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**Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19**

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## Abstract

**Objective:** The emergence of COVID-19 presents a challenge for neurologists caring for patients with pre-existing neurological conditions hospitalized for COVID-19 or for evaluation of patients who suffer neurological complications during COVID-19 infection. We conducted a scoping review of available literature on COVID-19 to assess the potential impact on neurologists in terms of prevalent comorbidities and incidence of new neurological events in patients hospitalized with COVID-19.

**Methods:** We searched Medline/PubMed, CINAHL (EBSCO), and SCOPUS databases for adult patients with pre-existing neurologic disease that were diagnosed and hospitalized for COVID-19, or reported incidence of secondary neurologic events following diagnosis of COVID-19. Pooled descriptive statistics of clinical data and comorbidities were examined.

**Results:** Among screened articles, 322 of 4014 (8.0 %) of hospitalized patients diagnosed and treated for COVID-19 had a pre-existing neurological illness. Four retrospective studies demonstrated an increased risk of secondary neurological complications in hospitalized patients with COVID-19 (incidence of 6%, 20% and 36.4%, respectively). Inconsistent reporting and limited statistical analysis among these studies did not allow for assessment of comparative outcomes.

**Conclusion:** Emerging literature suggests a daunting clinical relationship between COVID-19 and neurological illness. Neurologists need to be prepared to reorganize their consultative practices to serve the neurological needs of patients during this pandemic.

## Introduction

The recent outbreak of SARS-CoV-2, designated “COVID-19” by the World Health Organization (WHO), was officially declared a pandemic on March 11, 2020 and is expected to continue to spread globally.<sup>1,2</sup> The disease spectrum ranges from largely asymptomatic infections with or without mild pneumonia to severe hypoxic respiratory failure with multi-organ dysfunction and/or shock.<sup>2</sup> COVID-19 is spread through droplets with a highly variable incubation period (5-14 days) with a case-fatality rate of 1.8-3.4%.<sup>3</sup> The highly transmissible nature, asymptomatic carriage, and the wide spectrum of illness make this disease challenging for healthcare systems. Neurologists face the daunting task of caring for patients with pre-existing neurological disease that contract the virus, infected individuals who present with neurological emergencies requiring neurological consultation, and patients with COVID-19 who develop secondary neurological complications such as ischemic stroke, seizures, or encephalopathy during the course of their illness.<sup>4-6</sup> This necessitates personal protective equipment (PPE) for emergent neurological consultations as well as consideration of telehealth alternatives to reduce physical exposure for neurologists. A recent meta-analysis examining the prevalence of comorbidities in COVID-19 infections surprisingly reported no neurological comorbidities and risk stratification scores that qualify patients for therapies like chloroquine have not yet incorporated neurological illness.<sup>7,8</sup> Hence, we conducted a scoping review of available literature on COVID-19 to assess the prevalence of patients with pre-existing neurologic disease and the incidence of neurological complications following COVID-19 diagnosis.

## Materials and Methods

The authorship team designed a primary literature search to understand the incidence of patients with pre-existing neurological disease that were diagnosed with and hospitalized for COVID-19, or had reported incidence of secondary neurologic events following diagnosis of COVID-19.

*Eligibility Criteria:* Research studies were selected for inclusion if they met the following criteria: 1) adult patients ( $\geq 18$  years of age); 2) diagnosed and received inpatient treatment for COVID-19; and 3) reported data on pre-existing neurological comorbidities or neurological events occurring during the course of the illness. Additional articles were included through a “gray search” via Google search engine and manual review of references listed articles to find relevant articles. Studies were not restricted according to design and had to be available in the English language. Due to the rapidly evolving state of the COVID-19 pandemic, non-peer reviewed articles available via pre-acceptance open access were included. We did not find any pediatric literature relevant to this review.

*Information Sources and Search Strategy:* We searched electronic databases: Medline/PubMed, CINAHL (EBSCO), and Scopus from January 1, 2020 to April 15, 2020. We summarize the comprehensive search strategies with Boolean operators in Table 1.

*Study Selection and Data Collection:* At least two independent reviewers independently screened all publications, including title and abstract, to determine if studies met

inclusion criteria. After agreement on included manuscripts, one reviewer independently retrieved comorbidity and clinical variables from the selected manuscripts.

*Statistical Analysis:* Pooled descriptive statistics of clinical data and comorbidities were examined.<sup>9</sup> The primary goal of this scoping review was to report on the incidence of neurological comorbidities and occurrence of secondary neurological events; as such, meta-analysis was not performed.

## Results

**Pre-existing neurologic disease and COVID-19 diagnosis:** Articles were screened by title and abstract. Twenty-two studies met the inclusion criteria (Figure 1). Twenty retrospective studies,<sup>6, 10-28</sup> one prospective observational trial,<sup>29</sup> and one randomized controlled trial<sup>30</sup> were included. Twenty studies were conducted in China, one in Italy, and one in France. In total, 4014 patients were included with a mean age  $55.6 \pm 8.4$  and 57% male predominance. The pooled percentage for having a pre-existing neurological disease was 8.0% ( $n=322/4014$ , range of 0-40% for individual studies; Table 2). The presence of pre-existing neurological disease was frequently not specified and grouped only as “cerebrovascular disease,” “nervous system disease,” or history of prior “stroke.” Additionally, five studies grouped cerebrovascular disease and cardiovascular disease together, potentially inflating the incidence.<sup>17, 19-21</sup>

We found headache to be a commonly reported symptom at presentation as it was mentioned in 22 articles. However, headache was not reported as a comorbidity and hence not

included. Other neurological comorbidities rarely mentioned in screened articles included dementia and Parkinson's disease (Table 1). We did not find a mention of anosmia in any searched scientific literature. We attempted but were unable to assess comparative outcomes from COVID-19 in patients with pre-existing neurological disease due to inconsistency in reporting, potential overlap in multiple studies reporting similar patients, and limited statistical analysis of the included studies. However, a few studies assessed the risk of worse patient outcomes and considered demographic and clinical variables including comorbidities as predictors in the analysis.

Among all patients with COVID-19, those requiring treatment in an intensive care unit (ICU) were more likely to be older, male sex, and have an underlying comorbidity, specifically cerebrovascular disease (16.7% vs 1.0%).<sup>12</sup> Similarly, patients that did not have clinical improvement or remission of symptoms within the first ten days of hospitalization had higher incidence of pre-existing cerebrovascular disease (8.2% vs 0%).<sup>11</sup> Patients with COVID-19 and underlying cerebrovascular disease were also more likely to develop acute respiratory distress syndrome (ARDS) (11% vs 0%) in a cohort of 109 patients in Wuhan.<sup>18</sup> Univariate analysis in a prospective cohort of 179 patients with COVID-19 pneumonia showed that pre-existing cardiovascular or cerebrovascular disease was predictive of mortality (OR = 11.059, 95% CI = 4 – 30).<sup>29</sup> We also observed a reported co-incidence of Parkinson's disease in COVID-19 similar to previously reported with SARS-CoV.<sup>31, 32</sup> This correlation has been previously explored in several publications.<sup>33</sup>

**Incidence of secondary neurological disease after COVID-19 (Table 3):** We found ten publications reporting secondary neurological events in patients diagnosed with COVID-19. Four retrospective studies demonstrated a relationship between secondary neurological events and treatment for COVID-19. One study demonstrated that 36% of 214 patients hospitalized for COVID-19 developed neurological symptoms or secondary cerebral events.<sup>20</sup> Another study demonstrated that 6% of 221 patients hospitalized for COVID-19 suffered an acute cerebrovascular event (ischemic stroke, cerebral thrombosis, and/or cerebral hemorrhage) while undergoing treatment.<sup>21</sup> Hypoxic ischemic encephalopathy was reported in 20% of patients in another case series.<sup>24</sup> A French study reported confusion in 65% patients and diffuse corticospinal signs in 67% patients during hospitalization. This study also reported dysexecutive syndrome in 33% of patients at discharge. Among 13 patients undergoing MRI brain in this study, 3 had acute/subacute ischemic strokes, 11 had bilateral frontotemporal hypoperfusion, and 8 had leptomeningeal enhancement with negative CSF RT-PCR.<sup>28</sup> Older age, more severe illness, and underlying cardiovascular or cerebrovascular disease were risk factors for secondary cerebrovascular events.<sup>20, 21</sup> Further case reports have described various neurological illnesses including acute necrotizing encephalopathy, ischemic strokes, seizures, intracranial hemorrhage, Guillain Barre Syndrome, and meningo-encephalitis.<sup>22, 34-38</sup>

## Discussion

These data suggest that patients with underlying neurologic impairment are vulnerable to more severe illness when infected with COVID-19. We saw a trend towards patients with pre-existing cerebrovascular disease having higher risk of ICU admission as well as overall

mortality. In addition, patients hospitalized with COVID-19 showed a 6-36% incidence of neurological events during the course of their illness.

Whether the trend towards worse outcomes is related to vulnerability from neurological disorders or the presence of other cardiovascular comorbidities leading to neurological complications in these patients is difficult to discern without further data. The neurotropism of the coronavirus itself is being investigated as a possible mechanism behind the higher incidence of brainstem-mediated cardiopulmonary complications in patients who have more severe disease.<sup>39, 40</sup>

Experimental data including autopsy samples of human brain tissue suggest a neuroinvasive potential of respiratory pathogens including coronaviruses in patients with and without pre-existing neurologic disease.<sup>41-43</sup> Published case series of other corona respiratory viruses like MERS-CoV and SARS-CoV in prior years have listed similar neurological complications including intracranial hemorrhage, ischemic stroke, polyneuropathy, Bickerstaff's encephalitis, and Guillain Barre Syndrome.<sup>44</sup>

Further data on the vulnerability of patients with neurological illness may be impactful in targeting this population for proactive viral screening. Risk stratification scores that identify patients at high risk of deterioration or that qualify patients for empiric therapies like hydroxychloroquine also need to reconsider adding patients with cerebrovascular disease.<sup>8</sup>

The burden of neurological events occurring in hospitalized patients demonstrates the need for appropriate infrastructure to facilitate neurological assessments in this population that may be deterred by the cumbersome nature of protection required required for clinical assessments. This infrastructure may include a robust supply of PPE for neurologists to assess patients, telemedicine alternatives for remote assessment of bedside exam, and protocols for transporting these patients for neuroimaging including emergent evaluation for cerebrovascular disease.

This scoping review has several limitations. Our analyses are limited by small sample sizes, even smaller incidences of neurological comorbidities, lack of long-term follow-up, and the possibility of overlap in populations described in reviewed articles potentially biasing the results. The studies included in this scoping review also have inherent bias based on the study designs. The retrospective nature of most of the included studies potentially present selection and presentation bias. Retrospective studies are subject to misclassification bias with limited ability to control for all potential confounders. Additionally, retrospective studies require large sample sizes to generate statistical power to determine different in-study endpoints. We did not specifically perform a risk of bias assessment in this scoping review, but instead choose to focus on the overall prevalence. Lack of neurological history reported in medical records by an overstretched health care system, lack of exhaustive reporting of neurological comorbidities in acutely reported publications, and challenges of neurological assessments or neuroimaging in patients with COVID-19 may have contributed to the lower reported incidence of neurological comorbidities or secondary neurological events in hospitalized patients. Two meta-analyses reporting comorbidities in COVID-19 and MERS-CoV failed to report neurological

comorbidities, highlighting challenges of collecting such data.<sup>7, 45</sup> We were unable to perform meta-analysis or predict worse outcomes based on comorbidity status.

## **Conclusions**

The culmination of studies indicates a daunting clinical relationship between COVID-19 and secondary neurological complications and needs a concerted effort by neurologists to reorganize consultative practices to serve the neurological needs of patients during this pandemic. More sensitive data extraction measures and comprehensive clinical documentation are required to better understand the prevalence of neurological comorbidities and pre-existing neurological disorders in patients with COVID-19.

**Appendix. Authors**

<b>Author</b>	<b>Location</b>	<b>Contribution</b>
Collin Herman, MD	Department of Neurology Wake Forest Baptist Medical Center Winston Salem, NC	Drafted the manuscript for intellectual content
Kirby P. Mayer, DPT, PhD	Department of Physical Therapy University of Kentucky College of Health Sciences Lexington, KY	Major role in the acquisition of data; performed statistical review of results; interpreted the data; revised the manuscript for intellectual content
Aarti Sarwal, MD	Department of Neurology Wake Forest Baptist Medical Center Winston Salem, NC	Designed and conceptualized study; major role in the acquisition of data; interpreted the data; revised the manuscript for intellectual content

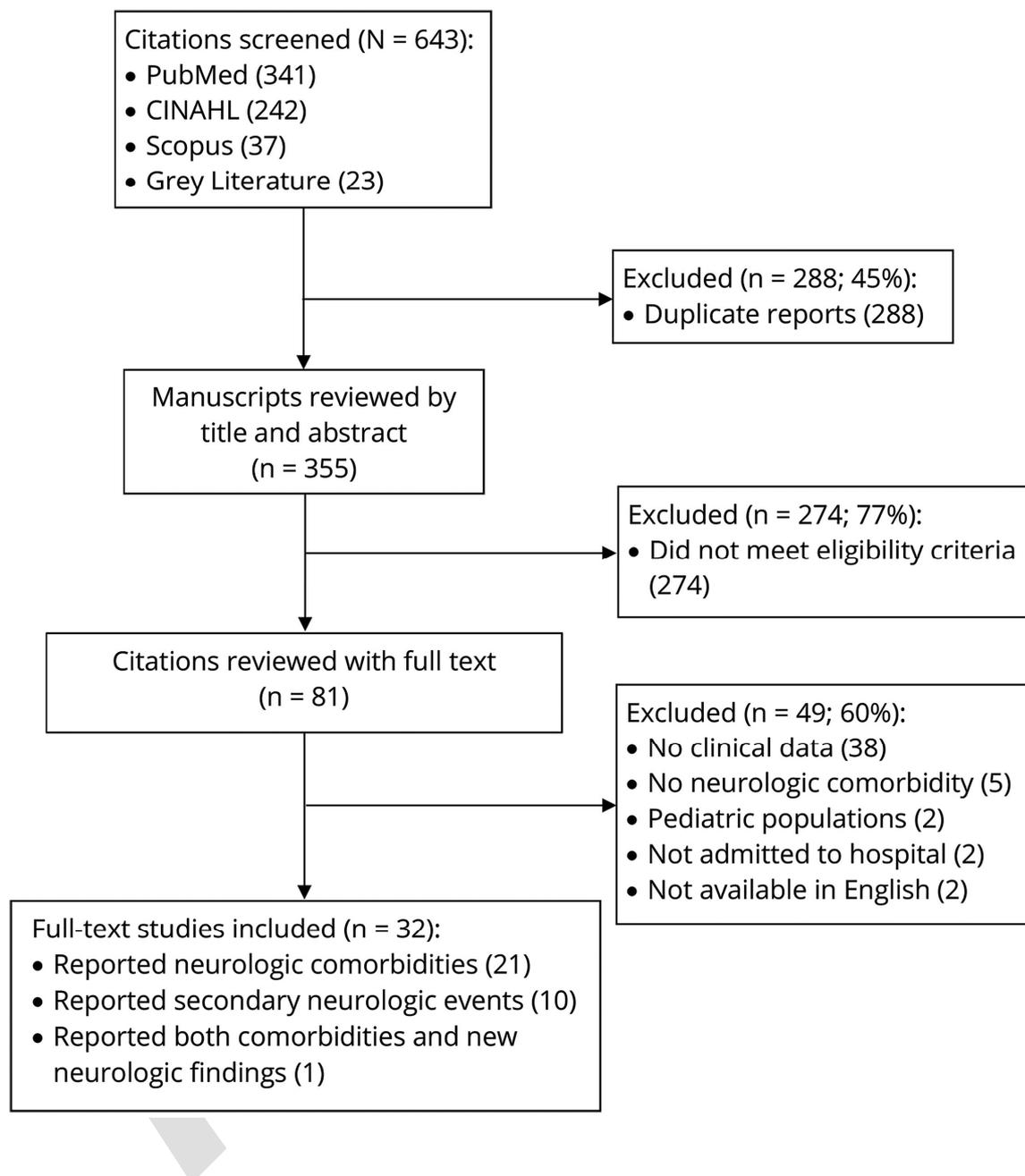
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**Figure 1. Prisma Flow Diagram of the Selection Process**



**Table 1: Electronic Database Search Strategy**

Aim	Search Strategy with Boolean operators	Results <sup>1</sup>		
		Pubmed	CINAHL	Scopus
Prevalence of neurologic comorbidity in patients hospitalized for Covid-19 <sup>2</sup>	("covid-19" AND (neuro* OR neurol manifestation))	190	156	8
	("covid-19") AND (brain* OR brain infarct))	63	41	7
	("covid-19") AND (stroke))	6	5	0
	("covid-19") AND (seizure OR epilepsy)	2	3	0
	("covid-19") AND (encephalitic OR encephalopathy))	15	3	2
	("covid-19") AND (coma OR unconsciousness))	5	2	1
	("covid-19" AND (cerebral edema OR "cereb*"))	22	7	0
	("covid-19" AND (cranial hemorrhage OR intracranial hemorrhage OR subarachnoid hemorrhage))	1	2	0
	("covid-19") AND (migraines OR "headache"))	28	20	18
	("covid-19") AND (neuropathy OR neuromuscular OR myasthenia))	6	2	0
("covid-19") AND (dementia or neurocognitive disorder))	3	1	1	
<b>Total</b>		341	242	37

<sup>1</sup>Search terms were applied with date filter of Jan 1, 2020 to April 12, 2020.

<sup>2</sup>Covid-19 MeSH term; <https://meshb.nlm.nih.gov/record/ui?ui=C000657245>

**Table 2: Prevalence of pre-existing neurologic diseases for patients hospitalized for COVID-19**

First Author	Study Design	Location	Sample	Diagnosis of COVID	Age (mean $\pm$ SD)	Male (%)	Neuro* comorbidity n (%)	Description of neuro* comorbidity	Clinical Notes
Guan <sup>6</sup>	Retro	552 hospitals in 30 provinces	1099	Confirmed with RT-PCR	44.2 $\pm$ 23.9	58	15 (1.4%)	cerebrovascular disease	Comorbidity was more common in severe cases of COVID-19 (38.2% vs. 22.5%)
Wu <sup>10</sup>	Retro	Wuhan Jinyintan Hospital, in China	201	Confirmed with RT-PCR	51.5 $\pm$ 17.9	64	7 (3.5%)	nervous system disease	Older patients with comorbidities of hypertension and diabetes more likely to develop ARDS
Mo <sup>11</sup>	Retro	Zhongnan Hospital, Wuhan University	155	Confirmed with RT-PCR	53.5 $\pm$ 10.3	55	7 (4.5%)	cerebrovascular disease	Patients with baseline cerebrovascular more likely to be in “refractory group”
Cao <sup>30</sup>	RCT	Jin Yin-Tan Hospital, Wuhan, China	199	Confirmed with RT-PCR	58.5 $\pm$ 11.2	60	13 (6.5%)	cerebrovascular disease	Statistical analysis focused on intervention
Wang <sup>14</sup>	Retro	First Affiliated Hospital of Zhengzhou University Zhengzhou, China	18	Confirmed with RT-PCR	40.5 $\pm$ 7.5	56	2 (11.1%)	stroke	2 patients with history of stroke; time or severity of stroke not documented
Shi <sup>13</sup>	Retro	Wuhan Jinyintan hospital or Union Hospital of Tongji Medical College, Wuhan, China	81	next-generation sequencing or RT-PCR	49.5 $\pm$ 11	52	6 (7%)	cerebrovascular disease	Older age, male sex, and presence of comorbidity increase risk of poor prognosis
Wang <sup>12</sup>	Retro	Zhongnan Hospital of Wuhan University, Wuhan, China	138	Confirmed with RT-PCR	56.5 $\pm$ 20.2	54	7 (5.1%)	cerebrovascular disease	Patients receiving ICU care were significantly older (66 vs 51) and had underlying cerebrovascular disease (16.7% vs 1.0%)
Deng <sup>15</sup>	Retro	Mainland China	26	NR	NR	NR	4 (15.4%) 2 (7.7%)	cerebral infarction Parkinson’s disease	Retrospective report of patients that died from COVID-19
Wang <sup>16</sup>	Retro	Wuhan, China	17	NR	71.5 $\pm$ 11.5	76	3 (18%) 2 (12%)	Cerebral infarction Parkinson’s Disease	Analysis of the first 17 patients that died in Wuhan, China
Chen <sup>17</sup>	Retro	Jinyintan Hospital in Wuhan, China	99	Confirmed with RT-PCR	55.5 $\pm$ 13.1	68	40 (40%) 1 (1%)	cardio-cerebrovascular disease, nervous system disease	
Liu <sup>18</sup>	Retro	Central Hospital, Wuhan	109	Confirmed with RT-PCR	55 $\pm$ 11	54	6 (5.5%)	cerebrovascular disease	Older patients with severe COVID-19 more likely to develop neurological complication

Chen <sup>19</sup>	Retro	Shanghai Public Health Clinical Center (SPHCC), Shanghai, China	249	Confirmed with RT-PCR	51 ± 10	51	55 (21.7%)	cardio-cerebrovascular disease	Older age and presence of any comorbidity associated with ICU stay
Mao <sup>20</sup>	Retro	Union Hospital of Huazhong University of Science and Technology, Wuhan, China.	214	Confirmed with RT-PCR	52.8 ± 15	41	15 (7.0)	cardio-cerebrovascular disease	Cerebrovascular disease prevalence was not different in severe and non-severe cases
Li <sup>21</sup>	Retro	Union Hospital, Wuhan, China	221	Confirmed with RT-PCR	53.3 ± 16	59	17 (7.7)	cardio-cerebrovascular disease	Older patients with severe COVID-19 more likely to develop neurological complications
Filatov <sup>22</sup>	Retro	Florida Atlantic University Hospital, Boca Rota, FL	1	NR	74	CR	1 (100)	cardioembolic stroke, Parkinson Disease	Case report of older male requiring ICU care with mechanical ventilation; developed encephalopathy
Onder <sup>23</sup>	Retro	Italy	355	Confirmed with RT-PCR	NR	NR	24 (6.8) 34 (9.6)	dementia stroke	Presence of comorbidities may have increased mortality risk
Chen <sup>24</sup>	Retro	Tongji Hospital, Wuhan, China	274	Confirmed with PT-PCR	60 (11.5)	62	4 (1.5)	cerebrovascular disease	Patients that died were older, predominantly male, and had pre-existing comorbidities
Du <sup>29</sup>	Prospec	Wuhan Pulmonary Hospital, Wuhan, China	179	Confirmed and probable cases	57.6 (13.7)	54%	29 (16.2)	Cardio-cerebrovascular disease	Older age (>65 years old) and presence of cardio-cerebrovascular disease was predictive of mortality
Du <sup>26</sup>	Retro	Hannan Hospital and Wuhan Union Hospital	85	Confirmed OR contact history	65.8 (14.2)	73	7 (8.2)	cerebrovascular disease	In 85 patients that died from COVID-19, most cases were males over age of 50 and had pre-existing comorbidity
Xu <sup>25</sup>	Retro	Multiple hospitals in Zhejiang, China	62	Confirmed with RR-PCR	42 (14.7)	56	1 (2)	cerebrovascular disease	Retrospective study of the clinical characteristics of cohort of patients with severe acute respiratory syndrome and COVID-19
Guo <sup>27</sup>	Retro	Wuhan Union hospital of Tongji Medical College, Huazhong University of Science & Tech	174	Confirmed with PT-PCR	58 (8.5)	44	13 (7.5)	cerebrovascular disease	Retrospective study focused on diabetes as a risk factor of the progression and prognosis of COVID-19
Helms <sup>28</sup>	Retro	Strasbourg France	58	Confirmed with RT-PCR	63	NR	7(12)	TIA, partial epilepsy, mild cognitive impairment	Retrospective study reporting neurological features in COVID-19 patients
<b>Totals</b>			<b>4014</b>		<b>55.68 (8.4)</b>	<b>57</b>	<b>322 (8.0%)</b>		

RCT: randomized control trial; ICU: intensive care unit; ARDS: acute respiratory distress syndrome

**Table 3: Incidence and risk of secondary neurologic events during respiratory corona virus infections**

First Author	Study design	Location	Sample	Outcomes
Li** <sup>21</sup>	Retro	Wuhan, China	221	13 (6%) patients suffered neurologic complication: 11 (5%) acute ischemic stroke, 1 (0.5%) cerebral venous sinus thrombosis, and 1 (0.5%) cerebral hemorrhage. Patients with event were older with higher severity of illness and had pre-existing hypertension or history of cerebrovascular disease.
Mao** <sup>20</sup>	Retro	Wuhan, China	214	78 (36.4%) had neurologic manifestations including 5 reports of ischemic stroke, 1 patient suffered cerebral hemorrhage, 23 reports of neuromuscular injury. Patient with higher severity of illness were more likely to develop neurological symptoms.
Chen <sup>24</sup>	Retro	Wuhan, China	274	23 (20%) developed hypoxic encephalopathy after diagnosis COVID-19. Older male patients with chronic hypertension and other comorbidities had higher mortality.
Helms <sup>28</sup>	Retro	Strasbourg, France	58	58 patients with median age 63 years. 26 of 40 patients examined after weaning sedation had confusion. 39 (67%) patients had diffuse corticospinal signs. 15 of 45 discharged (33%) had dysexecutive syndrome. 11 of 13 patients with MRI had bilateral frontotemporal hypoperfusion and 8 had leptomeningeal enhancement. 3 patients had acute/subacute ischemic stroke. 8 patients had EEG with nonspecific findings. 7 patients had CSF studies with all studies negative for RT-PCR, 1 with elevated IgG, 2 with elevated oligoclonal bands, 1 with elevated IgG and protein.
Poyiadji <sup>34</sup>	Retro	Detroit, MI, USA	1	Female patient (late fifties), diagnosed with acute necrotizing encephalopathy with CT images revealing symmetric hypoattenuation within the bilateral medial thalami and brain MRI showing hemorrhagic ring enhancing lesions.
Zhai <sup>35</sup>	Retro	Hubei Provincial Hospital	1	79 year old male diagnosed with acute ischemic stroke (lacunar infarction on CT imaging) after presenting to hospital with right extremity weakness and diagnosed with stroke and found to be COVID-19 positive.
Filatov <sup>22</sup>	Retro	Boca Raton, FA, USA	1	74 year old male with history of atrial fibrillation, cardioembolic stroke, Parkinson's disease, chronic obstructive pulmonary disease, and cellulitis presented to emergency department with cough and altered mentation, found to be encephalopathic, EEG demonstrated bilateral slowing and focal slowing in left temporal region.
Karimi <sup>36</sup>	Retro	Sari, Iran	1	30 year old female (previously healthy) admitted with tonic-clonic seizures; 5 seizures in 8-hour period. CT and MRI of head was negative.
Sharifi-Razavi <sup>37</sup>	Retro	Sari, Iran	1	79 year old male with 3 days of fever and cough, presented to the hospital and suffered acute loss of consciousness in emergency room. Brain CT showed massive intra-cerebral, intra-ventricular and subarachnoid hemorrhage. RT-PCR confirmed COVID-19.
Moriguchi <sup>38</sup>	Retro	Yamanashi, Japan	1	24 year old male with symptoms of headache, fatigue, and fever; 9 days after initial onset he was found down with loss of consciousness; multiple epileptic seizures, diagnosed with meningitis, ventriculitis, and encephalitis.
Zhao <sup>46</sup>	Retro	Wuhan, China	1	Travel history to Wuhan and possibly presented with Guillian Barre syndrome attributed to COVID-19.

ICU: intensive care unit; EMG/NCV: electromyography/nerve conduction velocity

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## Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19

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