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

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Abstract

Objective

The emergence of coronavirus disease 2019 (COVID-19) presents a challenge for neurologists caring for patients with preexisting neurologic conditions hospitalized for COVID-19 or for evaluation of patients who have neurologic complications during COVID-19 infection. We conducted a scoping review of the available literature on COVID-19 to assess the potential effect on neurologists in terms of prevalent comorbidities and incidence of new neurologic events in patients hospitalized with COVID-19.

Methods

We searched MEDLINE/PubMed, CINAHL (EBSCO), and Scopus databases for adult patients with preexisting neurologic disease who 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 4,014 (8.0%) of hospitalized patients diagnosed and treated for COVID-19 had a preexisting neurologic illness. Four retrospective studies demonstrated an increased risk of secondary neurologic 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 neurologic illness. Neurologists need to be prepared to reorganize their consultative practices to serve the neurologic needs of patients during this pandemic.

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Glossary

COVID-19 = coronavirus disease 2019; **ICU** = intensive care unit; **PPE** = personal protective equipment.

The recent outbreak of SARS-CoV-2, designated "coronavirus disease 2019 (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.[1,2] The disease spectrum ranges from largely asymptomatic infections with or without mild pneumonia to severe hypoxic respiratory failure with multiorgan dysfunction and/or shock.[2] 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%.[3] The highly transmissible nature, asymptomatic carriage, and the wide spectrum of illness make this disease challenging for health care systems. Neurologists face the daunting task of caring for patients with preexisting neurologic disease who contract the virus, infected individuals who present with neurologic emergencies requiring neurologic consultation, and patients with COVID-19 who develop secondary neurologic complications such as ischemic stroke, seizures, or encephalopathy during the course of their illness.[4–6] This necessitates personal protective equipment (PPE) for emergent neurologic 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 neurologic comorbidities and risk stratification scores that qualify patients for therapies like chloroquine have not yet incorporated neurologic illness.[7,8] Hence, we conducted a scoping review of the available literature on COVID-19 to assess the prevalence of patients with preexisting neurologic disease and the incidence of neurologic complications following COVID-19 diagnosis.

Methods

The authorship team designed a primary literature search to understand the incidence of patients with preexisting neurologic disease who 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 (aged ≥18 years); (2) diagnosed and received inpatient treatment for COVID-19; and (3) reported data on preexisting neurologic comorbidities or neurologic 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. Because of 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 2 independent reviewers independently screened all publications, including title and abstract, to determine whether studies met the inclusion criteria. After agreement on included articles, 1 reviewer independently retrieved comorbidity and clinical variables from the selected articles.

Statistical analysis

Pooled descriptive statistics of clinical data and comorbidities were examined.[9] The primary goal of this scoping review was to report on the incidence of neurologic comorbidities and occurrence of secondary neurologic events; as such, meta-analysis was not performed.

Results

Preexisting neurologic disease and COVID-19 diagnosis

Articles were screened by title and abstract. Twenty-two studies met the inclusion criteria (figure). Twenty retrospective studies,[6,10–28] 1 prospective observational trial,[29] and 1 randomized controlled trial[30] were included. Twenty studies were conducted in China, 1 in Italy, and 1 in France. In total, 4,014 patients were included, with a mean age of 55.6 ± 8.4 years and 57% male predominance. The pooled percentage for having a preexisting neurologic disease was 8.0% (n = 322/4,014, range of 0%–40% for individual studies; table 2). The presence of preexisting neurologic disease was frequently not specified and grouped only as cerebrovascular disease, nervous system disease, or history of prior stroke. In addition, 5 studies grouped cerebrovascular disease and cardiovascular disease together, potentially inflating the incidence.[17,19–21]

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 neurologic comorbidities rarely mentioned in screened articles included dementia and Parkinson 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 preexisting neurologic 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

Table 1 Electronic database search strategy

Aim	Search strategy with Boolean operators	Results[a]		
		PubMed	CINAHL	Scopus
Prevalence of neurologic comorbidity in patients hospitalized for COVID-19[b]	(("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
Total		341	242	37

[a] Search terms were applied with date filter of January 1, 2020, to April 12, 2020.
[b] COVID-19 MeSH term; meshb.nlm.nih.gov/record/ui?ui=C000657245.

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%).[12] Similarly, patients who did not have clinical improvement or remission of symptoms within the first 10 days of hospitalization had higher incidence of preexisting cerebrovascular disease (8.2% vs 0%).[11] Patients with COVID-19 and underlying cerebrovascular disease were also more likely to develop acute respiratory distress syndrome (11% vs 0%) in a cohort of 109 patients in Wuhan.[18] Univariate analysis in a prospective cohort of 179 patients with COVID-19 pneumonia showed that preexisting cardiovascular or cerebrovascular disease was predictive of mortality (odds ratio = 11.059, 95% confidence interval = 4–30).[29] We also observed a reported coincidence of Parkinson disease in COVID-19 similar to previously reported with SARS-CoV.[15,31] This correlation has been previously explored in several publications.[32]

Incidence of secondary neurologic disease after COVID-19

We found 10 publications reporting secondary neurologic events in patients diagnosed with COVID-19 (table 3). Four retrospective studies demonstrated a relationship between secondary neurologic events and treatment of COVID-19. One study demonstrated that 36% of 214 patients hospitalized for COVID-19 developed neurologic symptoms or secondary cerebral events.[20] Another study demonstrated that 6% of 221 patients hospitalized for COVID-19 had an acute cerebrovascular event (ischemic stroke, cerebral thrombosis, and/or cerebral hemorrhage) while undergoing treatment.[21] Hypoxic ischemic encephalopathy was reported in 20% of patients in another case series.[24] 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 brain MRI in this study, 3 had acute/subacute ischemic strokes, 11 had bilateral frontotemporal hypoperfusion, and 8 had leptomeningeal enhancement with negative CSF RT-PCR.[28] Older age, more severe illness, and underlying cardiovascular or cerebrovascular disease were risk factors for secondary cerebrovascular events.[20,21] Further case reports have described various neurologic illnesses including acute necrotizing encephalopathy, ischemic strokes, seizures, intracranial hemorrhage, Guillain-Barre syndrome, and meningoencephalitis.[22,33–37]

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 toward patients with preexisting 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 neurologic events during the course of their illness.

Table 2 Prevalence of preexisting neurologic diseases for patients hospitalized for COVID-19

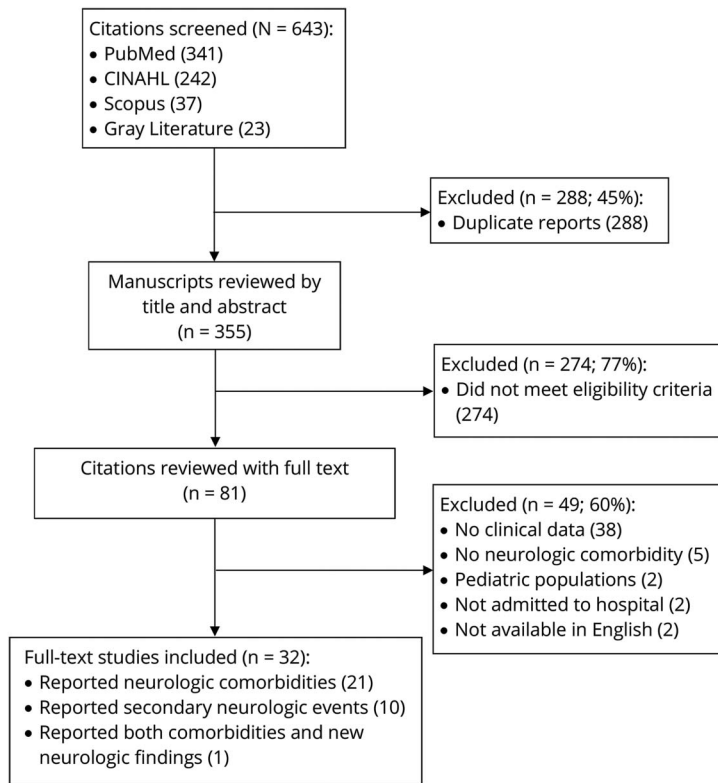| First author	Study design	Location	Sample	Diagnosis of COVID	Age (mean ± SD)	Male (%)	Neuro* comorbidity, n (%)	Description of neuro* comorbidity	Clinical notes
Guan et al.[6]	Retro	552 hospitals in 30 provinces	1,099	Confirmed with RT-PCR	44.2 ± 23.9	58	15 (1.4%)	Cerebrovascular disease	Comorbidity was more common in severe cases of COVID-19 (38.2% vs 22.5%)
Wu et al.[10]	Retro	Wuhan Jinyintan Hospital, in China	201	Confirmed with RT-PCR	51.5 ± 17.9	64	7 (3.5%)	Nervous system disease	Older patients with comorbidities of hypertension and diabetes more likely to develop ARDS
Mo et al.[11]	Retro	Zhongnan Hospital, Wuhan University	155	Confirmed with RT-PCR	53.5 ± 10.3	55	7 (4.5%)	Cerebrovascular disease	Patients with baseline cerebrovascular more likely to be in the refractory group
Cao et al.[30]	RCT	Jin Yin-Tan Hospital, Wuhan, China	199	Confirmed with RT-PCR	58.5 ± 11.2	60	13 (6.5%)	Cerebrovascular disease	Statistical analysis focused on intervention
Wang et al.[14]	Retro	First Affiliated Hospital of Zhengzhou University Zhengzhou, China	18	Confirmed with RT-PCR	40.5 ± 7.5	56	2 (11.1%)	Stroke	2 patients with a history of stroke; time or severity of stroke not documented
Shi et al.[13]	Retro	Wuhan Jinyintan Hospital or Union Hospital of Tongji Medical College, Wuhan, China	81	Next-generation sequencing or RT-PCR	49.5 ± 11	52	6 (7%)	Cerebrovascular disease	Older age, male sex, and presence of comorbidity increase the risk of poor prognosis
Wang et al.[12]	Retro	Zhongnan Hospital of Wuhan University, Wuhan, China	138	Confirmed with RT-PCR	56.5 ± 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% 1)
Deng and Peng[15]	Retro	Mainland China	26	NR	NR	NR	4 (15.4%) 2 (7.7%)	Cerebral infarction and Parkinson disease	Retrospective report of patients who died of COVID-19
Wang et al.[16]	Retro	Wuhan, China	17	NR	71.5 ± 11.5	76	3 (18%) 2 (12%)	Cerebral infarction and Parkinson disease	Analysis of the first 17 patients who died in Wuhan, China
Chen et al.[17]	Retro	Jinyintan Hospital in Wuhan, China	99	Confirmed with RT-PCR	55.5 ± 13.1	68	40 (40%) 1 (1%)	Cardio-cerebrovascular disease and nervous system disease	
Liu et al.[18]	Retro	Central Hospital, Wuhan	109	Confirmed with RT-PCR	55 ± 11	54	6 (5.5%)	Cerebrovascular disease	Older patients with severe COVID-19 more likely to develop neurologic complications
Chen et al.[19]	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

Table 2 Prevalence of preexisting neurologic diseases for patients hospitalized for COVID-19 *(continued)*

First author	Study design	Location	Sample	Diagnosis of COVID	Age (mean ± SD)	Male (%)	Neuro* comorbidity, n (%)	Description of neuro* comorbidity	Clinical notes
Mao et al.[20]	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 nonsevere cases
Li et al.[21]	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 neurologic complications
Filatov et al.[22]	Retro	Florida Atlantic University Hospital, Boca Rota, FL	1	NR	74	CR	1 (100)	Cardioembolic stroke and Parkinson disease	Case report of older male requiring ICU care with mechanical ventilation; developed encephalopathy
Onder et al.[23]	Retro	Italy	355	Confirmed with RT-PCR	NR	NR	24 (6.8) 34 (9.6)	Dementia and stroke	The presence of comorbidities may have an increased mortality risk
Chen et al.[24]	Retro	Tongji Hospital, Wuhan, China	274	Confirmed with PT-PCR	60 (11.5)	62	4 (1.5)	Cerebrovascular disease	Patients who died were older, predominantly male, and had preexisting comorbidities
Du et al.[29]	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) and presence of cardio-cerebrovascular disease were predictive of mortality
Du et al.[26]	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 who died of COVID-19, most cases were males older than 50 y and had preexisting comorbidity
Xu et al.[25]	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 the cohort of patients with severe acute respiratory syndrome and COVID-19
Guo et al.[27]	Retro	Wuhan Union Hospital of Tongji Medical College, Huazhong University of Science and Technology	174	Confirmed with PT-PCR	58 (8.5)	44	13 (7.5)	Cerebrovascular disease	Retrospective study focused on diabetes as a risk factor for the progression and prognosis of COVID-19
Helms et al.[28]	Retro	Strasbourg France	58	Confirmed with RT-PCR	63	NR	7 (12)	TIA, partial epilepsy, and mild cognitive impairment	Retrospective study reporting neurologic features in patients with COVID-19
Totals			4,014		55.68 (8.4)	57	322 (8.0%)		

Abbreviations: ARDS = acute respiratory distress syndrome; CR = case report; ICU = intensive care unit; NR = not reported; Prospec = prospective; Retro = retrospective; RCT = randomized control trial.

Figure PRISMA flow diagram of the selection process

Citations screened (N = 643):
• PubMed (341)
• CINAHL (242)
• Scopus (37)
• Gray Literature (23)

Excluded (n = 288; 45%):
• Duplicate reports (288)

Manuscripts reviewed by title and abstract (n = 355)

Excluded (n = 274; 77%):
• Did not meet eligibility criteria (274)

Citations reviewed with full text (n = 81)

Excluded (n = 49; 60%):
• No clinical data (38)
• No neurologic comorbidity (5)
• Pediatric populations (2)
• Not admitted to hospital (2)
• Not available in English (2)

Full-text studies included (n = 32):
• Reported neurologic comorbidities (21)
• Reported secondary neurologic events (10)
• Reported both comorbidities and new neurologic findings (1)

Whether the trend toward worse outcomes is related to vulnerability from neurologic disorders or the presence of other cardiovascular comorbidities leading to neurologic 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.[38,39]

Experimental data including autopsy samples of human brain tissue suggest a neuroinvasive potential of respiratory pathogens including coronaviruses in patients with and without preexisting neurologic disease.[40–42] Published case series of other corona respiratory viruses like Middle East respiratory syndrome-related coronavirus (MERS-CoV) and severe acute respiratory syndrome-related coronavirus (SARS-CoV) in prior years have listed similar neurologic complications including intracranial hemorrhage, ischemic stroke, polyneuropathy, Bickerstaff encephalitis, and Guillain-Barre syndrome.[43]

Further data on the vulnerability of patients with neurologic 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.[8]

The burden of neurologic events occurring in hospitalized patients demonstrates the need for appropriate infrastructure to facilitate neurologic assessments in this population that may be deterred by the cumbersome nature of protection 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 examination, 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 neurologic 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 presents selection and presentation bias. Retrospective studies are subject to misclassification bias with limited ability to control for all potential confounders. In addition, retrospective studies require large sample sizes to generate statistical power to determine different in-study end points. 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 neurologic history reported in medical records by an overstretched health care system, lack of exhaustive reporting of neurologic comorbidities in acutely reported publications, and challenges of neurologic assessments

Table 3 Incidence and risk of secondary neurologic events during respiratory coronavirus infections

First author	Study design	Location	Sample	Outcomes
Li et al.[21]	Retro	Wuhan, China	221	13 (6%) patients had neurologic complications: 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 preexisting hypertension or a history of cerebrovascular disease.
Mao et al.[20]	Retro	Wuhan, China	214	78 (36.4%) had neurologic manifestations including 5 reports of ischemic stroke; 1 patient had cerebral hemorrhage, 23 reports of neuromuscular injury. Patients with higher severity of illness were more likely to develop neurologic symptoms.
Chen et al.[24]	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 et al.[28]	Retro	Strasbourg, France	58	58 patients with median age 63 years. Twenty-six of 40 patients examined after weaning sedation had confusion. Thirty-nine (67%) patients had diffuse corticospinal signs. Fifteen of 45 discharged (33%) had dysexecutive syndrome. Eleven of 13 patients with MRI had bilateral frontotemporal hypoperfusion, and 8 had leptomeningeal enhancement. Three patients had acute/subacute ischemic stroke. Eight patients had EEG with nonspecific findings. Seven patients had CSF studies, with all studies negative for RT-PCR, 1 with elevated IgG, 2 with elevated oligoclonal bands, and 1 with elevated IgG and protein.
Poyiadji et al.[33]	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 et al.[34]	Retro	Hubei Provincial Hospital	1	79-year-old man 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 et al.[22]	Retro	Boca Raton, FA, USA	1	74-year-old man with a history of atrial fibrillation, cardioembolic stroke, Parkinson disease, chronic obstructive pulmonary disease, and cellulitis presented to the emergency department with cough and altered mentation, found to be encephalopathic, and EEG demonstrated bilateral slowing and focal slowing in the left temporal region.
Karimi et al.[35]	Retro	Sari, Iran	1	30-year-old woman (previously healthy) admitted with tonic-clonic seizures; 5 seizures in 8-hour period. CT and MRI of the head were negative.
Sharifi-Razavi et al.[36]	Retro	Sari, Iran	1	79-year-old man with 3 days of fever and cough presented to the hospital and had acute loss of consciousness in the emergency department. Brain CT showed massive intracerebral, intraventricular, and subarachnoid hemorrhage. RT-PCR confirmed COVID-19.
Moriguchi et al.[37]	Retro	Yamanashi, Japan	1	24-year-old man with symptoms of headache, fatigue, and fever; 9 days after the initial onset, he was found down with loss of consciousness; multiple epileptic seizures, diagnosed with meningitis, ventriculitis, and encephalitis.
Zhao et al.[45]	Retro	Wuhan, China	1	Travel history to Wuhan and possibly presented with Guillain-Barre syndrome attributed to COVID-19.

Abbreviations: ICU = intensive care unit; NCV = nerve conduction velocity; Retro = retrospective.

or neuroimaging in patients with COVID-19 may have contributed to the lower reported incidence of neurologic comorbidities or secondary neurologic events in hospitalized patients. Two meta-analyses reporting comorbidities in COVID-19 and MERS-CoV failed to report neurologic comorbidities, highlighting challenges of collecting such data.[7,44] 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 neurologic complications and needs a concerted effort by neurologists to reorganize consultative practices to serve the neurologic needs of patients during this pandemic. More sensitive data extraction measures and comprehensive clinical documentation are required to better understand the prevalence of neurologic comorbidities and preexisting neurologic disorders in patients with COVID-19.

Appendix Authors

Author	Location	Contribution
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; and revised the manuscript for intellectual content
Aarti Sarwal, MD	Department of Neurology, Wake Forest Baptist Medical Center, Winston Salem, NC	Designed and conceptualized the study; major role in the acquisition of data; interpreted the data; and revised the manuscript for intellectual content

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