ARTICLE

A Prospective Study of Neurologic Disorders in Hospitalized Patients With COVID-19 in New York City

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Abstract

Objective

To determine the prevalence and associated mortality of well-defined neurologic diagnoses among patients with coronavirus disease 2019 (COVID-19), we prospectively followed hospitalized severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–positive patients and recorded new neurologic disorders and hospital outcomes.

Methods

We conducted a prospective, multicenter, observational study of consecutive hospitalized adults in the New York City metropolitan area with laboratory-confirmed SARS-CoV-2 infection. The prevalence of new neurologic disorders (as diagnosed by a neurologist) was recorded and in-hospital mortality and discharge disposition were compared between patients with COVID-19 with and without neurologic disorders.

Results

Of 4,491 patients with COVID-19 hospitalized during the study timeframe, 606 (13.5%) developed a new neurologic disorder in a median of 2 days from COVID-19 symptom onset. The most common diagnoses were toxic/metabolic encephalopathy (6.8%), seizure (1.6%), stroke (1.9%), and hypoxic/ischemic injury (1.4%). No patient had meningitis/encephalitis or myelopathy/myelitis referable to SARS-CoV-2 infection and 18/18 CSF specimens were reverse transcriptase PCR negative for SARS-CoV-2. Patients with neurologic disorders were more often older, male, white, hypertensive, diabetic, intubated, and had higher sequential organ failure assessment (SOFA) scores (all $p < 0.05$). After adjusting for age, sex, SOFA scores, intubation, history, medical complications, medications, and comfort care status, patients with COVID-19 with neurologic disorders had increased risk of in-hospital mortality (hazard ratio [HR] 1.38, 95% confidence interval [CI] 1.17–1.62, $p < 0.001$) and decreased likelihood of discharge home (HR 0.72, 95% CI 0.63–0.85, $p < 0.001$).

Conclusions

Neurologic disorders were detected in 13.5% of patients with COVID-19 and were associated with increased risk of in-hospital mortality and decreased likelihood of discharge home. Many observed neurologic disorders may be sequelae of severe systemic illness.

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Glossary

aHR = adjusted hazard ratio; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **EMR** = electronic medical record; **GCS-NeuroCOVID** = Global Consortium Study of Neurologic Dysfunction in COVID-19; **ICD-10** = International Classification of Diseases–10; **ICH** = intracerebral hemorrhage; **ICU** = intensive care unit; **IDSA** = Infectious Diseases Society of America; **IQR** = interquartile range; **LOS** = length of stay; **NYU** = New York University; **RT-PCR** = reverse transcriptase PCR; **SAH** = subarachnoid hemorrhage; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **SOFA** = Sequential Organ Failure Assessment.

The prevalence of neurologic findings in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection ranges from 3.5% to 84% across studies.[1–5] Reported coronavirus disease 2019 (COVID-19)–related neurologic disorders include encephalopathy, anosmia, dysgeusia, headache, stroke, seizure, acute necrotizing encephalopathy, hypoxic ischemic brain injury, encephalitis, and demyelinating polyneuropathy.[6] However, discrepancies in methodology, neurologic event definitions, cohort size, and ascertainment have contributed to variable reporting. Furthermore, there is a paucity of prospective data evaluating neurologic findings among patients with COVID-19.

In this study, we aimed to prospectively identify the prevalence of specific neurologic diagnoses among patients with laboratory-confirmed SARS-CoV-2 infection and to determine the associated risk of in-hospital death compared to patients with COVID-19 without neurologic disorders. We additionally aimed to compare hospital complications and discharge disposition between these groups. In a secondary analysis, we compared patients with COVID-19 whose neurologic disorders occurred prior to, or at the time of admission, to patients who developed neurologic disorders later during hospitalization.

Methods

Study Design and Patient Cohort

A prospective, observational study was conducted including patients hospitalized between March 10, 2020, and May 20, 2020. Inclusion criteria were age ≥18 years, hospital admission, and reverse transcriptase PCR (RT-PCR)–positive SARS-CoV-2 infection. Exclusion criteria were SARS-CoV-2 RT-PCR negative test or no test performed, or evaluation in an outpatient or emergency department setting only (without hospital admission). Common data elements, case report forms, and the data repository were developed following the study protocol established by the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID), an international study including 189 adult and pediatric sites endorsed by the Neurocritical Care Society.[7] The first level of screening for inclusion was performed by the emergency department or admitting team, wherein a neurology consult would be triggered according to routine protocol for patients with new or worsened neurologic disorders. All inpatients evaluated by a neurologist across the health system were automatically added to a common list in the electronic medical record (EMR). This list was screened twice daily for study inclusion. Neurologic diagnoses were coded among SARS-CoV-2 RT-PCR–positive patients who were evaluated by a neurologist and found to have a new neurologic disorder (as defined below), excluding recrudescence of old neurologic deficits. SARS-CoV-2–infected patients under investigation were kept on the screening list until test results were finalized. Patients with COVID-19 with neurologic diagnoses were compared to SARS-CoV-2 RT-PCR–positive patients (aged ≥18 years) without neurologic diagnoses admitted during the same timeframe. Patients with COVID-19 who were prospectively excluded due to "no new neurologic disorder" after evaluation by a neurologist were included in the control group. Only initial patient admissions were included; readmissions were excluded.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved with a waiver of authorization and informed consent by the New York University (NYU) Grossman School of Medicine Institutional Review Board.

Setting

We included patients admitted to 4 NYU Langone hospitals (NYU Langone Tisch/Kimmel, Brooklyn, Winthrop, and Orthopedic Hospitals) located in Manhattan, Brooklyn, and Mineola, NY. During the COVID-19 New York City surge encompassing the time frame of this study, bed capacity was expanded and pre–COVID-19 admission and discharge criteria were followed. All transfers during this time period were accepted per protocol. The determination of level of care remained the same as during prepandemic times. All 4 hospitals utilize the same EMR (Epic Systems Corporation, Madison, WI) and information technology center and have integrated clinical protocols for patient management. Inpatient neurology teams covering all 4 sites included the stroke service (staffed by board-certified vascular neurologists), neurocritical care service (staffed by board-certified, neurology trained neurointensivists), acute inpatient neurology service, and neurology consult service. Patients with primary neurologic diagnoses (e.g., stroke, intracranial hemorrhage, encephalitis, seizure, neuromuscular disorders) were admitted to a neurology service (stroke, neurocritical care, general neurology) irrespective of COVID-19 status. Patients with a non-neurologic primary diagnosis and concomitant neurologic disorders (e.g., toxic/metabolic

encephalopathy) were evaluated by a neurology consult service. Neurointensivists routinely consult on all patients with cardiac arrest per hospital protocol. During the COVID-19 New York City surge, neurologists and neurointensivists routinely cross-covered medicine and intensive care unit (ICU) services that comprised SARS-CoV-2–positive patients with primary medical diagnoses, increasing the probability of case identification in this cohort.[8,9] All patients identified as having a possible neurologic disorder who were not on a primary neurology service were seen by a neurology consult service to ensure continuity of care and standardized neurologic evaluation.

Neurologic Diagnoses

Neurologic diagnoses were categorized as toxic/metabolic encephalopathy, stroke (ischemic, intracerebral/intraventricular hemorrhage, spontaneous subarachnoid hemorrhage [SAH]), hypoxic/ischemic brain injury, seizure, neuropathy (including Guillain-Barré syndrome), myopathy, movement disorder, encephalitis, meningitis, myelitis, and myelopathy. Diagnostic criteria followed the guidelines established by the GCS-NeuroCOVID consortium.[7] Toxic/metabolic encephalopathy was coded for patients with temporary/reversible changes in mental status in the absence of focal neurologic deficits or primary structural brain disease, excluding patients in whom sedative or other drug effects or hypotension (mean arterial pressure <60 mm Hg) were judged, on clinical grounds, to explain presentation. This diagnosis category also excluded patients in whom another specific neurologic diagnosis was present that could account for the observed examination findings. Etiologies included electrolyte abnormalities, uremia, liver failure, acid/base disorders, sepsis/active infection, hypertension, hypoxia, or hypercarbia. Ischemic and hemorrhagic strokes were diagnosed according to American Heart Association/American Stroke Association guidelines.[10] Ischemic strokes and TIAs were diagnosed and adjudicated by a board-certified vascular neurologist and verified by brain imaging. Traumatic intracranial hemorrhages were excluded and ischemic strokes with hemorrhagic conversion were coded as ischemic strokes. Hypoxic/ischemic brain injury was diagnosed among survivors of cardiac arrest with new CNS dysfunction, and among patients with prolonged or severe hypoxia or hypotension with new neurologic deficits and characteristic radiographic findings on head CT or MRI. Seizures were diagnosed clinically by the treating neurologist or electrographically by an epileptologist. Guillain-Barré syndrome was diagnosed according to international clinical, laboratory, and electrophysiologic criteria. Brighton diagnostic certainty level I and II patients were included.[11–13] Meningitis, encephalitis, and myelitis were diagnosed according to Infectious Diseases Society of America (IDSA), International Encephalitis Consortium, and American Academy of Neurology guidelines.[14–18] Initial neurologic diagnoses documented in the medical record were adjudicated by the abstracting physician (neurology attending or resident) following the criteria listed above. Subspecialty adjudication was performed for ischemic and hemorrhagic stroke diagnoses by subspecialist coauthors (K.I., S.Y., J.T., K.M., A.L.). Seizure diagnoses and EEG records were reviewed and adjudicated by epileptologist coauthors (Daniel Friedman, M.H.).

Clinical Management

A health system–wide inpatient COVID-19 treatment algorithm was developed by the hospital infection control and infectious diseases departments, which broadly followed IDSA guidelines for the treatment and management of COVID-19.[19] A protocol of early prone positioning was promoted for patients prior to intubation. Therapeutic anticoagulation was continued during hospitalization in patients with an underlying indication. In patients without a prior known indication, serial D-dimer levels were checked every 48 hours and therapeutic anticoagulation (monitoring heparin or enoxaparin specific Xa levels) was recommended in patients with D-dimer levels >10,000 ng/mL and suggested in those with D-dimer levels between 2,000 and 10,000 ng/mL. Prophylactic dosing of antithrombotics was recommended for patients with D-dimer levels <2000 ng/mL. In patients with high suspicion for a venous thromboembolic event, oral anticoagulation could be considered for at least 3 months following discharge. During the timeframe of this study (prior to publication of the RECOVERY trial[20]), corticosteroids could be considered in patients with bilateral opacities on chest imaging and a PaO_2/FiO_2 <250 mm Hg, as long as the patient did not have an active bacterial infection and was not immunosuppressed. Corticosteroids could also be used for other indications, such as brain tumor, autoimmune disease, chronic obstructive pulmonary disease exacerbation, refractory septic shock, or suspected adrenal insufficiency.

Data Collection

We collected common data elements developed by the GCS-NeuroCOVID consortium.[7] Demographics, past neurologic history, admission laboratory values, and in-hospital outcomes (including in-hospital mortality, discharge disposition, ventilator days, and hospital length of stay [LOS]) were recorded. The maximum recorded Sequential Organ Failure Assessment (SOFA) score was used to assess severity of illness; this has been shown to be predictive of organ failure and in-hospital mortality.[21–23] Patients could be coded for multiple different neurologic diagnoses. Neurologic diagnoses coding was performed by attending neurologists and neurology resident physicians during data abstraction applying the diagnostic criteria listed above. Past neurologic history was assessed via manual chart review and validated by EMR data query based on ICD-10 diagnoses. Data were recorded in a REDCap database.

Study Outcomes

The coprimary study outcomes were the prevalence of specific new neurologic diagnoses among SARS-CoV-2–positive hospitalized patients and in-hospital mortality rates compared between patients with COVID-19 with and without neurologic disorders. Secondary outcomes included the time from COVID-19 symptom onset to neurologic disorder onset, the time from neurologic disorder onset to admission, common COVID-19 hospital complications (acute respiratory failure

requiring mechanical ventilation and acute renal failure), discharge disposition, hospital LOS, and ventilator days.

Statistical Analyses

Demographic variables, past neurologic history, laboratory values, and in-hospital outcomes were compared between patients with COVID-19 with and without a neurologic disorder using the Mann-Whitney *U* (Wilcoxon rank-sum) for non-normally distributed continuous variables and χ^2 test or Fisher exact test for categorical values, as appropriate. A Cox proportional hazards model was fit for the time to in-hospital death using a time-dependent neurologic disorder covariate (to account for immortal time bias and the risk of neurologic disorders violating the proportional hazards assumption over the hospitalization period) and adjusting for confounders including age, sex, race, week of admission, hospital location, past medical history (hypertension, diabetes), past neurologic history, maximum SOFA score recorded during hospitalization, hospital complications of acute renal failure or intubation, comfort care only status, and treatment with therapeutic anticoagulation, hydroxychloroquine, corticosteroids, or lopinavir/ritonavir. These confounders were selected based on known predictors of in-hospital death, biological plausibility, and bivariate associations within our own data. To avoid time to event bias among patients who were discharged, a dummy variable of 75 days was used as the event time for right censored patients who were not dead or discharged to hospice. Seventy-five days was selected based on the prolonged LOS observed in this cohort (maximum LOS 71.4 days). All analyses were conducted using IBM SPSS Statistics for Windows version 25 (IBM, Armonk, NY).

Data Availability

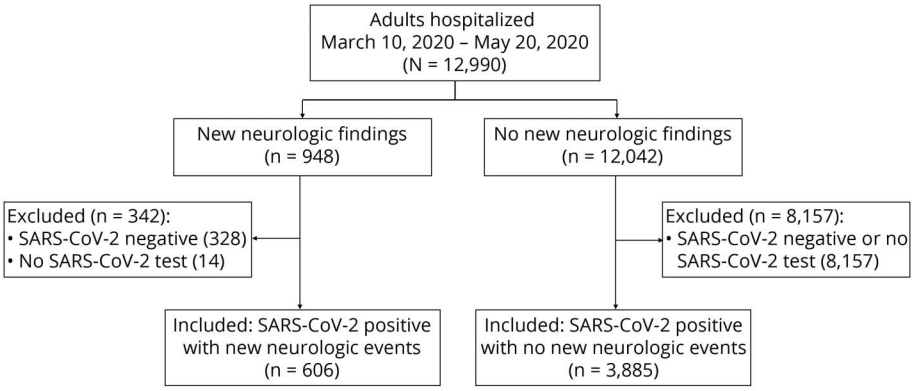
De-identified data will be made available to qualified investigators upon written request to the corresponding author.

Results

Of 12,990 hospitalized adult patients during the study time frame from March 10 through May 20, 2020, 1,072 (8.2%) were evaluated by a neurology service. Of these 1,072, 948 (88%) had a new neurologic disorder as diagnosed by a neurologist. We excluded 328/948 (35%) who had a negative SARS-CoV-2 test and 14/948 (1.5%) who were not tested (figure). A total of 606/948 (64%) patients with new neurologic disorders were SARS-CoV-2 RT-PCR positive and included in the analysis. During the same time frame, 3,885/12,042 (32%) SARS-CoV-2–positive patients were hospitalized without a neurologic disorder. The overall prevalence of neurologic disorders among hospitalized patients with COVID-19 was 13.5% (606/4,491). Among patients with COVID-19 with neurologic disorders, the most common were toxic/metabolic encephalopathy (309/606, 51%), stroke (84/606, 14%), seizure (74/606, 12%), and hypoxic/ischemic brain injury (65/606, 11%; table 1). No patient had meningitis, encephalitis, myelitis, or myelopathy referable to SARS-CoV-2 infection. Among patients with seizure, 34/74 (46%) had no prior history of seizure or epilepsy. Of 27 patients with COVID-19 who underwent CSF analyses, 18 had SARS-CoV-2 RT-PCR testing and all 18 were negative (table 2).

The median time from first COVID-19 symptom (e.g., fever, cough, nausea, vomiting, diarrhea) to neurologic disorder onset was 2 days (interquartile range [IQR] 0–13) and the median time from hospital admission to first neurologic symptom was −0.6 days (IQR −1.8 to 4.1), indicating that most patients had neurologic symptoms prior to admission, but after initial COVID-19 symptom onset. Overall, 419/606 (69%) patients with neurologic disorders developed neurologic symptoms prior to hospital admission. Only 10 (2%) patients developed neurologic symptoms prior to traditional viral symptoms associated with COVID-19 (cough, shortness of breath, fever, sore throat, gastrointestinal abnormalities), while 263 (43%) developed neurologic and traditional COVID-19 symptoms at approximately the same time, and 326 (54%) developed neurologic symptoms after traditional COVID-19 symptoms in a median of 12 days (IQR 5–22). The majority of patients who developed neurologic symptoms prior to or at the same time as traditional COVID-19

Figure Flowchart of Patient Inclusion and Exclusion



SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 1 Prevalence of Neurologic Disorders Among Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 Infection

Variable	Patients (n = 4,491), n (%)
Any new neurologic disorder	606 (13.5)
Neurologic disorders	
Toxic/metabolic encephalopathy	309 (6.8)
Stroke (any type)	84 (1.9)
Ischemic/TIA	61 (1.4)
Intracerebral/intraventricular hemorrhage	20 (0.4)
Spontaneous subarachnoid hemorrhage	3 (0.1)
Seizure (clinical or electrographic)	74 (1.6)
Hypoxic/ischemic brain injury	65 (1.4)
Movement disorder	41 (0.9)
Neuropathy	35 (0.8)
Myopathy	21 (0.5)
Guillain-Barré syndrome	3 (0.1)
Encephalitis/meningitis	0
Myelopathy/myelitis	0

symptoms had neurologic symptom onset prior to hospitalization (9/10 [90%] and 256/263 [97%], respectively). Of the 326 patients who developed neurologic disorders after COVID-19 symptom onset, 172/326 (53%) had neurologic disorder onset while hospitalized.

Compared to patients who developed neurologic findings prior to or at the time of admission, patients who were diagnosed with neurologic disorders after admission were significantly older, and were more severely ill based on SOFA scores, intubation rates, and acute renal failure rates (table 3). Patients who had neurologic disorders postadmission were more often diagnosed with stroke, hypoxic/ischemic brain injury, seizure, neuropathy, and myopathy (all $p < 0.05$). Patients diagnosed with neurologic disorders after admission were less likely to be discharged home than those with events prior to or at the time of admission.

Compared to the 3,885 patients with COVID-19 hospitalized during the same time frame without neurologic disorders, patients with neurologic disorders were significantly older (median age 71 vs 63 years), male (66% vs 57%), and white (63% vs 45%). Comorbidities including hypertension, diabetes, atrial fibrillation, venous thromboembolism, and history of neurologic illness were also significantly more common among those with neurologic diagnoses (table 4). Similarly, patients with neurologic disorders were more severely ill with higher SOFA scores (median 4 vs 3, $p < 0.001$), higher rates of invasive mechanical ventilation (40% vs 19%, $p < 0.001$), higher rates of acute renal failure (28% vs 12%, $p < 0.001$), and higher rates of ICU admission (40% vs 19%, $p < 0.001$). The majority of patients with neurologic events were admitted to a general internal medicine service (425/600 [70%]), while only 33/600 (6%) were admitted to a neurology service. Admission inflammatory biomarkers (interleukin-6, D-dimer) were increased in patients with neurologic disorders compared to those without (both $p < 0.01$, table 4). Patients with neurologic disorders were more likely to receive corticosteroids and therapeutic anticoagulation (for clinical indications such as atrial fibrillation, mechanical heart valves, or venous thromboembolism and for elevated D-dimer levels) than patients without neurologic disorders (table 4). Anticoagulation use was significantly associated with intracerebral hemorrhage (ICH) (17/20 [85%] of patients with ICH were anticoagulated vs 1,128/4,471 [25%] of those without ICH, $p < 0.001$) and SAH (3/3 [100%] of patients with SAH were anticoagulated vs 1,142/4,488 (25%) of those without SAH, $p = 0.003$).[24,25]

We observed higher rates of in-hospital mortality and lower rates of discharge home among patients with COVID-19 with neurologic disorders compared to those without (table 4). After adjusting for age, sex, race, date, and location of hospitalization, past history of medical and neurologic diseases, severity of illness (invasive mechanical ventilation and SOFA scores), acute renal failure, comfort care status, and differences in COVID-19–specific medication administration (therapeutic anticoagulation, hydroxychloroquine, corticosteroid, lopinavir/ritonavir use), the occurrence of a neurologic disorder was significantly associated with in-hospital death (35% with a neurologic disorder died vs 19% without, adjusted hazard ratio [aHR] 1.38, 95% confidence interval [CI] 1.17–1.62, $p < 0.001$). Similarly, after adjusting for the same factors and excluding patients who died or were in comfort care, the occurrence of a neurologic disorder was associated with a significantly reduced likelihood of discharge home (aHR 0.72, 95% CI 0.63–0.85, $p < 0.001$). Median hospital LOS (9.8 vs 5.9 days) and ventilator days (11.8 vs 5.0) were longer among those with neurologic disorders compared to those without (both $p < 0.001$). Corticosteroid use was independently associated with a reduced risk of in-hospital mortality (aHR 0.81, 95% CI 0.69–0.95, $p = 0.009$).

Discussion

In this large prospective study of neurologic disorders among hospitalized patients with COVID-19, 13.5% of patients had a neurologic diagnosis, most commonly toxic/metabolic encephalopathy, stroke, seizure, or hypoxic/ischemic brain injury. The occurrence of a neurologic disorder in the context of SARS-CoV-2 infection was associated with a 38% increased risk of in-hospital death and a 28% reduced likelihood of discharge home, after adjusting for other factors.

In contrast to prior retrospective studies that focused on the conglomerate prevalence of nonspecific neurologic symptoms (agitation, dysexecutive function, myalgia, dizziness, headache[1–4]) along with neurologic diagnoses (e.g., stroke, seizures, Guillain-Barré syndrome), we applied rigorous, standardized diagnostic criteria to identify the prevalence of specific neurologic diagnoses in a prospective fashion. All patients with neurologic disorders were evaluated by a neurologist, which strengthens the validity of the diagnoses. Unlike studies that included patients with suspected COVID-19 (without laboratory confirmation)[26] or categorized neurologic disorders based on clinical suspicion alone (without imaging, laboratory, or pathologic diagnosis verification),[26] we included only RT-PCR SARS-CoV-2–positive patients and coded neurologic disorders based on accepted diagnostic criteria. This is important because inclusion of patients with nonspecific symptoms, unsubstantiated diagnoses, or unverified SARS-CoV-2 infection may lead to inaccurate estimations of prevalence rates. Furthermore, nonspecific symptoms often do not confer the same prognostic implications as specific neurologic diagnoses. Smaller retrospective studies that excluded patients with nonspecific symptoms found much lower neurologic disorder prevalence rates (3.5% in one study[4]) compared to studies with more liberal inclusion criteria (57%–84% in studies[1,3] that included agitation and fever as possible neurologic disorders). The aforementioned retrospective studies all depended on EMR coding for data extraction and are thus limited by the quality and extent of available documentation. There was limited reporting on imaging studies performed in these retrospective studies, which may indicate an underestimation of neurologic disease or a degree of diagnostic uncertainty. Despite logistical difficulties obtaining neuroimaging in patients with COVID-19 (many of whom were critically ill, intubated, hypoxic, and on multiple vasopressors), 84% of patients with neurologic disorders in our cohort had head CT imaging and 15% had brain MRI. As with other centers that faced a surge of patients with COVID-19, workforce strains and contagion containment may have contributed to delays in neurologic diagnoses.

Table 2 CSF Findings Among Patients With Coronavirus Disease 2019 (COVID-19) With Neurologic Disorders[a] (n = 26)

CSF variable	CSF values
WBC count/mm^3	2 (1–4)
RBC count	37 (3–656)
Glucose	73 (59–92)
Protein	61 (42–106)
Abnormal WBC count[b]	5/26 (19)
Abnormal glucose	0
Abnormal protein[c]	20/26 (77)
SARS-CoV-2 CSF PCR negative	18/18 (100)

Abbreviations: RBC = red blood cells; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; WBC = white blood cells.
Normal laboratory reference range for CSF: WBC <5/mm^3; glucose 40–70 mg/dL or ≥2/3 of plasma glucose; protein 15–40 mg/dL. Values are median (interquartile range) or n/total n (%).
[a] The CSF studies were normal among all 4 patients who had CSF collected but no new neurologic disorder.
[b] One patient with pleocytosis had a brain mass since September 2019, prior to COVID-19 diagnosis; 1 patient had pleocytosis that was not present after correcting for RBCs; 2 patients with intracerebral and intraventricular hemorrhage had pleocytosis referable to the hemorrhage; and 1 patient had pleocytosis in the context of herpes encephalitis that predated his COVID-19 symptom onset by 4 weeks. Repeat CSF studies during his COVID-19 admission showed improving pleocytosis.
[c] CSF protein was elevated in 3 patients with Guillain-Barré syndrome and 17 patients with traumatic lumbar punctures with elevated RBC.

Overall, toxic/metabolic encephalopathy, seizure, and hypoxic/ischemic brain injury were particularly common in our cohort. These complications are also common among critically ill patients, especially those with acute respiratory distress syndrome, sepsis,[27] hypoxia, acute renal failure, and hypotension, which were prevalent complications among patients with severe COVID-19. Indeed, seizure, hypoxic/ischemic brain injury, myopathy, neuropathy, and stroke constituted a higher proportion of neurologic complications diagnosed postadmission compared to preadmission (or concurrent with admission). Many of the cases of neuropathy and myopathy in this cohort were attributed to critical illness. There was also a significant association between severity of illness markers (intubation, SOFA scores, acute renal failure) and the occurrence of neurologic disorders, particularly among those who developed neurologic findings after admission, suggesting that critical illness itself may have contributed to neurologic complications. Notably, toxic/metabolic encephalopathy manifested more frequently prior to or at the time of admission. This may be an artifact of the fact that we were unable to diagnose encephalopathy in patients in whom sedation may have confounded the neurologic examination.

We did not identify any neurologic cases (meningitis, encephalitis, myelitis, or other) that were conclusively related to direct SARS-CoV-2 invasion of the CNS. Indeed, 18/18 (100%) CSF samples that were tested were RT-PCR–negative for SARS-CoV-2. We did not have any neuropathologic specimens available in this cohort. Our findings do not eliminate the possibility of direct nervous system invasion of SARS-CoV-2; however, given our large sample size it is likely that such a complication is rare. The possibility of endothelial or microvascular viral invasion[28,29] has been hypothesized to account for some of the unusual strokes and ICHs reported in the context of SARS-CoV-2 infection, yet this remains speculative without pathologic verification. Autopsy series have reported primarily hypoxic-ischemic neuropathologic changes, without evidence of primary viral CNS invasion among patients who presented with nonspecific symptoms of headache, dysgeusia, and myalgias.[30] An autopsy report of a patient with baseline confusion related to Parkinson disease

Table 3 Neurologic Disorders Prior to or at the Time of Admission Compared to Neurologic Disorders After Admission Among Patients With Coronavirus Disease 2019[a]

	Neurologic disorder preadmit or at time of admission (n = 419)	Neurologic disorder postadmission (n = 180)	*p* Value
Days from admission to first neurologic symptom	−0.8 (−3.5 to −0.5)	12.3 (5.2–21.2)	<0.001
Demographics and clinical findings			
Age, y	74 (62–83)	64 (57–72)	<0.001
Male sex	248/419 (62)	135/180 (75)	0.002
Race (white vs other)	268/419 (64)	109/180 (61)	0.429
Maximum SOFA score	3 (0–4)	11 (4–14)	<0.001
Invasive mechanical ventilation	97/419 (23)	138/180 (77)	<0.001
Acute renal failure	84/419 (20)	80/180 (44)	<0.001
Comfort care status	72/419 (17)	39/180 (22)	0.195
Neurologic disorder type			
Toxic/metabolic encephalopathy[a]	240/419 (57)	71/180 (40)	<0.001
Stroke (any type)	33/419 (8)	25/180 (14)	0.023
Ischemic/TIA	37/419 (9)	43/180 (24)	<0.001
ICH/IVH	3/419 (1)	17/180 (10)	<0.001
Spontaneous subarachnoid hemorrhage	0	2/180 (1)	0.031
Seizure (clinical or electrographic)	38/419 (9)	29/180 (16)	0.013
Hypoxic/ischemic brain injury	29/342 (9)	35/154 (23)	<0.001
Movement disorder	23/419 (5)	17/180 (9)	0.076
Neuropathy	17/419 (4)	17/180 (9)	0.012
Myopathy	9/418 (2)	12/178 (7)	0.013
Guillain-Barré syndrome	3 (100)	0	0.255
Encephalitis/meningitis	0	0	—
Myelopathy/myelitis	0	0	—
Outcomes			
Discharged home	161/219 (38)	40/180 (22)	0.001
Died in hospital	134/419 (32)	72/180 (40)	0.058

Abbreviations: ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage; SOFA = Sequential Organ Failure Assessment.
Values are median (interquartile range) or n/total n (%).
[a] Timing of neurologic disorders missing in 7 patients.

described the presence of virus in neural and capillary endothelium in the frontal lobe,[31] but immunohistochemistry studies were not performed and rough endoplasmic reticulum may be mistaken for virions in the absence of immunohistochemical or electron microscopy confirmation. Neuropathologic data among patients with specific neurologic events in the context of SARS-CoV-2 infection are lacking. One study of patients with ischemic and hemorrhagic stroke included brain biopsy pathology on 2 patients, but one of these was both SARS-CoV-2 RT-PCR–negative and antibody-negative (and included based on chest CT imaging characteristics alone), while the other was RT-PCR–positive. The authors identified a paucity of endothelial cells in arterioles, venules, and capillaries, but no evidence of inflammation to suggest direct viral involvement or endotheliitis.[32]

Conversely, there are clinical and pathologic data to support the occurrence of postinfectious complications of SARS-CoV-

Table 4 Demographic, Clinical, and Hospital Outcomes Among Patients With Coronavirus Disease 2019 (COVID-19) With and Without Neurologic Disorders During Hospitalization

Characteristics	COVID-19 positive with neurologic disorder (n = 606)	COVID-19 positive without neurologic disorder (n = 3,885)	*p* Value
Demographics			
Age, y	71 (60–80)	63 (50–75)	<0.001
Male sex	397/606 (66)	2,210/3,885 (57)	<0.001
Body mass index	27 (24–31)	28 (25–33)	<0.001
Race			<0.001
White	382/606 (63)	1734/3,885 (45)	
Black	98/606 (16)	606/3,885 (16)	
Asian	65/606 (11)	248/3,885 (6)	
Other	61/606 (10)	1,297/3,885 (33)	
Past medical history			
Hypertension	287/606 (47)	1,425/3,885 (37)	<0.001
Diabetes	190/606 (31)	986/3,885 (25)	0.002
Hyperlipidemia	190/606 (31)	979/3,885 (25)	0.001
Chronic kidney disease	97/606 (16)	400/3,885 (10)	<0.001
Obstructive sleep apnea	29/600 (5)	156/3,863 (4)	0.363
Atrial fibrillation	85/600 (14)	322/3,863 (8)	<0.001
Venous thromboembolism	58/600 (10)	217/3,863 (6)	<0.001
Past neurologic history[a]			
Ischemic stroke	116/606 (19)	275/3,885 (7)	<0.001
Seizure/epilepsy	89/606 (15)	124/3,885 (3)	<0.001
Dementia	73/606 (12)	143/3,885 (4)	<0.001
Neuropathy	38/606 (6)	141/3,885 (4)	0.002
ICH/IVH	28/606 (5)	25/3,885 (1)	<0.001
Movement disorder	20/606 (3)	59/3,885 (2)	0.002
Traumatic brain injury	15/606 (3)	36/3,885 (1)	0.003
Multiple sclerosis/demyelinating disease	5/606 (1)	15/3,885 (0.4)	0.176
Myasthenia gravis	1/606 (0.2)	5/3,885 (0.1)	0.581
Hydrocephalus	10/606 (2)	9/3,885 (0.2)	<0.001
Brain tumor	5/606 (1)	6/3,885 (0.2)	0.010
Clinical findings			
ICU vs non-ICU unit	242/600 (40)	737/3,852 (19)	<0.001
Maximum SOFA score	4 (3–9)	3 (0–4)	<0.001
Medications			
Corticosteroids	146 (24)	697 (18)	<0.001
Hydroxychloroquine	445/606 (73)	2,570/3,885 (66)	<0.001
Azithromycin	380/606 (63)	2,295/3,885 (59)	0.090

Continued

Table 4 Demographic, Clinical, and Hospital Outcomes Among Patients With Coronavirus Disease 2019 (COVID-19) With and Without Neurologic Disorders During Hospitalization *(continued)*

Characteristics	COVID-19 positive with neurologic disorder (n = 606)	COVID-19 positive without neurologic disorder (n = 3,885)	*p* Value
Lopinavir/ritonavir	60/606 (10)	254/3,885 (7)	0.003
Zinc	204/606 (34)	1,359/3,885 (35)	0.527
Ascorbic acid (vitamin C)	160/606 (26)	918/3,885 (24)	0.137
Tocilizumab	81/606 (13)	458/3,885 (12)	0.266
Remdesivir	1/606 (0.2)	13/3,885 (0.3)	0.709
Therapeutic anticoagulation[b] (based on D-dimer)	176/606 (29)	678/3,885 (18)	<0.001
Therapeutic anticoagulation[b] (clinical indication[c])	75/606 (12)	216/3,885 (6)	<0.001
Acute renal failure	167/606 (28)	479/3,885 (12)	<0.001
Invasive mechanical ventilation	241/602 (40)	746/3,885 (19)	<0.001
Hospital length of stay, d	9.8 (4.9–22.6)	5.9 (3.0–10.7)	<0.001
Ventilator, d[d]	11.8 (3.7–24.0)	5.0 (1.2–12.7)	<0.001
Comfort care status	111/606 (18)	156/3,885 (4)	<0.001
Radiographic and laboratory findings			
Head CT	510/606 (84)	374/3,885 (10)	<0.001
Brain MRI	89/606 (15)	38/3,885 (1)	<0.001
Lumbar puncture	26/606 (4)	4/3,885 (0.1)	<0.001
Admission interleukin-6, pg/mL[e]	32 (14–66)	21 (10–52)	0.007
Admission C-reactive protein, mg/L[f]	93 (35–157)	107 (50–170)	0.001
Admission D-dimer, ng/mL[g]	532 (309–1,112)	425 (272–791)	<0.001
Admission ferritin, ng/mL[h]	667 (317–1,541)	677 (317–1,387)	0.379
Hospital outcomes			
Discharged home	201/596 (34)	2,548/3,803 (67)	<0.001
Died in-hospital	211/606 (35)	751/3,885 (19)	<0.001
Other discharge dispositions	187/596 (32)	504/3,803 (13)	<0.001
Hospitalized	13/596 (2)	27/3,803 (1)	<0.001
LTACH	14/596 (2)	28/3,803 (1)	<0.001
Nursing home	122/596 (21)	357/3,803 (9)	<0.001
Acute inpatient rehabilitation	32/596 (5)	89/3,803 (2)	<0.001
Subacute rehabilitation	4/596 (1)	3/3,803 (0.1)	0.001

Abbreviations: ICH/IVH = intracerebral hemorrhage or intraventricular hemorrhage; ICU = intensive care unit; LTACH = long-term acute care hospital; SOFA = Sequential Organ Failure Assessment.
Values are median (interquartile range) or n/total n (%).
[a] Patients could have more than 1 past neurologic history diagnosis.
[b] Includes therapeutic dosing of enoxaparin or heparin.
[c] Indications include atrial fibrillation, venous thromboembolism, or mechanical heart valve.
[d] Includes only patients who received invasive mechanical ventilation.
[e] Data available in 161 patients with neurologic disorders and 841 patients without neurologic disorders (normal range ≤5 pg/mL).
[f] Data available in 577 patients with neurologic disorders and 3,466 patients without neurologic disorders (normal range 0.0–3.0 mg/L).
[g] Data available in 492 patients with neurologic disorders and 2,993 patients without neurologic disorders (normal range <230 ng/mL).
[h] Data available in 573 patients with neurologic disorders and 3,449 patients without neurologic disorders (normal range 8.0–388.0 ng/mL).

2. We identified 3 patients with Guillain-Barré syndrome occurring within 2–4 weeks of documented SARS-CoV-2 infection. All 3 patients had RT-PCR SARS-CoV-2–negative CSF, but antibody testing in the CSF was not available. Because a number of other studies have reported SARS-CoV-2 complications including Guillain-Barré syndrome and acute disseminated encephalomyelitis, the possibility of post-infectious or parainfectious COVID-19–related complications seems plausible.[5,6,33–36] One neuropathology report of a critically ill patient with COVID-19 identified atypical white matter lesions, microscopic infarcts, necrosis, and axonal injury on an autopsy performed weeks after SARS-CoV-2 diagnosis. This case was thought to represent a postinfectious, possibly autoimmune manifestation of COVID-19.[37]

In our cohort, patients with COVID-19 with neurologic disorders had significantly higher risk of in-hospital mortality and lower rates of discharge home compared to patients with COVID-19 without neurologic findings. One strength of our analysis was that we were able to adjust for a variety of other factors including comfort care status, which often confounds mortality analyses. In a separate study, we found that patients with laboratory-confirmed COVID-19 and ischemic stroke have higher mortality rates than contemporary and historical patients with ischemic stroke who did not have COVID-19.[25] Others have found similar increases in mortality rates among patients with a spectrum of SARS-CoV-2–related neurologic diseases[38] compared to contemporary COVID-19–negative neurologic patients. We studied neurologic events as a time-dependent variable to avoid the immortal time bias, which can occur when an event is observed more frequently in patients who survive long enough to be diagnosed. This methodology also allowed us to account for the duration of exposure to neurologic injury when predicting the hazard of in-hospital death.

There are limitations to this study that should be mentioned. First, patients with limited neurologic examinations due to sedation or paralysis may have had neurologic disorders that were undetected, leading to underestimations in the prevalence of COVID-19–related neurologic injury. Furthermore, neurology may not have been consulted on patients with mild neurologic symptoms. Logistical difficulties in transporting patients for neuroimaging studies may have also led to underestimations of neurologic disorders. However, the fact that neurologists and neurointensivists in our health system cross covered COVID-19 medicine patients during the time epoch of this study increases the likelihood that neurologic disorders were detected. Second, neurologic disorders may have occurred in patients who did not come to hospital[25,39,40] due to fear of contracting COVID-19. Third, due to illness severity, many patients may not have been able to provide a detailed history of neurologic symptoms, which could contribute to underestimations of prevalence. Lastly, due to high rates of missing data, we were unable to report rates of Hispanic ethnicity.

Neurologic disorders were detected in 13.5% of patients with COVID-19 during the study timeframe. Many of these neurologic disorders occur commonly among patients with critical illness. Encephalitis, meningitis, or myelitis referable to SARS-CoV-2 infection did not occur, although post-infectious Guillain-Barré syndrome was identified. Overall, neurologic disorders in the context of SARS-CoV-2 infection confer a higher risk of in-hospital mortality and reduced likelihood of discharge home.

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Appendix *(continued)*

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Appendix *(continued)*

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Continued

Appendix *(continued)*

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