC, protein and glucose. No OCBs were sent CRP 41.3 mg/L
Paniz-Mondolfi et al. 2020 [35]	74, M	Pos	NA	Confusion and falls	CT head: no acute findings Autopsy revealed 80 to 110 nm viral particles in frontal lobe brain (neurons & endothelial cells)	Postmortem presence of virus in neural and capillary endothelial cells in frontal lobe from a patient infected with COVID-19	CRP 183.5 mg/L. D-dimers 2925 ng/mL
González-Pinto et al. 2020 [36] ¥	36, F	Pos	NA	Aphasia, right side hemiplegia. She was found down in her apartment	CT and CTA: Occlusion of left ICA, MCA, ACA	Left ICA stroke	CRP 156 mg/L. D-Dimer 7540 ng/ml.
Zhou et al. 2020 [37]	75, F	Pos	NA	Left hemiplegia and right hemiparesis	CT: bilateral cerebral infarcts	Right MCA and ACA stroke. Left ACA stroke. Bilateral legs DVTs	CRP: 42.52 mg/L. D-dimer >8000 ng/mL
Valderrama et al. 2020 [38]	52, M	Pos	NA	Right hemiparesis and aphasia. Left gaze, right partial hemianopia, facial weakness	CT: left MCA hyperdense sign CTA: left ICA occlusion CTP: favorable mismatch ratio of 4.1	Left ICA stroke	CRP 11 mg/L. D dimer > 10000 ng/ml. Fibrinogen 235 mg/dl
Viguier et al 2020. [39]X	66, M	Pos	NA	Right hemiparesis and aphasia.	CT: left frontal hypoattenuation CTA: left CCA intraluminal floating thrombus	Multiple scattered infarcts within left carotid territory	CRP 219 mg/L. D-dimer 2220 ng/ml. fibrinogen 820 mg/dl.
Hughes 2020. et al [40]	59, M	Pos	NA	Right fronto-temporal headache followed by right sided weakness and numbness	CTV: Filling defect in the right sigmoid and transverse sinus	CVT	CRP: 20 mg/l. APTT: 19.7. Fibrinogen 490 mg/dl
Sharifi-Razavi et al. 2020 [41] §	79, M	Pos	NA	Acute loss of consciousness	CT: right hemispheric massive intracerebral hemorrhage with intraventricular and subarachnoid hemorrhage	ICH	CRP 10 mg/L. INR 1. PTT 64 seconds

elevation of C-reactive protein (>100mg/L), 22.8% (n=8) had elevated fibrinogen (> 500 mg/dl), and 14.3% (n=5) were tested positive for lupus anticoagulant antibodies. Out of the 27 LVO stroke patients, 7 were under the age of 50, 6 underwent thrombectomy, 4 were given IV tPA, 6 were given therapeutic low molecular weight heparin (LMWH), 3 were given apixaban, 4 were given dual antiplatelets (DAPs), and one was given rivaroxaban and DAPs, and 6 died. One of the ischemic stroke patients developed hemorrhagic conversion after thrombectomy. The LVO stroke were distributed in the following territories: left middle cerebral artery territory (MCA) (n=6), right MCA (n=6), left internal carotid artery (ICA) (n=2), right ICA (n=2), left

Table 1. Summary of the case reports of COVID-19 with neurological complications

*c, CSF analysis was limited due to traumatic LP; #, DWI: hyperintensity along the wall of the inferior horn of the right lateral ventricle; *, SARS-CoV-2 infection was entirely confined to the central nervous system;**, CSF anti-SARS-CoV-2 IgM& IgG were not detected; R, CT head revealed left PCA distribution encephalomalacia. CSF was negative for bacterial cultures, HSV PCR, RSV, and CMV PCR. ; ***, Myelin oligodendrocyte glycoprotein antibody (MOG-IgG) and aquaporin 4 antibody results were requested, but no results reported;Q, Negative serum Anti-gangliosides;^, The patient has history of well-controlled post-encephalitic epilepsy;* T, MRI also reveals bulbo-medullary and C2-T6 focal intramedullary hyperintensities. No contrast enhancement; *¥, The patient had free medical history but smoker. CTA revealed free-floating thrombus in the ascending aorta with no signs of aortic atheromatosis; §, The patient did not have history of hypertension or anticoagulation therapy. Platelets of 210 × 10^9/L; X, Antiphospholipid antibodies were negative*

AMS: altered mental status. OP: opening pressure. GBS: Guillain barre syndrome. ACA: anterior cerebral artery. AMSAN: Acute motor-sensory axonal neuropathy. CCA: common carotid artery. CK: Creatine Kinase. CMAP: compound muscle action potential. CMV: Cytomegalovirus. COVID-19: Coronavirus disease 2019. CT: Computed tomography. CTA: CT angiography. CTP: CT perfusion. CTV: CT venogram. DVT: deep vein thrombosis. DWI: Diffusion Weighted Images. EEG: Electroencephalography. EMG: Electromyography. HSV: Herpes Simplex Virus. ICA: Internal carotid artery. ICU: Intensive care unit. INR: International normalized ratio. LDH: Lactate dehydrogenase. MCA: middle cerebral artery. MRI: Magnetic Resonance Imaging. NA: not applicable. NCS: nerve conduction studies. Neg: negative. Pos: positive. OCBs: oligoclonal bands. PMN: Polymorphonuclear cells. RT-PCT: Real-Time Polymerase Chain Reaction. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2. SNAP: sensory nerve action potential. T2WI/FLAIR: T-2 weighted Images/Fluid Attenuation Inversion Recovery. VZV: Varicella Zoster Virus. CRP: C-reactive protein. PTT: partial thromboplastin time. WBCs: white blood cells. CSF: cerebral spinal fluid. ICH: intracerebral hemorrhage. CVT: cerebral vein thrombosis.

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common carotid artery (n=1), basilar artery (n=1), left vertebral artery (n=1), left posterior cerebral artery (PCA) (n=1), right PCA (n=1), bilateral multiple vascular territory infarcts (n=2), and unspecified (n=4). Stroke with LVO was the presenting manifestation of COVID-19 infection in 8 patients, 3 of which were under the age of 45 **[Figure 3]**.

17.4% (n=4) of the NMDs patients had rhabdomyolysis, 4.3 % (n=1) had polyneuritis cranialis, 4.3% (n=1) had oculomotor nerve palsy, and 73.9% (n=17) had Guillain Barre syndrome (GBS). 7 out of the 17 GBS cases had facial weakness. One of which had solely facial diplegia as a neurologic syndrome. In 2 cases, GBS was the first presentation of SARS-CoV-2 infection. While in 14 other patients, GBS developed 3-24 days after the onset of flu-like symptoms. One patient presented 2 weeks after anosmia and ageusia without respiratory or GI symptoms. Electrophysiologic studies showed evidence of acute motor and sensory axonal variant (AMSAN) in 5 patients, mixed axonal and demyelinating pattern in 2 patients, and demyelinating patterns in 6 patients. EMG was not performed in 4 patients, one of which was diagnosed with Miller Fisher syndrome with positive serum GD1b-IgG antibody. CSF studies revealed albuminocytologic dissociation in 10 patients, were normal in 3 patients (protein <45 mg/dl, WBCs 0-5 cells/μ). In one patient CSF protein and WBCs were 54 mg/dl and 9 cells/μL respectively. 14 out of 17 patients received IVIG, one patient received IVIG and plasmapheresis, 1 patient showed spontaneous recovery and one patient received prednisone. 6 out of the 17 patients developed respiratory failure, one of which died **(Table 2)**.

Author, Year	Mean age (y)	Patients, Number	Male/Female, Number	SARS-CoV-2		Neurological Presentation	Neurological investigations	Neurological Diagnosis
				Nasal Swab	CSF			
*Toscano et al. 2020 [42] **	58.4	5	4/1	Pos (4) Neg (1)	Neg (5)	Tetraparesis (2), paraplegia (1), paresthesia (2), facial weakness (4), ataxia (2). Areflexia (5)	Days 3-12 EMG/NCS: axonal (3), demyelination (2). MRI: caudal nerves enhancement (2), facial nerves enhancement (1), normal (2)	GBS: AMSAN variant (3), AIDP variant (2)
*Gutiérrez-Ortiz et al. 2020 [43] **	44.5	2	2/0	Pos (2)	Neg (2)	1.Vertical diplopia, perioral paresthesia, gait instability. Areflexia	Pos GD1b-IgG antibody CSF: protein 80 mg/dl, WBCs 0 cells. No EMG was performed	Miller Fisher syndrome (right INO and right fascicular oculomotor palsy)
						2. Diplopia. Areflexia	CSF: protein 62 mg/dl, WBCs 2 cells /µL	Polyneuritis cranialis (bilateral abducent nerve palsy)
Chan et al. 2020 [44]	73	2	1/1	Pos (2)	NA	Generalized weakness (2), leg twitching (1)	Serum (ave): CK 2313 U/L: LDH 517.5 U/L. CRP: 11.25 mg/dl	Rhabdomyolysis
Bernard-Valnet et al. 2020 [45] ∞	65.5	2	0/2	Pos (2)	Neg (2)	1. tonic-clonic seizure. Verbal and motor perseverations	EEG: status epilepticus MRI brain: normal CSF: protein 46.6 mg/dl, WBCs 17 cells /mm^3 (97% lymphs)	Meningoencephalitis
						2. Intense headache and AMS. Left hemianopia and sensory hemineglect	MRI brain: normal CSF: 46.1 mg/dl, WBCs 21 cells /mm3 (89% lymphs)	Meningoencephalitis
Dogan et al. 2020 [46]W	49.1	6	5/1	Pos (6)	Neg (6)	Failure to recover consciousness or severe agitation during weaning from mechanical ventilation (6)	MRI: Cortical or WM hyperintensities, contrast enhancement, and sulcal hemorrhages (3)	Autoimmune Meningoencephalitis
Avula et al 2020. [47]q	81	4	1/3	Pos (4)	NA	1. AMS	CT head and CTA. CRP 260 mg/L	Left MCA stroke
						2. Dysarthria, left facial droop, left hemiparesis and hemineglect	CT head and CTA	Right MCA stroke
						3. AMS, left hemiparesis	CT head, CTA, CTP. CRP 162.4 mg/L. D-dimer 13966 ng/ml	Right ICA stroke
						4. Fifteen minutes of right arm weakness, numbness, aphasia	MRI (positive for stroke) and MRA. D-dimer 3,442ng/ml	TIA/Left MCA stroke
Al Saiegh et al. 2020. [48]V	46.5	2	1/1	Pos (2)	Neg (2)	1. Sudden headache, loss of consciousness	CT head, conventional angiography and CSF testing	Posterior fossa aneurysmal SAH and ICH
						2. Right hemiparesis, aphasia	CT head, CTA and CSF testing	Left MCA stroke
Beyrouti et al.	69.33	6	5/1	Pos (6)	NA	1. Left arm incoordination, 7 days later,	MRI brain. Pos lupus anticoagulant, D-dimer > 80,000 ng/mL. CRP 305.4	Left vertebral artery occlusion-> left PICA

2020. [49] €						bilateral incoordination and right homonymous hemianopia	mg/L. Fibrinogen 950 mg/dl	stroke-> 7 days later left PCA stroke
						2. Confusion, incoordination	CT head,.Pos lupus anticoagulant. D-dimer 7,750 ng/mL. CRP 150.1 mg/L. Fibrinogen 703 mg/dl	Left cerebellar and right parietooccipital infarcts
						3. Dysarthria, right hemiparesis	CT head,.Neg lupus anticoagulant, D-dimer 16,100 ng/mL. CRP 161.2mg/L. Fibrinogen 530 mg/dl	Left PCA stroke
						4. Dysarthria, left hemiparesis	MRI brain. Pos lupus anticoagulant, D-dimer 27,190 ng/mL. CRP 12.8 mg/L. Fibrinogen 463 mg/dl	Right MCA stroke
						5. Dysarthria, left hemiparesis	CT head and CTA. Pos lupus anticoagulant, D-dimer 19,450 ng/mL. CRP 27.7 mg/L. Fibrinogen 496 mg/dl	Right MCA stroke
						6. Dysphasia, right hemiparesis	MRI. Pos lupus anticoagulant, D dimer 1,080 ng/mL. CRP 179.9 mg/L	Basilar artery thrombus and bilateral P2 stenosis
Oxley et al. 2020. [50] Δ	40.4	5	4/1	Pos (5)	NA	1. Left hemiplegia, homonymous hemianopia, right gaze preference	CT, CTA, CTP, MRI. D-dimer 460 ng/ml, Fibrinogen 501 mg/dl	Right ICA stroke
						2. AMS, dysphasia, right hemiplegia	CT, CTA, MRI. D-dimer 52 ng/ml, Fibrinogen 370 mg/dl.	Left MCA stroke
						3. AMS, left hemiplegia, homonymous hemianopia, right gaze preference, ataxia	CT, CTA, CTP, MRI. D-dimer 2230 ng/ml, Fibrinogen 739 mg/dl	Right PCA stroke
						4. AMS, global aphasia, right hemiplegia, left gaze	CT, CTA, MRI. D-dimer 1388 ng/ml, Fibrinogen 443 mg/dl	Left MCA stroke
						5. AMS, left hemiplegia, dysarthria, left facial droop	CT, CTA, CTP. D-dimer 1750 ng/ml, Fibrinogen 531 mg/dl.	Right MCA stroke
Tunç et al 2020. [51]	65.25	4	2/2	Pos (4)	NA	1. Left hemiparesis, dysarthria, left facial droop	MRI brain. D-dimer 803 ng/mL. CRP 142 mg/L	Right MCA stroke
						2. Right hemiparesis, dysarthria	MRI brain. D-dimer 1040 ng/mL CRP 4 mg/L	Left lenticulostriate artery infarction
						3. Right hemiparesis, loss of consciousness	MRI brain. D-dimer 644 ng/mL. CRP 33 mg/L	Left MCA stroke
						4. Left hemi-	MRI brain. D-dimer 378	Right pontine

						hypoesthesia, mild ataxia	ng/mL. CRP 366 mg/L	infarction
Li et al. 2020. [52]	71.61	13	7/6	Pos (13)	NA	No neurological presentations were reported	CTV (1), CT head (1 R MCA and 1 L BG hg). CRP (median) 51.1 mg/L (13). D-dimer (median) 6900 ng/ml (13)	ICH (1). CVT (1). LVO (5). SVD stroke (3). CE stroke (3)

Table 2. Summary of the case series of COVID-19 with neurological complications

n (mg/dl): 101, 123, 193, normal protein, 40. WBCs (cells per mm^3): 4,0,0,0,3. Antiganglioside antibodies: negative (3), not , Case#1: Exam revealed limited adduction and downgaze movements of his right eye, and left eye nystagmus on left gaze. n revealed limited abduction in both eyes, and fixation nystagmus, with the upper gaze more impaired; ∞, Case#1 Negative DA antibodies. Case #1&2: Negative HSV/VZV PCRs; W, serum ferritin levels remarkably improved post plasmapheresis in atients. CSF (median): protein 69.4 mg/dl. WBCs 0 cells/µL. Glucose 116. OCBs neg (5); q, Case # 4: MRI/MRA revealed left oral lobe small infarct and left M1 stenosis; V, After 10 days, patient#2 presented with hemorrhagic conversion and is; €, patient 1 and 4 had PEs. Patient 2 INR was 3.6 (patient was already on warfarin). Patient 6 had right thalamus, left ccipital lobe and right cerebellar infarcts. 1 patient had non-treated atrial fibrillation, 1 had treated atrial fibrillation, 1 had ke; Δ, 2 patients had diabetes, 1 patient had hyperlipidemia and hypertension; , 9 out 13 patients had hypertension, 6 out betes mellitus, 3 out of 13 had cardiovascular disease, 1 out of 13 had malignancy, and 11 out of 13 had severe COVID-19 an failure.

l mental status. GBS: Guillain barre syndrome. ACA: anterior cerebral artery. AMSAN: Acute motor-sensory axonal CK: Creatine Kinase. CMAP: compound muscle action potential. COVID-19: Coronavirus disease 2019. CT: Computed CTA: CT angiography. CTP: CT perfusion. CTV: CT venogram. DVT: deep vein thrombosis. DWI: Diffusion Weighted : Electroencephalography. EMG: Electromyography. ICA: Internal carotid artery. ICU: Intensive care unit. INR: normalized ratio. LDH: Lactate dehydrogenase. MCA: middle cerebral artery. MRI: Magnetic Resonance Imaging. icable. NCS: nerve conduction studies. Neg: negative. Pos: positive. OCBs: oligoclonal bands. PMN: Polymorphonuclear s: lymphocytes. RT-PCT: Real-Time Polymerase Chain Reaction. SARS-CoV-2: severe acute respiratory syndrome coronavirus ensory nerve action potential. CRP: C-reactive protein. PTT: partial thromboplastin time. WBCs: white blood cells. CSF: al fluid. SAH: subarachnoid hemorrhage. ICH: intracerebral hemorrhage. L: left. R: right. PICA: posterior inferior cerebellar pulmonary embolisms. LVO: large vessel occlusion. SVD: small vessel disease. CE: cardioembolic. CVT: cerebral vein WM: white matter. AIDP: acute inflammatory demyelinating polyradiculoneuropathy.

80% (n=12) of the CNS infection related complications were meningoencephalitis, 6.6 % (n=1) had rhombencephalitis, 6.6% (n=1) had acute necrotizing hemorrhagic encephalopathy, and 6.6 % (n=1) had encephalopathy. In the 12 meningoencephalitis cases, only 4 CSFs revealed lymphocytic pleocytosis, two of which had positive CSF SARS-CoV-2 RT-PCR. 9 patients developed respiratory failure, 6 of which received plasmapheresis and one died. Furthermore, one of the status epilepticus patients was focal status epilepticus. Finally, The CSF of the patient with CNS demyelinating lesions was normal and oligoclonal bands were not sent **(Table 3)**.

Table 3. Chronological summery of patients' hospital course

*onset after respiratory or gastrointestinal symptoms or anosmia or dysgeusia, if the onset of neurological presentation (zero) the initial presentation of SARS-CoV-2 infection; *, 8,7,7,2 days respectively after the neurological presentation, the patients spiratory symptoms; **, The patients neurological presentation proceeded by anosmia and dysgeusia, there were no ymptoms; ***, 5 days after neurological presentation, CXR showed BL lungs densities; q, two patients had neurological 3,2 days respectively after gastroenterological symptoms, there were no respiratory symptoms; V, Patients regained after the 3rd cycle (1), 2nd cycle (1), and 1st cycle (2) of plasmapheresis.*

leptic drugs. DAPs: dual antiplatelet therapy. AP: antiplatelet. EVD: external ventricular drain. IVF: intravenous fluid. nous immunoglobulin. LMWH: low molecular weight heparin. NA: not applicable. Plex: plasmapheresis. RS: respiratory cough and or shortness of breath. LVO: large vessel occlusion. SVD: small vessel disease. CE: cardioembolic. CVT: cerebral sis.

Author, Year	Patients, Number	Onset of neurologic syndrome, Days `	Respiratory Failure (0=no, 1=yes)	Treatment	Outcome (0=no, 1=yes)			
					Good	Recovering	Poor	Deceased
Poyiadji et al. 2020 [10]	1	3	NA	IVIG	NA	NA	NA	NA
Moriguchi et al. 2020 [11]	1	9	1	Antimicrobials, steroid	0	0	1	0
Duong et al & Haung et al. 2020 [12&13]	1	0	0	AEDs, transient antimicrobials	0	1	0	0
Ye et al. 2020 [14]	1	13	1	Antimicrobials	1	0	0	0
Yin et al. 2020 [15]	1	13	0	Antimicrobials	1	0	0	0
Filatov et al. 2020 [16]	1	1	1	AEDs, antimicrobials	0	0	1	0
Wong et al. 2020 [17]	1	12	0	Antimicrobials, gabapentin	1	0	0	0
*Zhao et al. 2020 [18] **	1	-8	0	IVIG	1	0	0	0
Sedaghat et al. 2020 [19]	1	14	0	IVIG	NA	NA	NA	NA
Virani et al. 2020 [20]	1	10	1	IVIG	0	1	0	0
El-Otmani et al. 2020 [21]	1	3	0	IVIG	0	0	1	0
Alberti et al. 2020 [22]	1	7	1	IVIG	0	0	0	1
Camdessanche et al. 2020 [23]	1	11	1	IVIG	NA	NA	NA	NA
Padroni et al. 2020 [24]	1	24	1	IVIG	0	0	1	0
*Scheidl et al. 2020 [25] ***	1	14	0	IVIG	1	0	0	0
Ottaviani et al. 2020 [26]	1	10	1	IVIG	0	0	1	0
*Abdelnour et al. 2020 [27] **	1	-7	0	NA	1	0	0	0
Caamaño DS et al. 2020 [28]	1	7	0	Steroid	0	1	0	0
*Wei et al. 2020 [29] **	1	-7	1	IVIG, steroid, antimicrobials	0	0	0	1
Jin et al. 2020 [30]	1	15	1	IVF	0	1	0	0
Suwanwongse et al. 2020 [31]	1	0	0	IVF	0	1	0	0
Vollono et al. 2020 [32]	1	0	0	AEDs	1	0	0	0
Sohal et al. 2020 [33]	1	3	1	AEDs	0	0	0	1
*Zanin et al. 2020 [34] ***	1	NA	1	AEDs	0	1	0	0

*Paniz-Mondolfi et al. 2020 [35] ******	1	0	1	NA	0	0	0	1
González-Pinto et al. 2020 [36]	1	NA	1	NA	0	0	0	1
Zhou et al. 2020 [37]	1	24	1	DAPs + rivaroxaban	0	1	0	0
Valderrama et al. 2020 [38]	1	7	0	IV tPA + Thrombectomy	0	1	0	0
Viguier et al 2020. [39]	1	7	0	LMWH	0	1	0	0
Hughes et al. 2020 [40]	1	0	0	LMWH	0	1	0	0
Sharifi-Razavi et al. 2020 [41]	1	3	1	NA	NA	NA	NA	NA
Toscano et al. 2020 [42]	5	7 (2), 10 (2), 5 (1)	1(3)	IVIG (5), Plex (1)	1(1)	1(2)	1(2)	0
Gutiérrez-Ortiz et al. 2020 [43] q	2	5 (1), 3 (1)	0	IVIG (1)	1(2)	0	0	0
Chan et al. 2020 [44]	2	0 (2)	1(2)	IVF	0	1(1)	1(1)	0
Bernard-Valnet et al. 2020 [45]	2	5 (1), 17 (1)	NA	AEDs & transient antimicrobials (2)	1(2)	0	0	0
Dogan et al. 2020 [46]V	6	NA	1(6)	Plex (6)	0	1(4)	1(1)	1(1)
Avula et al 2020. [47] q	4	2 (1), 0 (3)	1 (3)	Aspirin + statin (1), no acute treatment (4)	0	1(1)	0	1(3)
Al Saiegh et al. 2020. [48]	2	7 (1), 0 (1)	1(2)	FD stent + EVD (1), thrombectomy (1)	0	1(2)	0	0
*Beyrouti et al. 2020. [49] **	6	-2 (1), 8 (1), 10 (1), 15 (2), 24 (1)	1(3)	DAPs (1), apixaban (1), LMWH (3), IV tPA (2)	0	0	1(5)	1(1)
Oxley et al. 2020. [50]	5	0(3), 7(1)	NA	Aspirin (2), Apixaban (2), stent (1), DAPs (1), IV tPA (1), thrombectomy (4), hemicraniectomy (1)	1(1)	1(3)	1(1)	0
Tunç et al 2020. [51]	4	4 (1), 1 (1), 7 (1), 2 (1)	0	DAPs (2), aspirin + low dose LMWH (2)	1(2)	2(2)	0	0
Li et al. 2020. [52]	13	12 (median)	NA	LMHW (2 LVO, 2 CE, 1 CVT). AP (3 SVD, 3 LVO, 1 CE)	0	1 (2)	1 (6)	1(5; one of them LVO)

Discussion

It became clear that the respiratory tract is not the sole target of SARS-CoV-2 virus. In an analysis of 214 cases of COVID-19 in Wuhan, China, 78 (36.4%) had neurological complications. Patients with severe infection were more likely to have neurological manifestations like alteration in sensorium and muscle weakness (45.5% Vs 30.2% in non-severe). The manifestations involved both the central and peripheral nervous system. The severity of these manifestations ranged from acute cerebrovascular disease and impaired consciousness to dizziness and headache. [53] Our systematic review confirms that neurological complications are not uncommon. Therefore, physicians should be attentive to such conditions like ischemic and non-ischemic stroke, Guillain Barre syndrome and its variants, CNS infection and seizure.

In our review, ischemic stroke was the most common neurological manifestation, occurring in 42.7% of the subjects. More than 75% of which was LVO stroke. According to a series of 388 COVID-19 patients from Italy, thromboembolic events occurred in 21% of the patients. Including venous thromboembolism, ischemic stroke, and acute coronary syndrome. [54] The exact mechanism of the hypercoagulable state is not well understood. D-dimers might play a major prothrombotic role in COVID-19 patients. In this review, more than 25% of the ischemic stroke patients had significant elevation of D-dimer level (>7000 ng/ml). High D-dimer levels are independently associated with poor outcome in SARS-CoV-2 infection. [55]. Severe COVID-19 respiratory infection often leads to sepsis induced hypercoagulability. Which is evident by increased D-dimer levels, increased intravascular platelet activation, increased fibrinogen, and mild prolongation of PT and aPTT. [56] Indeed, a study in Wuhan, China, showed that 71.4% of patients who died of COVID-19 had disseminated intravascular coagulation (DIC) with significant D dimer elevation. [55] Moreover, SARS-CoV-2 virus is known to bind angiotensin converting enzyme 2 (ACE2) receptor on endothelial cells which promotes a proinflammatory and vasoconstrictive state of endothelial dysfunction leading to end organ damage, including stroke. ACE2 recombinant therapy, therefore, may be a promising targeted therapy for COVID-19 related stroke. [57] Transient production of antiphospholipid antibodies may also play a role. In a study by Harzallah et al, 25 out of 56 patients with confirmed or suspected SARS-CoV-2 infection were positive for lupus anticoagulants, and 5 patients had either anticardiolipin or anti–β2-glycoprotein I antibodies. [58] Zhang et al detected antiphospholipid antibodies in 3 COVID-19 patients, all of them had multiple cerebral infarcts. [59] in this review, 5 of the LVO stroke were tested positive for lupus anticoagulant.

When presenting in the appropriate time window, thrombolytic treatment of COVID-19 patients with ischemic stroke is reasonable. While the role of anticoagulation, like LMWH, in this clinical context is still unclear. [57] Harzallah et al recommended early anticoagulation therapy for individuals with COVID-19 infection and positive lupus anticoagulant. [58] Previous investigations suggested that COVID-19 is associated with both platelet and clotting cascade activation. [60] In our review, 6 patients were given therapeutic LMWH, 3 were given apixaban, 4 were given dual antiplatelets (DAPs), 1 was given rivaroxaban and DAPs. Along those lines, further clinical trials are necessary to determine the role of antiplatelets and/or anticoagulation for the treatment and prevention of thrombotic events in COVID-19 infection, including milder cases.

Previously identified coronaviruses, including SARS-CoV1 and MERS, were associated with GBS. [61] In our review, neuromuscular disorders are the second most commonly encountered neurological complication of COVID-19 infection (28%), especially GBS. The mechanisms of GBS related to SARS-CoV-2 are still incompletely understood. Both para- and post-infectious mechanisms were proposed. [18 & 24] Two of the GBS patients in our review did not experience preceding respiratory or GI symptoms or fever and GBS was the initial presentation. This suggests para-infectious process, as has been reported recently with other viral infections like Zika virus. [62] COVID-19 infection is associated with macrophage activating syndrome, cytokine storm (IL-1β, IL-2, IL-6, IL-17, IL-8, TNF and CCL2) [63], immune system dysregulation, and lymphocyte alterations [64], all of which could induce an autoimmune damage to the peripheral nervous system. Expectantly, each molecule in this cascade might represent a future therapeutic target. With the emergence of more cases of acute neuropathies temporally linked to COVID-19 infection, we should gain better understanding of the underlying pathophysiology. Since these neuropathies are treatable and they pose increased morbidity and mortality, neurologists, intensivists and internists working with COVID-19 patients must be vigilant of this association.

The potential of the virus for direct invasion of the CNS has now been convincingly demonstrated by CSF analysis and postmortem examination. Two patients in our review have positive CSF SARS-CoV-2 RT-PCR. In one of which, the infection was entirely confined to the CNS and no other organs were affected. The other patient has negative NP swab testing while having positive CSF PCR. On postmortem examination, Paniz-Mondolfi et al documented evidence of viral particles in the neurons and capillary endothelial cells of the frontal lobe. They concluded that there was an active viral entry across the brain microvasculature into the neurons, as there was blebbing of viral particles coming in and out of the endothelial membrane. [35] Mechanistically, SARS-CoV2 virus may enter the CNS through hematogenous route or retrograde synaptic transmission. ACE 2 receptors, which are abundantly expressed in the endothelial cells, supporting glia and neurons, might be the binding site facilitating hematogenous entry. The systemic hyper-inflammation increases the permeability of the

blood-brain and blood-CSF barriers, which might facilitate CNS entry as well. [63] Retrograde synaptic transmission is probably associated with the olfactory nerve. [65] This possibility is supported by the fact that anosmia is a frequent early sign of COVID-19 infection. [66] It has been proposed that SARS-CoV-2 neurotropism may explain not only the common symptoms of encephalitis, but also the respiratory failure, by involvement of the medullary respiratory centers. This mechanism has been demonstrated in animal models, but not yet in humans. [67] Detailed investigations, including CSF studies, imaging, and when possible, autopsy, are required to better elucidate those mechanisms.

Although two COVID-19 patients in our review presented with status epilepticus, one of them had an established history of epilepsy from another cause. Lu et al studied 304 COVID-19 patients and concluded that none of these patients had acute symptomatic seizures or status epilepticus. [68] The current data are too limited to make any conclusions about the effects of COVID-19 on developing seizures.

Finally, Lovati et al reported a case of HSV-1 encephalitis, where the diagnosis and treatment were delayed because of anchoring on COVID-19 and its neurological complications. [69] Despite all the reports of COVID-19 neurological complications, other pathologies are still more common. Ignoring this would result in significant delays in diagnosing and treating neurological patients.

Our study has some limitations. First, most of the used evidence is based on single case reports or small series, which limits its generalizability. Second, some case reports did not complete or report the full workup required to exclude alternative causes of the neurological syndrome presented. Third, many cases are reported from specific ethnic populations, and hence, a number of demographics, genetic, or microbiologic variables, might preclude the applicability of the conclusions in different populations. Fourth, we have not studied the severity of COVID-19 infection and how it correlates with different neurological complications. Last, but not least, several stroke patients had multiple comorbidities and potentially causative vascular risk factors, that we did not include in our analysis.

Conclusions

Neurological manifestations of COVID-19 infection are not rare, especially large vessel stroke, Guillain barre syndrome and meningoencephalitis. They could be related to the direct cytopathic effect of the virus, the inflammatory response, hypercoagulable state, or complications of treatment and ICU stay. Moving forward, further studies are needed to clarify the prevalence of the neurological complications of COVID-19, investigate their biological background, and treatment options. Physicians should be cautious not to overlook other neurological diagnoses that can mimic COVID-19 during the pandemic.

Declarations

Conflict of Interest

The authors declare that they have no competing interests

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Not Applicable

Authors Contributions

Dr. Ghannam and Dr. Manousakis planned the search strategy, made the inclusion and exclusion criteria and built the key words for the systematic review. Dr. Ghannam, Dr. Alshaer and Dr. Manousakis participated in articles screening and assessing their eligibility to the study. Both Dr. Ghannam and Dr. Manousakis completed the final form of PRISMA flowchart of the selection of the studies for this review. Dr. Ghannam, Dr. Alshaer, Dr. Al-Chalabi and Dr. Zakarna were responsible for drafting and editing of the manuscript. Dr. Ghannam and Dr. Robertson were responsible of making the tables and the

figures. Dr. Manousakis participated in critical revision of the manuscript for intellectual content. All authors read and approved the final manuscript.

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There was no ethics committee approval as the data has been analyzed in a retrospective manner and has no effect on treatment of the patient

Data Sharing Statement

All the data supporting our findings is contained within manuscript

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Figures

Figure 1. PRISMA flowchart of the selection of the studies for this review.

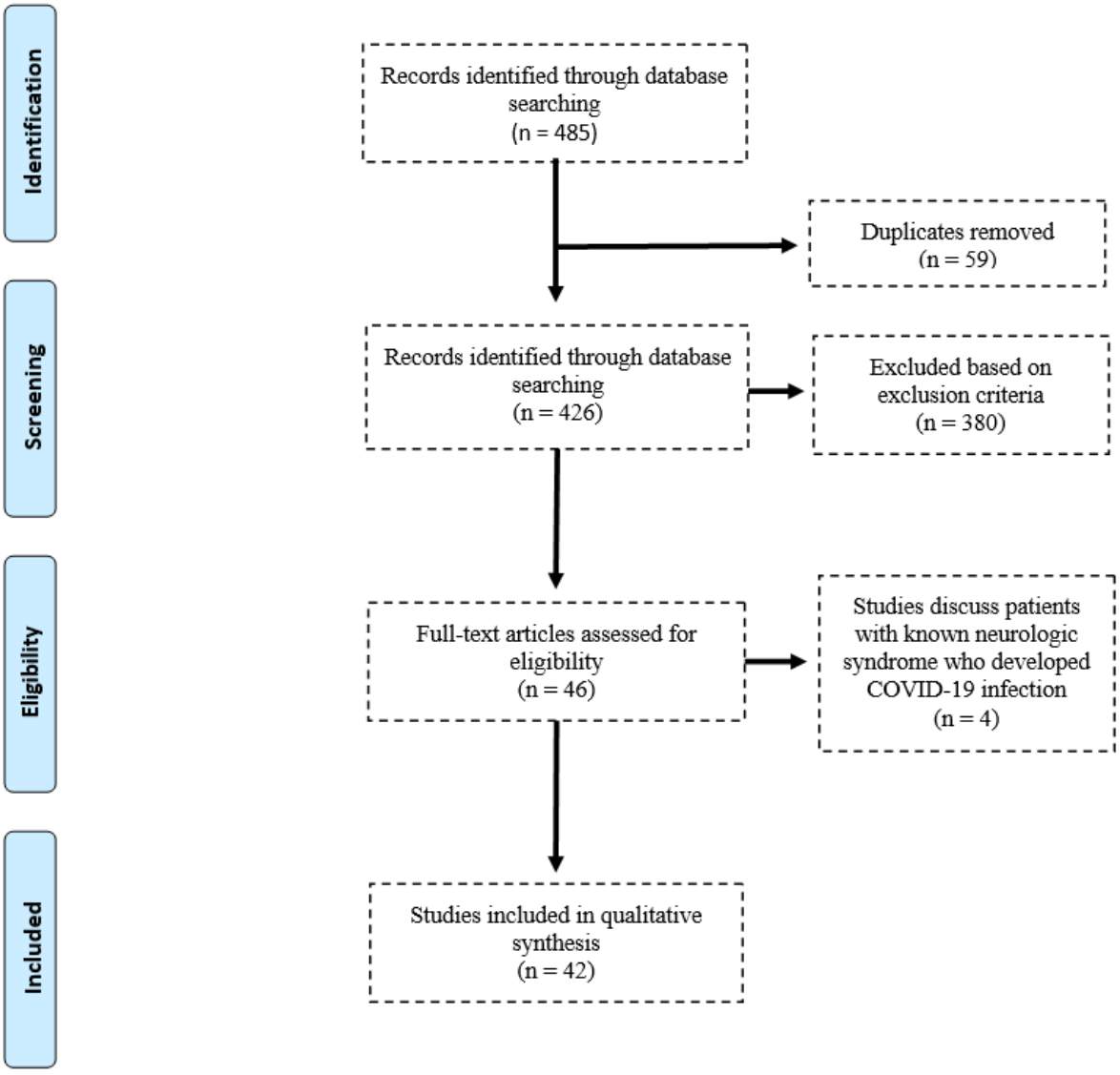

Figure 1

PRISMA flowchart of the selection of the studies for this review.

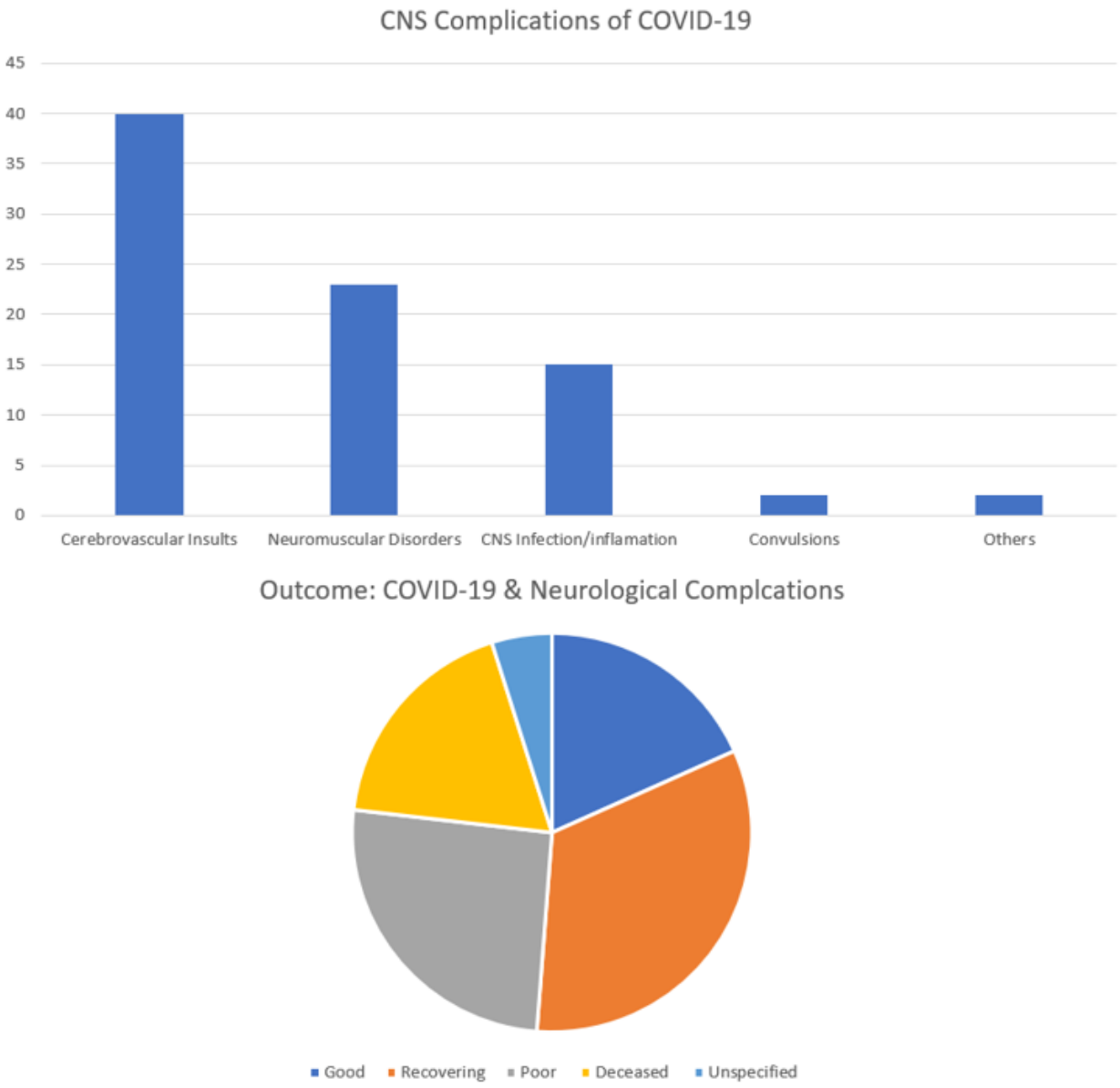

Figure 2

CNS complications of COVID-19

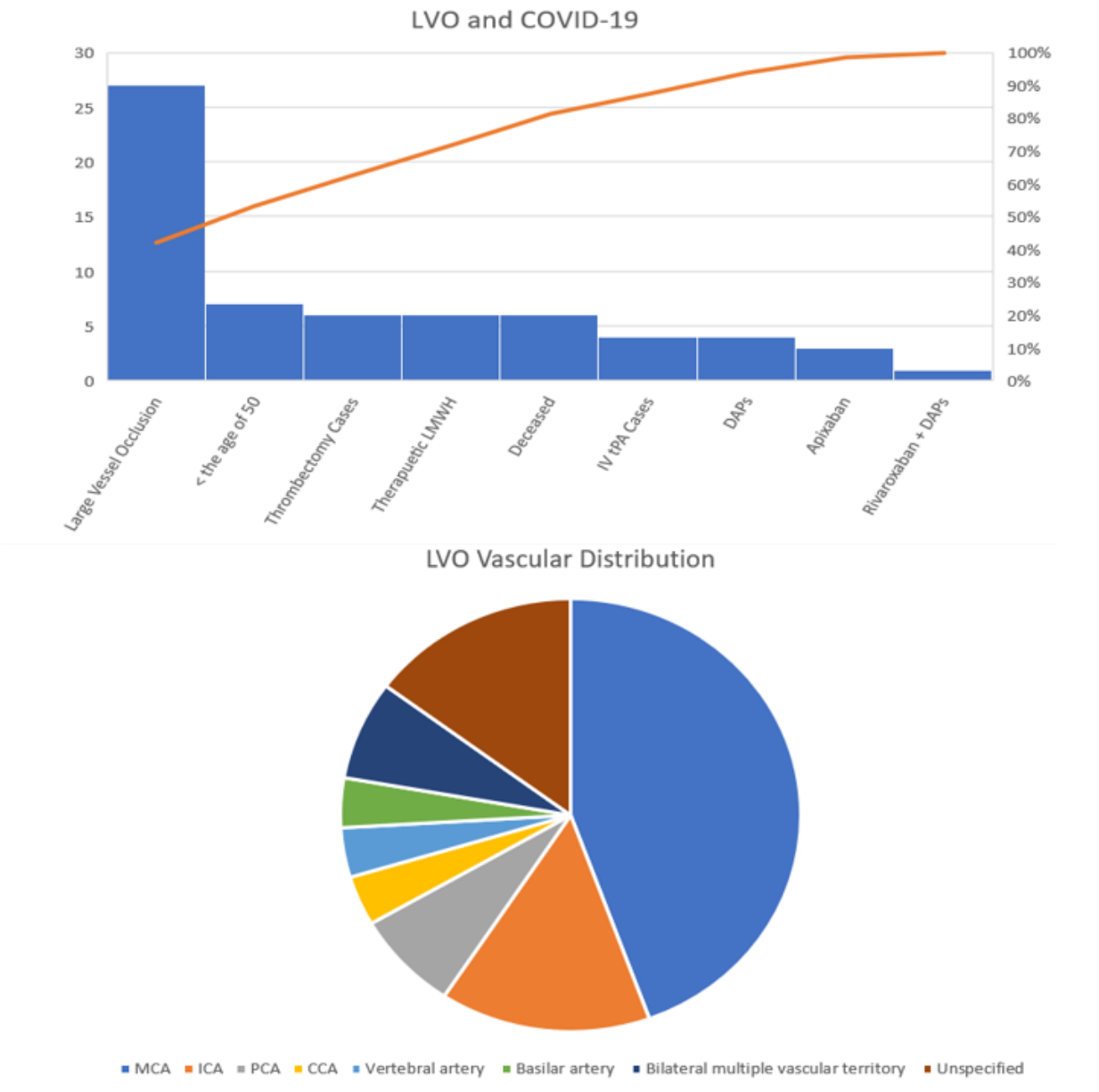

Figure 3

Large vessel stroke and COVID-19

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table3Final.docx
- Table2Final.docx
- Table1Final.docx