

# Neurological Complications of COVID-19: A Systematic Review of Literature

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## Research article

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## Abstract

**Background:** To study the nature and frequency of occurrence of “significant” neurological complications in coronavirus disease-2019 (COVID-19) via a systematic review of the literature.

**Methods:** We screened all articles resulting from a search of PubMed, Cochrane, Google Scholar and Scopus, using the keywords “COVID-19 and CNS”, “SARS-CoV-2 and CNS”, “COVID-19 and neurological manifestation”, “SARS2 and neurological manifestation” and “COVID-19 and Brain” looking for reports of significant neurological manifestations that would potentially have an impact on the outcome.

**Results:** Twenty-six articles met the inclusion criteria. The significant neurological diagnoses reported were stroke, Guillain Barre Syndrome (GBS) and its variants, encephalitis, seizures, acute hemorrhagic necrotizing encephalopathy, acute disseminated encephalomyelitis (ADEM) and transverse myelitis. Although stroke, predominantly ischemic, was observed in ~ 6% of COVID-19 patients from Wuhan, China, mortality in this cohort was 38%. Of the 24 pooled patients with reports of etiology, 17 had large vessel occlusions. GBS occurred in 5/1200 (0.4%) of the COVID-19 cohort from Italy. One of the six reported encephalitis cases, the ADEM case and the report of transverse myelitis do not have data for conclusive diagnosis.

**Conclusion:** The most frequent significant neurological association with COVID-19 is stroke, predominantly ischemic. In a cohort from Wuhan, China, this was as frequent as ~ 6%, with a 38% mortality. Most common reported etiology is large vessel occlusion. Other reported significant neurological complications are GBS/variants, encephalitis, seizures and acute hemorrhagic necrotizing encephalopathy. The reports of ADEM and transverse myelitis lacked diagnostically conclusive data.

## Background

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic started as a cluster of cases of pneumonia in Wuhan, China. As the viral spread continues, it is critically important that health care workers are aware of emerging data on the constantly widening clinical manifestations of SARS-CoV-2 [1, 2].

While people infected with SARS-CoV-2 typically present with fever, cough, and shortness of breath, more severe infections may lead to pneumonia, acute respiratory distress syndrome, acute cardiac problems and multiorgan failure [1, 3]. There have been reports of neurological manifestations albeit in fewer numbers. The virus is potentially neurotropic, with spread via the systemic circulation or across the cribriform plate [4, 5]. ACE-2 receptors on the capillary endothelium may be the target for SARS-CoV-2 spike protein facilitating viral entry into the nervous system [4]. Infection of the CNS can cause manifestations such as anosmia, dysgeusia, and in more severe cases, encephalitis [4-7]. In addition to direct viral invasion, the brain may be affected secondarily due to extensive endothelial dysfunction from cytokine storm that predisposes to arterial/venous thrombosis or hemorrhage and resultant stroke [5, 8]. Parainfectious complications secondary to dysregulated immunity may lead to antibody-mediated damage to the central or peripheral nervous system leading to Bickerstaff's encephalitis and Guillain Barre Syndrome (GBS) that was described in MERS-CoV. Prolonged ICU stay and mechanical ventilation may lead to critical care neuropathy/myopathy [9, 10].

The first cohort study that described neurological manifestations of COVID-19 included 214 patients from China and described 36.4% of individuals with neurological manifestations. Six (2.8%) patients from this cohort suffered cerebrovascular complications, with the majority included for milder neurological symptoms of headache (13%), dizziness (16%), impaired consciousness (8%), hypogeusia (5%), or hyposomia (5%) [7]. These minor manifestations such as hyposmia and dysgeusia do not typically affect the outcome but may be of diagnostic significance when used as screening for the disease [6, 7]. Less common, but more serious neurological manifestations reported are cerebrovascular disease [7, 11], encephalitis [12], seizures, and GBS [7, 12-14].

In our systematic review, therefore, we sought to summarize the significant neurological manifestations associated with COVID-19 disease. Our study focused on the less frequent but more severe and potentially more clinically meaningful neurological manifestations in patients with COVID-19 [11, 12, 14-16].

## Methods

Using the keywords “COVID-19 and CNS”, “SARS-CoV-2,” and “CNS COVID-19 and neurological manifestation”, “SARS2 and neurological manifestation”, “COVID-19 and Brain”, we searched PubMed, Google Scholar, Scopus and Cochrane library. Of the resulting articles, we included original research, case series and case reports (Fig. 1), excluded review articles, consensus statements and editorials. Of the articles thus selected, we again excluded articles reporting minor central nervous system manifestations only, thus generating articles reporting confirmed cases of COVID-19 with significant CNS manifestations with potential for impact on the outcome. Neurological manifestations obtained from these studies that were considered significant and included for analysis were, ischemic stroke, cerebral hemorrhage, cerebral venous thrombosis, encephalitis, GBS and its variants, seizures, ADEM and transverse myelitis. Neurological manifestations considered minor and excluded from this analysis were: taste, smell, or vision impairment (without a specific neurologic diagnosis), nerve pain, dizziness, headache, encephalopathy and skeletal muscle injury. We used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) for the display of inclusions and exclusions (Fig. 1) [17].

### *Data acquisition:*

From the selected articles, we extracted the study type, month and year of publication, various significant neurological complications reported, the number of cases with major neurological manifestations in each study, age (either patient age or mean/median age from the study) and mortality. We did not pool the data of Mao et al. with Li et al. due to the assumption of duplication, as these studies targeted the same hospital during an overlapping period.

## Results

Of the twenty-six articles that qualified for inclusion, four were retrospective cohort studies, six were case series describing 2–6 patients and sixteen were case reports of single patient descriptions. Of the four cohort studies, two studies used the same cohort of patients from Wuhan, China. One of these (Mao et al) [7] reviewed all neurological manifestations including stroke and minor manifestations such as anosmia, dysgeusia and the other (Li et al) [11] reported cerebrovascular complications only. Of the 26 articles (Table 1) included in this study for the discussion, data was pooled from 25 (excluding Mao et al due to assumption of overlapping cohort with Li et al) and generated 1520 patients. In all patients, COVID-19 was diagnosed based on nasopharyngeal reverse transcriptase polymerase chain reaction (RT-PCR) except two where diagnosis was made based on cerebrospinal fluid RT-PCR [12, 18]. Of the 1520, 56 patients qualified as having significant neurological manifestations (Table 1, Fig. 2). Thirty-one patients experienced a cerebrovascular complication, with 27 ischemic strokes [11, 19–23], 3 hemorrhagic strokes [11, 15, 23] and 1 cerebral venous sinus thrombosis [11]. There were 15 patients with GBS [13, 14, 24–30] or its variants, 6 reported as encephalitis [12, 18, 31–33], one with seizures [34], one with acute hemorrhagic necrotizing encephalopathy [16] one reported as transverse myelitis [35], and one reported as ADEM [36]. Nine of these cases were reported as fatal. The neurological diagnosis in these reported fatal cases were stroke - ischemic and hemorrhagic, encephalitis and GBS. CSF was reportedly tested by RT-PCR for SARS-CoV-2 in 13 and out of these 2 were positive [12, 18].

Table 1  
Significant Neurological Complications of COVID-19 reported between December 1st, 2019 to May7th, 2020

Publication	Total patients	Gender	Age (years)	Ischemic Stroke	Hemorrhagic Stroke	Cerebral Venous Thrombosis	Encephalitis	Seizure	Necrotizing hemorrhagic encephalopathy	Transverse Myelitis	ADE
Mao et al. (03/2020)	214	127 F/ 87 M	52.7*	5 / 214	1 / 214	0 / 214	0 / 214	0 / 214	0/214	0 / 214	0
Yanan Li et al. (03/2020)	221	113 F/ 108 M	55**	11 / 221	1 / 221	1 / 221	0 / 221	0 / 221	0/221	0 / 221	0
Helms et al. (04/2020)	64	NA	63*	3 / 64	0 / 64	0 / 64	0 / 64	0/64	0/64	0 / 64	0
Toscano et al. (04/2020)	1200	NA	NA	0 / 1200	0 / 1200	0 / 1200	0 / 1200	0 / 1200	0/1200	0 / 1200	0
Beyrouti et al. (04/2020)	6	1F/5M	68.5**	6/6	0	0	0	0	0	0	0
Oxley et al. (04/2020)	5	1F/4M	39**	5/5	0	0	0	0	0	0	0
Dinkin et al. (04/2020)	2	1F/1M	53.5**	0	0	0	0	0	0	0	0
Al Saiegh et al. (04/2020)	2	1F/1M	46.5**	1	1	0	0	0	0	0	0
Bernard-Valnet et al. (04/2020)	2	2F	65.5**	0	0	0	2	0	0	0	0
Gutierrez-Ortiz et al. (04/2020)	2	1 F/1 M	45**	0	0	0	0	0	0	0	0
Mingxiang Ye et al. (04/2020)	1	M	NA	0	0	0	1	0	0	0	0
Sedaghat, Karimi (04/2020)	1	M	65	0	0	0	0	0	0	0	0
Sharifi-Razavi et al. (03/2020)	1	M	79	0	1	0	0	0	0	0	0
Karimi et al. (03/2020)	1	F	30	0	0	0	0	1	0	0	0
Zhao H et al. (04/2020)	1	F	61	0	0	0	0	0	0	0	0

\* Mean, \*\*Median, NA data unavailable

Mao et al and Li et al had overlapping cohort of patients, the stroke patients reported by Mao et al are accounted for in Li et al cohort.

F = Female, M = Male, CNS = Central Nervous System, GBS = Guillain-Barre Syndrome, ADEM = Acute Disseminated Encephalomyelitis

Publication	Total patients	Gender	Age (years)	Ischemic Stroke	Hemorrhagic Stroke	Cerebral Venous Thrombosis	Encephalitis	Seizure	Necrotizing hemorrhagic encephalopathy	Transverse Myelitis	ADEM
Zhao K et al. (04/2020)	1	M	68	0	0	0	0	0	0	1	0
Poyiadji et al. (03/2020)	1	F	51	0	0	0	0	0	1	0	0
Sun et al. (03/2020)	1	M	56	0	0	0	1	0	0	0	0
Virani et al. (04/2020)	1	M	54	0	0	0	0	0	0	0	0
Alberti et al. (04/2020)	1	1M	71	0	0	0	0	0	0	0	0
Padroni et al. (04/2020)	1	1F	70	0	0	0	0	0	0	0	0
Coen et al. (04/2020)	1	1M	70	0	0	0	0	0	0	0	0
Moriguchi et al. (03/2020)	1	M	24	0	0	0	1	0	0	0	0
Zhail et al. (03/2020)	1	M	79	1	0	0	0	0	0	0	0
Duong et al. (04/2020)	1	F	41	0	0	0	1	0	0	0	0
Zhang et al. (04/2020)	1	F	40	0	0	0	0	0	0	0	1
* Mean, **Median, NA data unavailable											
Mao et al and Li et al had overlapping cohort of patients, the stroke patients reported by Mao et al are accounted for in Li et al cohort.											
F = Female, M = Male, CNS = Central Nervous System, GBS = Guillain-Barre Syndrome, ADEM = Acute Disseminated Encephalomyelitis											

Of the four cohort studies selected, 2/4 (Mao et al. and Helms et al.) included both major and minor neurological manifestations; pooling these together, 9/272 (3.3%) qualified as significant based on our study criteria. All nine patients experienced strokes; 8 ischemic and one hemorrhagic including 1 fatality. Li et al. looked exclusively at cerebrovascular complications and reported a rate of 13/221 (5.8%), among which 5/13 (38%) were fatal. Pooling the Li et al. and Helms et al. data, the frequency of stroke was 16/279 (5.7%). In the Li et al. series, "the patients with new-onset stroke were significantly older (median 71.6, range 57–91), were more likely to present with severe disease (per American Thoracic Society guidelines for pneumonia) [37], and were more likely to have cardiovascular risk factors such as hypertension and diabetes. Further, they were more likely to have higher C reactive protein and D-dimer, reflecting a higher degree of inflammation and coagulability. The median duration from the first symptoms of SARS-CoV to stroke was 10 days". Among patients with ischemic stroke, 5 had large vessel disease, 3 had small vessel disease, and 3 had cardioembolic phenomena [11]. All six patients in the Beyrouti et al series from UK "had large vessel occlusion with markedly elevated D-dimer levels ( $\geq 1000 \mu\text{g/L}$ ). Three patients had multi-territory infarcts, two had concurrent venous thrombosis, and in two, ischemic strokes occurred despite therapeutic anticoagulation". All had severe disease per ATS criteria for pneumonia [37] and four had cardiovascular risk factors such as hypertension and diabetes, one was fatal [21]. In the Oxley et al series as well, all 5 patients had large vessel occlusion as the cause of ischemic stroke. All patients were young, with ages ranging from 33 to 49 years. Three had cardiovascular risk factors such as hypertension, diabetes and/or prior mild CVA. Three had elevated D-dimer > 1000 ng/ml. In Al Saiegh et al series, one had subarachnoid hemorrhage and the second was ischemic large vessel occlusion, SARS-CoV-2 was negative on CSF in both patients.

Toscano et al looked at the occurrence of GBS and reported a frequency of 5/1200 (0.4%). There have been eight other individual case reports of GBS or variants (Miller-Fisher syndrome and polyneuritis cranialis) [13, 14, 24–30]. Of the total of 15 pooled cases of GBS/variants, 2 were reported as fatal.

Altogether, there have been six reports of encephalitis [12, 18, 31–33], one of seizures [34], one of acute hemorrhagic necrotizing encephalopathy [16], one transverse myelitis and one of ADEM [35, 36]. Of the six patients reported as having encephalitis, CSF pleocytosis was reported in 4/6, elevated CSF protein in 3/6, CSF RT-PCR was tested in 5/6 and was positive in 2/5 [12, 18]. The one patient reported as having seizures had multiple generalized tonic-clonic seizures

in the setting of fever, fatigue, and shortness of breath. MRI and CSF analysis (5 lymphocytes, normal glucose, and chemistry) were reported as normal [34]. One patient diagnosed with acute hemorrhagic necrotizing encephalopathy presented with impaired consciousness, brain MRI revealed bilaterally symmetric rim enhancing hemorrhagic lesions in thalami, medial temporal lobes and sub-insular regions hemorrhage. CSF was negative for HSV, VZV, WNV, but traumatic tap limited testing for SARS-CoV-2. CSF cell count and chemistry were not reported [16]. One patient presented with presumed transverse myelitis in the setting of COVID-19. The authors reported acute flaccid paralysis with bowel and bladder impairment and a sensory level at T10 and there is no confirmatory CSF or spine imaging to support the diagnosis of acute transverse myelitis [35, 38]. One patient reported as ADEM [36] presented with fever, dysarthria, dysphagia and change in mentation. CSF showed normal glucose, protein and cell count. MRI was found to have extensive patchy lesions involving the bilateral frontoparietal, temporal, basal ganglia and thalami. With area of DWI and ADC changes and “minimal questionable enhancement”. CSF for VZV, HSV 1, 2 and 6 and WNV pcr, Cryptococcal ag test was all negative. She was treated with hydroxychloroquine and intravenous immunoglobulins following which she improved in her clinical course.

## Discussion

From the analysis of the included studies, the most frequent significant neurologic manifestation in COVID-19 patients is a stroke with a frequency of ~ 6%. Li et al. studied exclusively cerebrovascular disease in COVID-19 patients and reported a mortality of 38% in their cohort with stroke as a complication [8, 11]. Out of 11 ischemic stroke cases, 5 had large vessel disease, 3 had small vessel disease and 3 had cardioembolic phenomena [11]. Two subsequent series, one from UK and the other from NY reported all large vessel strokes [21, 22]. Pooling all the stroke patients where TOAST classification [39] was discussed, 17/24 had large vessel occlusions, 4 had small vessel disease and 3 had cardio-embolic etiology. One possible mechanism for thrombosis leading to ischemic stroke in patients with COVID-19 is the cytokine storm caused by SARS-CoV-2 viremia, leading to severe endothelial dysfunction and progressive microvascular thrombosis. Rise in D-dimer and the prolonged prothrombin time seen clinically support this phenomenon [40]. Activation of the coagulation cascade leading to disseminated intravascular coagulation can significantly contribute to the multiorgan involvement in patients with COVID-19, resulting in acute ischemic stroke, cerebral venous sinus thrombosis or intracerebral hemorrhage [8, 40, 41]. Moreover, the adhesion of SARS-CoV-2 to ACE2 receptors gains particular importance in the cases of intracerebral hemorrhage due to the inactivation of the receptor and subsequent dysfunction in blood pressure regulation [8, 11, 15, 20, 40]. It is also possible that some cases of ischemic stroke in COVID-19 patients have a cardio-embolic source from virus-related cardiac injury [11]. The large vessel occlusion (LVO) strokes have been shown to be associated with cardioembolic etiology [42].

There have been six reports described as encephalitis, but one of these lacks basic CSF data, and encephalitis was presumed due to the detection of viral DNA by RT-PCR in CSF [18]. However, mere detection of SARS-CoV-2 DNA by RT-PCR in the CSF is not necessarily equivalent to CNS infection. A traumatic lumbar puncture could have contaminated the CSF sample with the patient's blood, which contained the genetic material of SARS-CoV-2. More conclusive evidence of SARS-CoV-2 associated meningitis/encephalitis is depicted by a case report of a comatose patient with positive RT-PCR for SARS-CoV-2 in the CSF and neuroimaging features indicative of right lateral ventriculitis and encephalitis mainly on the right mesial lobe and hippocampus. Nasopharyngeal swab testing, however, was negative for SARS-CoV-2 [12]. Viral neuroinvasion and subsequent neuronal injury have also been proposed to contribute to the pathogenesis of these severe inflammatory complications of the central nervous system in coronavirus diseases [7, 41]. New-onset seizures were reported in one patient with SARS-CoV-2 without accompanying evidence of encephalitis [34]. Patients with severe SARS-CoV-2 illness may have hypoxia, multiorgan failure, metabolic and electrolyte derangements that may predispose to encephalopathy and seizures [43]. Pro-inflammatory cytokines release interleukins 2, 6, 7, and 10, tumor necrosis factor  $\alpha$ , and the granulocyte colony-stimulating factor, causing neuronal hyperexcitability through glutamate receptor activation leading to seizure [34].

The report of transverse myelitis has no objective data (CSF or spinal imaging) to confirm a diagnosis; acute flaccid paraparesis with sensory level at T10 and bowel and bladder involvement was the basis of diagnosis in this case. Therefore, the diagnosis is possible but not confirmed based on presented data [35]. One patient with possible acute disseminated encephalomyelitis (ADEM) did not have definite evidence of inflammation and/or demyelination and did not fulfill the criteria for ADEM [36, 44].

In addition to the central nervous system manifestations described above, the peripheral nervous system may also be affected and is particularly vulnerable to immune-mediated diseases. GBS occurred in 5/1200 (0.4%) patients with COVID-19 in one of the studies [13]. There were six other case report of GBS, one Miller Fisher syndrome, and two polyneuritis cranialis [14, 24–30]. Interestingly, neurotropism of human coronaviruses has been suggested by in vitro and in vivo studies that showed that certain strains of the viruses could persist in the human CNS by targeting oligodendrocytic and neuroglial cell lines [41]. Immune-mediated disorders have also been reported in patients with MERS-CoV [10], such as Bickerstaff's encephalitis, GBS and acute disseminated encephalomyelitis [45].

As neurologists practicing during this pandemic, recognition of the extra-pulmonary consequences of COVID-19 infection will optimize these patients' management. A subpopulation potentially even more susceptible to neuroinflammation are those patients who already have immune-mediated neurological disorders and whose immunosuppressive therapy raises their risk of COVID-19 infection. Other populations of special interest are neurologically frail patients with previous diagnoses of stroke, traumatic brain injury, treatment-refractory epilepsy or severe neurodegenerative disorders. These patients are prone to pulmonary infections and may reside in nursing homes that increase the risk of infection with SARS-CoV-2.

## Study Limitations

The results of this study were influenced mainly by two large cohorts (Li et al. and Toscano et al.) [11, 13], one of these was from China that looked at cerebrovascular disease alone and the other from Italy that looked at GBS alone. These results may not be applied widely due to genetic and environmental differences individual to regional geography. As discussed above, the diagnosis of possible encephalitis in one patient and possible transverse myelitis in one patient were not confirmed as these reports lacked conclusive data. Further, we can infer an association of these neurological complications with COVID-19;

however, we cannot presume causality. The high mortality reported in stroke with the COVID-19 cohort cannot be presumed to be related to stroke; it may reflect the severity of underlying illness.

## Conclusion

Although most SARS-CoV-2 infections predominantly involve the respiratory system, the brain is not immune to injury, and when neurologic complications associated with the virus occur, they can be severe or even fatal. The most frequent significant neurological reported complication associated with COVID-19 is stroke, mainly ischemic, with a frequency of ~ 6% and 38% mortality. The most common etiology reported is large vessel occlusions. Neurologists should also be aware of less common neurological associations of COVID-19, such as GBS/variants, encephalitis, seizures, and acute hemorrhagic necrotizing encephalopathy. Reports of transverse myelitis and ADEM lacked data for a conclusive diagnosis. Overall, of all cases with neurological complications, 2 had CSF RT-PCR positivity for SARS-CoV-2 of the 13 patients that were tested. Observational data is key to gaining a better understanding of the disease's natural history and plays a central hypothesis-forming role in pathophysiology and treatment trials. Further studies, however, are needed to identify subpopulations who may be at increased risk and to provide evidence-based treatment paradigms.

## Abbreviations

COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ATS/IDSA, American Thoracic Society and Infectious Disease Society of America; CT, Computed Tomography; RT PCR, Reverse Transcription Polymerase Chain Reaction; PRISMA, Preferred reporting items for systematic reviews and meta-analyses; GBS, Guillain Barre Syndrome; ADEM, Acute disseminated encephalomyelitis; CSF, Cerebrospinal fluid; CVA, Cerebrovascular accident; LVO, Large vessel occlusion; DWI, Diffusion weighted imaging; ADC, Apparent diffusion coefficient; HSV, Herpes simplex virus; VZV, Varicella zoster virus; WNV, West Nile virus; MERS, Middle East Respiratory Syndrome; MRI, Magnetic resonance imaging.

## Declarations

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Availability of data and materials:** Data was extracted from the articles published in Google Scholar, PUBMED, Scopus. This will be provided on request.

**Competing interests:**

Shitiz Sriwastava - Reports no disclosure

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Drafting the manuscript: SKS, SS, SK, VM, AA

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## References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. [10.23750/abm.v91i1.9397](https://doi.org/10.23750/abm.v91i1.9397)
2. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. *Acta Biomed.* 2020;91 1:157 – 60; doi: 10.23750/abm.v91i1.9397.

3. Lai CC, Wang CY, Wang YH, Hsueh SC, Ko WC, Hsueh PR. Global epidemiology of coronavirus disease 2019 (COVID-19): disease incidence, daily cumulative index, mortality, and their association with country healthcare resources and economic status. *Int J Antimicrob Agents*. 2020:105946; doi: 10.1016/j.ijantimicag.2020.105946.
4. Baig AM, Khaleeq A, Ali U, Syeda H. Evidence of the COVID-19 Virus Targeting the CNS: Tissue Distribution, Host-Virus Interaction, and Proposed Neurotropic Mechanisms. *ACS Chem Neurosci*. 2020;11 7:995–8. doi:10.1021/acscchemneuro.0c00122.
5. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. *Behavior Immunity*. 2020. doi:https://doi.org/10.1016/j.bbi.2020.03.031.
6. Lechien JR, Chiesa-Estomba CM, De Siati DR, Horoi M, Le Bon SD, Rodriguez A, et al. Olfactory and gustatory dysfunctions as a clinical presentation of mild-to-moderate forms of the coronavirus disease (COVID-19): a multicenter European study. *Eur Arch Otorhinolaryngol*. 2020. doi:10.1007/s00405-020-05965-1.
7. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol*. 2020. doi:10.1001/jamaneurol.2020.1127.
8. Umapathi T, Kor AC, Venketasubramanian N, Lim CC, Pang BC, Yeo TT, et al. Large artery ischaemic stroke in severe acute respiratory syndrome (SARS). *J Neurol*. 2004;251 10:1227–31. doi:10.1007/s00415-004-0519-8.
9. Kim JE, Heo JH, Kim HO, Song SH, Park SS, Park TH, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. *Journal of clinical neurology (Seoul Korea)*. 2017;13 3:227–33. doi:10.3988/jcn.2017.13.3.227.
10. Peeri NC, Shrestha N, Rahman MS, Zaki R, Tan Z, Bibi S, et al. The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned? *Int J Epidemiol*. 2020. doi:10.1093/ije/dyaa033.
11. Li Y, Wang M, Zhou Y, Chang J, Xian Y, Mao L, et al. Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study.
12. Moriguchi T, Harii N, Goto J, Harada D, Sugawara H, Takamino J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. *Int J Infect Dis*. 2020;94:55–8. doi:10.1016/j.ijid.2020.03.062.
13. Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain-Barre Syndrome Associated with SARS-CoV-2. *N Engl J Med*. 2020. doi:10.1056/NEJMc2009191.
14. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, San Pedro-Murillo E, Bermejo-Guerrero L, Gordo-Manas R, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology*. 2020. doi:10.1212/wnl.0000000000009619.
15. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental?.
16. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology*. 2020:201187; doi:10.1148/radiol.2020201187.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151 4:264–9. doi:10.7326/0003-4819-151-4-200908180-00135. w64.
18. Sun T, Guan J. Novel coronavirus and central nervous system. *Eur J Neurol*. 2020. doi:10.1111/ene.14227.
19. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med*. 2020. doi:10.1056/NEJMc2008597.
20. Li Y, Zhai P, Ding Y. The impact of COVID-19 on ischemic stroke: A case report.
21. Beyrouti R, Adams ME, Benjamin L, Cohen H, Farmer SF, Goh YY, et al. Characteristics of ischaemic stroke associated with COVID-19. *J Neurol Neurosurg Psychiatry*. 2020. doi:10.1136/jnnp-2020-323586.
22. Oxley TJ, Mocco J, Majidi S, Kellner CP, Shoirah H, Singh IP, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. *N Engl J Med*. 2020. doi:10.1056/NEJMc2009787.
23. Al Saiegh F, Ghosh R, Leibold A, Avery MB, Schmidt RF, Theofanis T, et al. Status of SARS-CoV-2 in cerebrospinal fluid of patients with COVID-19 and stroke. *Journal of Neurology, Neurosurgery & Psychiatry*. 2020.
24. Dinkin M, Gao V, Kahan J, Bobker S, Simonetto M, Wechsler P, et al. COVID-19 presenting with ophthalmoparesis from cranial nerve palsy. *Neurology*. 2020. doi:10.1212/wnl.0000000000009700.
25. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barré syndrome associated with SARS-CoV-2 infection: causality or coincidence?.
26. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. *J Clin Neurosci*. 2020. doi:10.1016/j.jocn.2020.04.062.
27. Virani A, Rabold E, Hanson T, Haag A, Elrufay R, Cheema T, et al. Guillain-Barre Syndrome associated with SARS-CoV-2 infection. In: *IDCases*. Netherlands: (c) 2020 The Author(s). Published by Elsevier Ltd.; 2020. p. e00771.
28. Alberti P, Beretta S, Piatti M, Karantzoulis A, Piatti ML, Santoro P, et al. Guillain-Barre syndrome related to COVID-19 infection. *Neurol Neuroimmunol Neuroinflamm*. 2020;7 4; doi:10.1212/nxi.0000000000000741.
29. Padroni M, Mastrangelo V, Asioli GM, Pavolucci L, Abu-Rumeileh S, Piscaglia MG, et al. Guillain-Barre syndrome following COVID-19: new infection, old complication? In: *J Neurol*. Germany; 2020.
30. Coen M, Jeanson G, Alejandro Culebras Almeida L, Hubers A, Stierlin F, Najjar I, et al. Guillain-Barre Syndrome as a Complication of SARS-CoV-2 Infection. *Brain Behav Immun*. 2020. doi:10.1016/j.bbi.2020.04.074.
31. Bernard-Valnet R, Pizzarotti B, Anichini A, Demars Y, Russo E, Schmidhauser M, et al. Two patients with acute meningo-encephalitis concomitant to SARS-CoV-2 infection. *medRxiv*. 2020.

32. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun*. 2020. doi:10.1016/j.bbi.2020.04.017.
33. Duong L, Xu P, Liu A. Meningoencephalitis without Respiratory Failure in a Young Female Patient with COVID-19 Infection in Downtown Los Angeles, Early April 2020. *Brain Behav Immun*. 2020. doi:10.1016/j.bbi.2020.04.024.
34. Karimi N, Sharifi Razavi A, Rouhani N. Frequent Convulsive Seizures in an Adult Patient with COVID-19: A Case Report.
35. Zhao K, Huang J, Feng Y, Liu L, Nie S. Acute myelitis after SARS-CoV-2 infection: a case report. 2020.
36. Zhang T, Rodricks MB, Hirsh E. COVID-19-Associated Acute Disseminated Encephalomyelitis: A Case Report. *medRxiv*. 2020.
37. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med*. 2019;200 7:e45–67. doi:10.1164/rccm.201908-1581ST.
38. Jacob A, Weinschenker BG. An approach to the diagnosis of acute transverse myelitis. *Semin Neurol*. 2008;28 1:105 – 20; doi: 10.1055/s-2007-1019132.
39. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24(1):35–41. doi:10.1161/01.str.24.1.35.
40. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395 10229:1033–4. doi:10.1016/s0140-6736(20)30628-0.
41. Nath A. Neurologic complications of coronavirus infections. *Neurology*. 2020. doi:10.1212/wnl.0000000000009455.
42. Matias-Guiu JA, Serna-Candel C, Espejo-Domínguez JM, Fernández-Matarrubia M, Simal P, Matias-Guiu J. Large artery occlusion diagnosed by computed tomography angiography in acute ischaemic stroke: frequency, predictive factors, and safety. *Neurologia*. 2014;29 5:261–6. doi:10.1016/j.nrl.2013.06.013.
43. Zhao J, Rudd A, Liu R. Challenges and Potential Solutions of Stroke Care During the Coronavirus Disease 2019 (COVID-19) Outbreak. *Stroke*. 2020;trokeaha120029701; doi:10.1161/strokeaha.120.029701.
44. Krupp LB, Tardieu M, Amato MP, Banwell B, Chitnis T, Dale RC, et al. International Pediatric Multiple Sclerosis Study Group criteria for pediatric multiple sclerosis and immune-mediated central nervous system demyelinating disorders: revisions to the 2007 definitions. *Mult Scler*. 2013;19 10:1261–7. doi:10.1177/1352458513484547.
45. Yuan J, Yang S, Wang S, Qin W, Yang L, Hu W. Mild encephalitis/encephalopathy with reversible splenic lesion (MERS) in adults—a case report and literature review. *BMC Neurol*. 2017;17(1):103-. doi:10.1186/s12883-017-0875-5.

## Figures

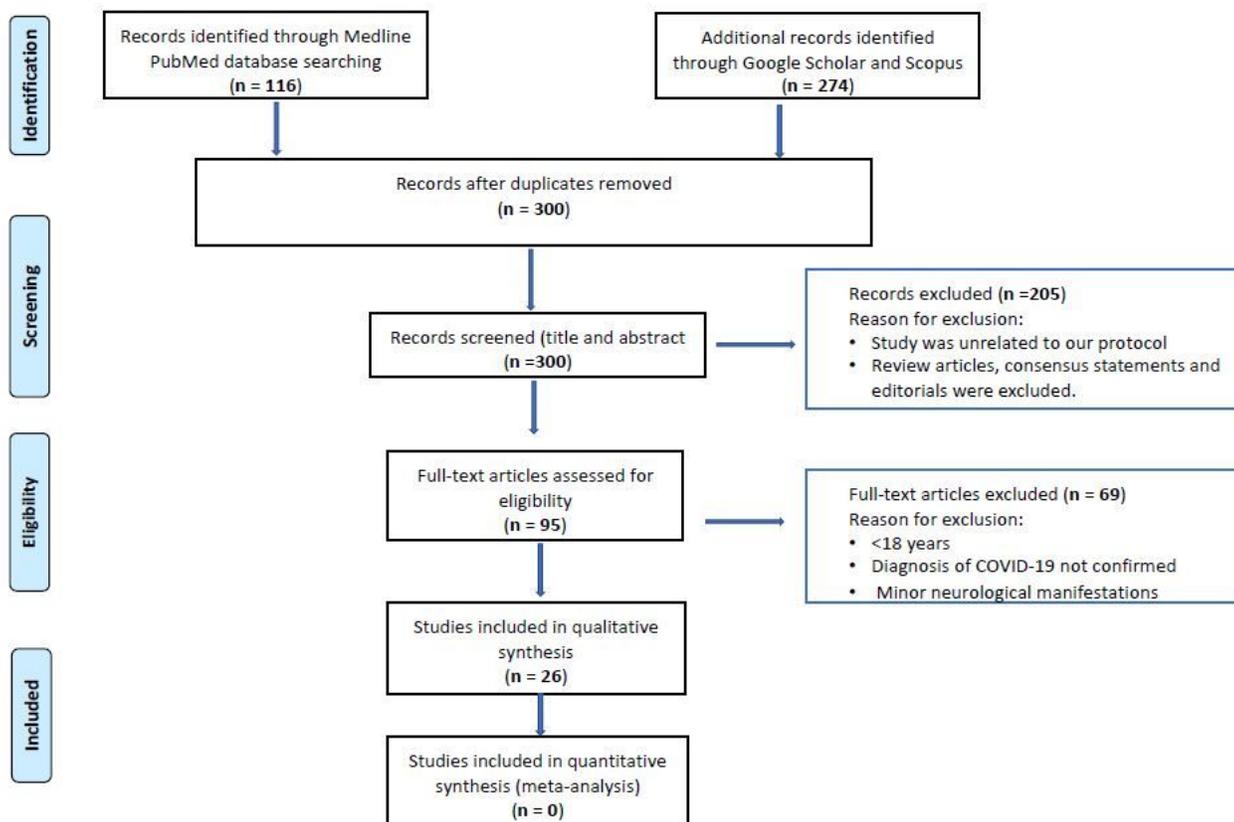


Figure 1

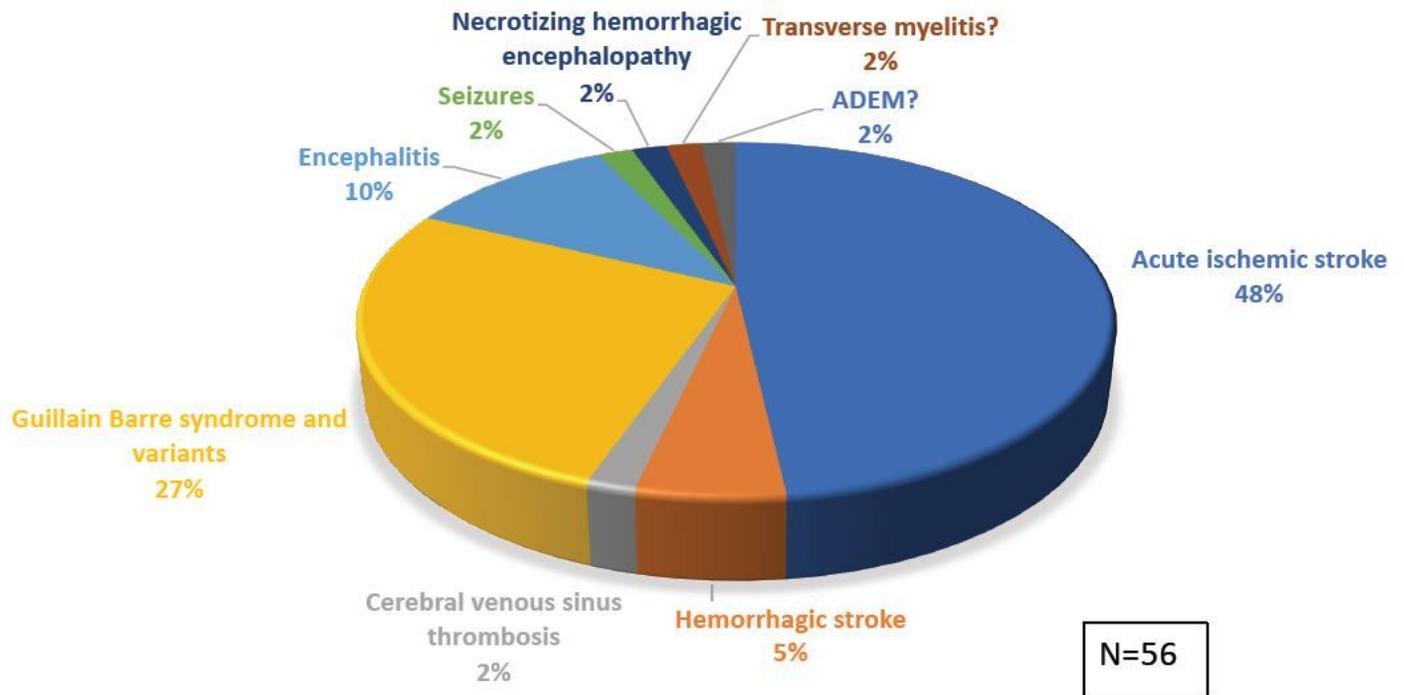


Figure 2

REPORTING FREQUENCY OF NEUROLOGICAL COMPLICATIONS OF COVID-19 ? = data for conclusive diagnosis was lacking. The distribution of neurological complications was Ischemic stroke = 48.2% (27), Hemorrhagic stroke = 5.4% (3), Cerebral venous sinus thrombosis = 1.8% (1), Encephalitis = 10.7% (6), Seizure = 1.8% (1), Necrotizing hemorrhagic encephalopathy = 1.8% (1), Transverse myelitis = 1.8% (1), Guillain-Barre Syndrome and its variants = 26.8% (15), ADEM = Acute disseminated Encephalomyelitis = 1.8% (1), n = 56

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