

# Neurology®

The most widely read and highly cited peer-reviewed neurology journal  
The Official Journal of the American Academy of Neurology



---

Neurology Publish Ahead of Print  
DOI: 10.1212/WNL.0000000000010979

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

*Neurology*® Published Ahead of Print articles have been peer reviewed and accepted for publication. This manuscript will be published in its final form after copyediting, page composition, and review of proofs. Errors that could affect the content may be corrected during these processes.

Jennifer A. Frontera<sup>1</sup>, MD; Sakinah Sabadia<sup>1</sup>, MD; Rebecca Lalchan<sup>1</sup>, DO; Taolin Fang<sup>1</sup>, MD; Brent Flusty<sup>1</sup>, DO; Patricio Millar-Verneti<sup>1</sup>, MD; Thomas Snyder,<sup>1</sup> MD; Stephen Berger<sup>1</sup>, MD; Dixon Yang<sup>1</sup>, MD; Andre Granger<sup>1</sup>, MD; Nicole Morgan<sup>1</sup>, MD; Palak Patel<sup>1</sup>, MD; Josef Gutman<sup>1</sup>, MD; Kara Melmed<sup>1</sup>, MD; Shashank Agarwal<sup>1</sup>, MD; Matthew Bokhari<sup>1</sup>, MD; Andres Andino<sup>1</sup>, MD; Eduard Valdes<sup>1</sup>, MD; Mirza Omari<sup>1</sup>, MD; Alexandra Kvernland<sup>1</sup>, MD; Kaitlyn Lillemo<sup>1</sup>, MD; Sherry H.-Y. Chou<sup>2</sup>, MD, MSc; Molly McNett<sup>3</sup>, RN, PhD; Raimund Helbok<sup>4</sup>, MD, PhD; Shraddha Mainali<sup>3</sup>, MD; Ericka L. Fink<sup>2</sup>, MD; Courtney Robertson<sup>5</sup>, MD, Michelle Schober<sup>6</sup>, MD; Jose I. Suarez<sup>5</sup>, MD; Wendy Ziai<sup>5</sup>, MD; David Menon<sup>7</sup>, MD, PhD; Daniel Friedman<sup>1</sup>, MD; David Friedman<sup>1</sup>, MD; Manisha Holmes<sup>1</sup>, MD; Joshua Huang<sup>1</sup>, MSc; Sujata Thawani<sup>1</sup>, MD; Jonathan Howard<sup>1</sup>, MD; Nada Abou-Fayssal<sup>1</sup>, MD; Penina Krieger<sup>1</sup>, MPhil; Ariane Lewis<sup>1</sup>, MD; Aaron S. Lord<sup>1</sup>, MD; Ting Zhou<sup>1</sup>, MD; D. Ethan Kahn<sup>1</sup>, DO; Barry M. Czeisler<sup>1</sup>, MD; Jose Torres<sup>1</sup>, MD; Shadi Yaghi<sup>1</sup>, MD; Koto Ishida<sup>1</sup>, MD; Erica Scher<sup>1</sup>, RN, MPH; Adam de Havenon<sup>6</sup>, MD; Dimitris Placantonakis<sup>1</sup>, MD, PhD; Mengling Liu<sup>1</sup>, PhD; Thomas Wisniewski<sup>1</sup>, MD; Andrea B. Troxel<sup>1</sup>, ScD; Laura Balcer<sup>1</sup>, MD, MSCE; and Steven Galetta<sup>1</sup>, MD

<sup>1</sup> New York University Grossman School of Medicine, New York, NY, USA

<sup>2</sup> University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

<sup>3</sup> The Ohio State University, Columbus, OH, USA

<sup>4</sup> Medical University of Innsbruck, Innsbruck, Austria.

<sup>5</sup> The Johns Hopkins University School of Medicine, Baltimore, MD, USA

<sup>6</sup> University of Utah School of Medicine, Salt Lake City, UT, USA

<sup>7</sup> University of Cambridge, Cambridge, UK

**Address for correspondence:**

Jennifer A. Frontera

Email: [jennifer.frontera@nyulangone.org](mailto:jennifer.frontera@nyulangone.org)

Tables: 4, Appendix Tables: 1

Figures: 1

Word Count: Title- 94 characters; Abstract-246; Manuscript: 3,917

Keywords: COVID-19, SARS-CoV-2, neurologic, mortality, prevalence

Study Funding: No targeted funding reported.

Disclosures:

J. Frontera- received grant support from NIH/NIA 3P30AG066512-01S1 and NIH/NINDS 3U24NS11384401S1 for the study of neurological disorders in COVID-19

S. Sabadia- reports no disclosures

R. Lalchan- reports no disclosures

T. Fang- reports no disclosures

B. Flusty- reports no disclosures

P. Millar-Vernetti- reports no disclosures

T. Snyder- reports no disclosures

S. Berger- reports no disclosures

D. Yang- reports no disclosures

A. Granger- reports no disclosures

N. Morgan- reports no disclosures

P. Patel- reports no disclosures

J. Gutman- reports no disclosures

K. Melmed- reports no disclosures

S. Agarwal- reports no disclosures

M. Bokhari- reports no disclosures

A. Andino- reports no disclosures

E. Valdes -reports no disclosures

M. Omari- reports no disclosures

A. Kvernland- reports no disclosures

K. Lillemoe- reports no disclosures

S. Chou- reports University of Pittsburgh CTSI award for study of neurologic manifestations of COVID-19

M. McNett- reports no disclosures

R. Helbok- reports no disclosures

S. Mainali- reports no disclosures

E. Fink- reports no disclosures

C. Robertson- reports no disclosures

M. Schober- reports no disclosures

J. Suarez- reports no disclosures

W. Ziai- reports no disclosures

D. Menon- reports no disclosures

D. Friedman- reports no disclosures

D. Friedman- reports no disclosures

M. Holmes- reports no disclosures

J. Huang- reports no disclosures

S. Thawani- reports no disclosures

J. Howard- reports no disclosures

N. Abou-Fayssal- reports no disclosures

P Krieger- reports no disclosures

A. Lewis- reports no disclosures

A. Lord- reports no disclosures

T. Zhou- reports no disclosures

D.E. Kahn- reports no disclosures

B. Czeisler- reports no disclosures

J. Torres- reports no disclosures

S. Yaghi- reports no disclosures

K. Ishida- reports no disclosures

E. Scher- reports no disclosures

A. de Havenon- reports no disclosures

D. Placantonakis- reports no disclosures

M. Liu- reports no disclosures

T. Wisniewski- received grant support from NIH/NIA 3P30AG066512-01S1 for the study of COVID-19 effects on the aging

A. Troxel-- received grant support from NIH/NINDS 3U24NS11384401S1 for the study of neurological disorders in COVID-19

L. Balcer- received grant support from NIH/NIA 3P30AG066512-01S1 for the study of COVID-19 effects on the aging

S. Galetta- reports no disclosures

## ABSTRACT

**Objective:** To determine the prevalence and associated mortality of well-defined neurologic diagnoses among COVID-19 patients, we prospectively followed hospitalized SARS-Cov-2 positive patients and recorded new neurologic disorders and hospital outcomes.

**Methods:** We conducted a prospective, multi-center, observational study of consecutive hospitalized adults in the NYC 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 COVID-19 patients with and without neurologic disorders.

**Results:** Of 4,491 COVID-19 patients 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 RT-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, past history, medical complications, medications and comfort-care-status, COVID-19 patients with neurologic disorders had increased risk of in-hospital mortality (Hazard Ratio[HR] 1.38, 95% 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 COVID-19 patients 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.

## **INTRODUCTION:**

The prevalence of neurologic findings in patients with SARS-CoV-2 infection ranges from 3.5-84% across studies<sup>1-5</sup>. Reported COVID-19 related neurologic disorders include encephalopathy, anosmia, dysgeusia, headache, stroke, seizure, acute necrotizing encephalopathy, hypoxic ischemic brain injury, encephalitis and demyelinating polyneuropathy<sup>6</sup>. 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 COVID-19 patients.

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 COVID-19 patients without neurologic disorders. We additionally aimed to compare hospital complications and discharge disposition between these groups. In a secondary analysis, we compared COVID-19 patients 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  $\geq 18$  years, hospital

admission and reverse-transcriptase-polymerase-chain-reaction (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<sup>7</sup>. 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 neurological disorders. All inpatients evaluated by a neurologist across the health system were automatically added to a common list in the electronic medical record. 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 patients under investigation were kept on the screening list until test results were finalized. COVID-19 patients with neurologic diagnoses were compared to SARS-CoV-2 RT-PCR positive patients (aged  $\geq 18$  years) *without* neurologic diagnoses admitted during the same timeframe. COVID-19 patients who were prospectively excluded due to “no new neurological 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 NYU Grossman School of Medicine Institutional Review Board.

*Setting-*

We included patients admitted to four NYU Langone hospitals (NYU Langone Tisch/Kimmel, Brooklyn, Winthrop and Orthopedic Hospitals) located in Manhattan, Brooklyn and Mineola, New York. 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 pre-pandemic times. All four hospitals utilize the same electronic medical record (Epic Systems Corporation, Madison, WI) and information technology center, and have integrated clinical protocols for patient management. Inpatient neurology teams covering all four 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 cardiac arrest patients per hospital protocol. During the COVID-19 New York City surge neurologists and neurointensivists routinely cross-covered medicine and intensive care unit services that were comprised of SARS-CoV-2 positive patients

with primary medical diagnoses, increasing the probability of case identification in this cohort<sup>8</sup>.  
<sup>9</sup>. 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 neurological evaluation.

### *Neurologic Diagnoses-*

Neurologic diagnoses were categorized as: toxic/metabolic encephalopathy, stroke (ischemic, intracerebral/intraventricular hemorrhage, spontaneous subarachnoid hemorrhage), hypoxic/ischemic brain injury, seizure, neuropathy (including Guillain-Barre Syndrome), myopathy, movement disorder, encephalitis, meningitis, myelitis and myelopathy. Diagnostic criteria followed the guidelines established by the GCS-NeuroCOVID consortium<sup>7</sup>. 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 mmHg) 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 exam 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<sup>10</sup>. Ischemic strokes and TIAs (transient ischemic attacks) 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 central nervous system dysfunction, and among patients with prolonged and/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 and/or electrographically by an epileptologist. Guillain-Barre Syndrome was diagnosed according to international clinical, laboratory and electrophysiological criteria. Brighton diagnostic certainty level I and II patients were included<sup>11-13</sup>. Meningitis, encephalitis and myelitis were diagnosed according to Infectious Diseases Society of America (IDSA), International Encephalitis Consortium and American Academy of Neurology (AAN) guidelines<sup>14-18</sup>. Initial neurological diagnoses documented in the medical record were adjudicated by the abstracting physician (neurology attending or resident) following the criteria listed above. Additionally, sub-specialty adjudication was performed for ischemic and hemorrhagic stroke diagnoses by sub-specialist co-authors (KI, SY, JT, KM, AL). Seizure diagnoses and electroencephalogram records were reviewed and adjudicated by epileptologist co-authors (DF, MH).

### *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<sup>19</sup>. 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 2,000-10,000 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<sup>20</sup>), corticosteroids could be considered in patients with bilateral opacities on chest imaging and a PaO<sub>2</sub>/FiO<sub>2</sub> <250 mmHg, 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, COPD exacerbation, refractory septic shock or suspected adrenal insufficiency.

#### *Data Collection-*

We collected common data elements developed by the GCS-NeuroCOVID consortium<sup>7</sup>. Demographics, past neurologic history, admission laboratory values and in-hospital outcomes (including in-hospital mortality, discharge disposition, ventilator days and hospital length of stay) 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<sup>21-23</sup>. 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 co-primary study outcomes were the prevalence of specific new neurologic diagnoses among SARS-CoV-2 positive hospitalized patients and in-hospital mortality rates compared among COVID-19 patients 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 length of stay and ventilator days.

#### *Statistical Analyses-*

Demographic variables, past neurologic history, laboratory values, and in-hospital outcomes were compared between COVID-19 patients with and without a neurologic disorder using the Mann-Whitney U (Wilcoxon rank-sum) for non-normally distributed continuous variables and Chi-square test or Fisher's 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 and/or intubation, comfort care only status, and treatment with therapeutic anticoagulation, hydroxychloroquine, corticosteroids and/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 length of stay (LOS) observed in this cohort (maximum LOS 71.4 days). All analyses were conducted using IBM SPSS Statistics for Windows version 25 (IBM Corp., 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 3/10/20-5/20/20, 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 1). A total of 606/948 (64%) patients with new neurological 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 COVID-19 patients was 13.5% (606/4,491). Among COVID-19 patients 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 a no prior history of seizure or epilepsy. Of 27 COVID-19 patients that underwent cerebrospinal fluid (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 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 neurological 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 symptoms had neurologic symptom onset prior to hospitalization (9/10 [90%] patients 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). Additionally, patients who had neurologic disorders post-admission 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 COVID-19 patients 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%). Co-morbidities 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% versus 12%,  $P<0.001$ ) and higher rates of intensive care unit (ICU) admission (40% versus 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 (both for clinical indications such as atrial fibrillation, mechanical heart valves or venous thromboembolism and for elevated D-Dimer levels) than patients without neurological disorders (Table 4). Anticoagulation use was significantly associated with intracerebral hemorrhage (17/20 [85%] of patients with ICH were anticoagulated versus 1128/4471 [25%] of those without ICH,  $P<0.001$ ) and subarachnoid hemorrhage (3/3 [100%] of SAH were anticoagulated versus 1142/4488 (25%) of those without SAH,  $P=0.003$ )<sup>24, 25</sup>.

We observed higher rates of in-hospital mortality and lower rates of discharge home among COVID-19 patients 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 and/or 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 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 length of stay (9.8 vs 5.9 days) and ventilator days (11.8 versus 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 COVID-19 patients, 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 non-specific neurologic symptoms (agitation, dysexecutive function, myalgia, dizziness, headache<sup>1-4</sup>) along with neurologic diagnoses (e.g. stroke, seizures, Guillain-Barre syndrome etc.), we applied rigorous, standardized diagnostic criteria to identify the prevalence of specific

neurologic diagnoses in a prospective fashion. Additionally, all patients with neurologic disorders were evaluated by a neurologist, which strengthens the validity of the diagnoses. Unlike studies which included patients with suspected COVID-19 (without laboratory confirmation)<sup>26</sup> or categorized neurologic disorders based on clinical suspicion alone (without imaging, laboratory or pathological diagnosis verification)<sup>26</sup>, 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 non-specific symptoms, unsubstantiated diagnoses or unverified SARS-CoV-2 infection may lead to inaccurate estimations of prevalence rates. Furthermore, non-specific symptoms often do not confer the same prognostic implications as specific neurologic diagnoses. Smaller retrospective studies that excluded patients with non-specific symptoms found much lower neurologic disorder prevalence rates (3.5% in one study<sup>4</sup>), compared to studies with more liberal inclusion criteria (57-84% in studies<sup>1,3</sup> that included agitation, and fever as possible neurologic disorders). The aforementioned retrospective studies all depended on electronic medical record coding for data extraction and are, thus, limited by the quality and extent of available documentation. Additionally, 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 neuro-imaging in COVID-19 patients (many of whom were critically ill, intubated, hypoxic and on multiple vasopressors), 84% of patients with neurologic disorders in our cohort had head computed tomography imaging and 15% had brain MRI. As with other centers that faced a surge of COVID-19 patients, workforce strains, and contagion containment may have contributed to delays in neurologic diagnoses.

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 ARDS (acute respiratory distress syndrome), sepsis<sup>27</sup>, 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 even stroke constituted a higher proportion of neurologic complications diagnosed post-admission compared to pre-admission (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 where sedation may have confounded the neurological exam.

We did not identify any neurologic cases (meningitis, encephalitis, myelitis or other) that were conclusively related to direct SARS-CoV-2 invasion of the central nervous system (CNS). Indeed, 18/18 (100%) cerebrospinal fluid (CSF) samples that were tested were RT-PCR negative for SARS-CoV-2. We did not have any neuropathological 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<sup>28, 29</sup> has been hypothesized to account for some of the unusual strokes and intracerebral hemorrhages reported in the context of SARS-CoV-2

infection, yet this remains speculative without pathological verification. Autopsy series have reported primarily hypoxic-ischemic neuropathological changes, without evidence of primary viral CNS invasion among patients who presented with non-specific symptoms of headache, dysgeusia and myalgias<sup>30</sup>. An autopsy report of a patient with baseline confusion related to Parkinson's disease described the presence of virus in neural and capillary endothelium in the frontal lobe<sup>31</sup>, however, immunohistochemistry studies were not performed and rough endoplasmic reticulum may be mistaken for virions in the absence of immunohistochemical or electron microscopy confirmation. Neuropathological data among patients with specific neurological 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 two patients, however, 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<sup>32</sup>.

Conversely, there is clinical and pathologic data to support the occurrence of post-infectious complications of SARS-CoV-2. We identified three patients with Guillain-Barre syndrome occurring within 2-4 weeks of documented SARS-CoV-2 infection. All three patients had RT-PCR SARS-CoV-2 negative CSF, but antibody testing in the CSF was not available. Since a number of other studies have reported SARS-CoV-2 complications including Guillain-Barre Syndrome and acute disseminated encephalomyelitis (ADEM), the possibility of post- or para-infectious COVID-19 related complications seems plausible<sup>5, 6, 33-36</sup>. One neuropathology report of a critically ill COVID-19 patient 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 post-infectious, possibly autoimmune manifestation of COVID-19<sup>37</sup>.

In our cohort, COVID-19 patients with neurologic disorders had significantly higher risk of in-hospital mortality and lower rates of discharge home compared to COVID-19 patients 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 ischemic stroke patients who did not have COVID-19<sup>25</sup>. Others have found similar increases in mortality rates among patients with a spectrum of SARS-CoV-2 related neurologic diseases<sup>38</sup> compared to contemporary COVID-19 negative neurologic patients. Additionally, we studied neurological 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 neurological 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 neuro-intensivists 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<sup>25, 39, 40</sup> 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 additionally contribute to underestimations of prevalence. Last, due to high rates of missing data, we were unable to report rates of Hispanic ethnicity.

### **CONCLUSIONS:**

Neurologic disorders were detected in 13.5% of COVID-19 patients 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, though post-infectious Guillain-Barre 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.

## REFERENCES

1. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med* 2020;382:2268-2270.
2. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol* 2020.
3. Romero-Sanchez CM, Diaz-Maroto I, Fernandez-Diaz E, et al. Neurologic manifestations in hospitalized patients with COVID-19: The ALBACOVID registry. *Neurology* 2020.
4. Xiong W, Mu J, Guo J, et al. New onset neurologic events in people with COVID-19 infection in three regions in China. *Neurology* 2020.
5. Ellul MA, Benjamin L, Singh B, et al. Neurological associations of COVID-19. *Lancet Neurol* 2020.
6. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features. *Radiology* 2020:201187.
7. Frontera J, Mainali S, Fink EL, et al. Global Consortium Study of Neurological Dysfunction in COVID-19 (GCS-NeuroCOVID): Study Design and Rationale. *Neurocrit Care* 2020.
8. Agarwal S, Sabadia S, Abou-Fayssal N, Kurzweil A, Balcer LJ, Galetta SL. Training in neurology: Flexibility and adaptability of a neurology training program at the epicenter of COVID-19. *Neurology* 2020;94:e2608-e2614.
9. Agarwal SR, N.; Marolia, D.; Butnar, M.; Torres, J.; Zhang, C.; Kim, S.; Sanger, M.; Humber, K.; Tanweer, O.; Shapiro, M.; Raz, E.; Nossek, E.; Nelson, P.K.; Riina, H.A.; de Havenon, A.; Wachs, M.; Farkas, J.; Tiwari, A.; Arcot, K.; Turkel-Parella, D.; Liff, J.; Wu, T.; Wittman, I.; Caldwell, R.; Frontera, J.A.; Lord, A.; Ishida, K.; Yaghi S. . Acute stroke care in a New York City comprehensive stroke center during the COVID-19 pandemic. *J Stroke Cerebrovasc Dis* 2020;29 (9).
10. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:2064-2089.
11. Fokke C, van den Berg B, Drenthen J, Walgaard C, van Doorn PA, Jacobs BC. Diagnosis of Guillain-Barre syndrome and validation of Brighton criteria. *Brain : a journal of neurology* 2014;137:33-43.
12. Kalita J, Misra UK, Das M. Neurophysiological criteria in the diagnosis of different clinical types of Guillain-Barre syndrome. *Journal of neurology, neurosurgery, and psychiatry* 2008;79:289-293.
13. Sejvar JJ, Kohl KS, Gidudu J, et al. Guillain-Barre syndrome and Fisher syndrome: case definitions and guidelines for collection, analysis, and presentation of immunization safety data. *Vaccine* 2011;29:599-612.
14. Tunkel AR, Glaser CA, Bloch KC, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis* 2008;47:303-327.
15. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis* 2004;39:1267-1284.

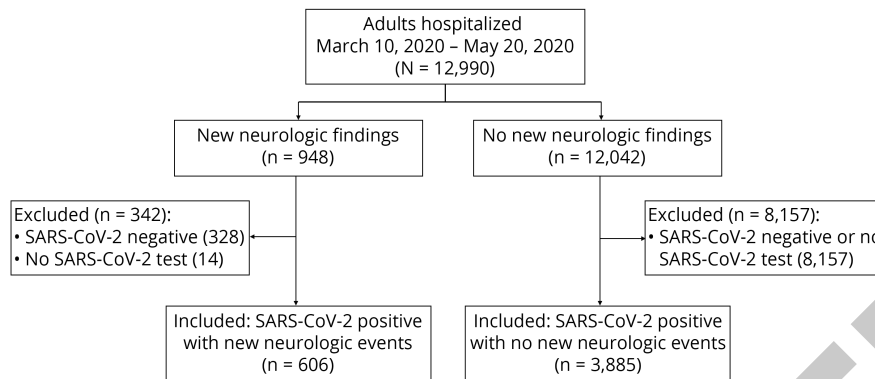
16. Venkatesan A, Tunkel AR, Bloch KC, et al. Case definitions, diagnostic algorithms, and priorities in encephalitis: consensus statement of the international encephalitis consortium. *Clin Infect Dis* 2013;57:1114-1128.
17. Tunkel AR, Hasbun R, Bhimraj A, et al. 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis. *Clin Infect Dis* 2017;64:e34-e65.
18. Scott TF, Frohman EM, De Seze J, et al. Evidence-based guideline: clinical evaluation and treatment of transverse myelitis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2011;77:2128-2134.
19. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020.
20. Group RC, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. *N Engl J Med* 2020.
21. Ferreira FL, Bota DP, Bross A, Melot C, Vincent JL. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA* 2001;286:1754-1758.
22. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996;22:707-710.
23. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26:1793-1800.
24. Valderrama EV, Humbert K, Lord A, Frontera J, Yaghi S. Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Ischemic Stroke. *Stroke* 2020;51:e124-e127.
25. Yaghi S, Ishida K, Torres J, et al. SARS-CoV-2 and Stroke in a New York Healthcare System. *Stroke* 2020;51:2002-2011.
26. Paterson RW, Brown RL, Benjamin L, et al. The emerging spectrum of COVID-19 neurology: clinical, radiological and laboratory findings. *Brain* 2020.
27. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med* 2009;37:2051-2056.
28. Puelles VG, Lutgehetmann M, Lindenmeyer MT, et al. Multiorgan and Renal Tropism of SARS-CoV-2. *N Engl J Med* 2020.
29. Jaunmuktane Z, Mahadeva U, Green A, et al. Microvascular injury and hypoxic damage: emerging neuropathological signatures in COVID-19. *Acta Neuropathol* 2020.
30. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological Features of Covid-19. *N Engl J Med* 2020.
31. Paniz-Mondolfi A, Bryce C, Grimes Z, et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). *J Med Virol* 2020;92:699-702.
32. Hernandez-Fernandez F, Valencia HS, Barbella-Aponte RA, et al. Cerebrovascular disease in patients with COVID-19: neuroimaging, histological and clinical description. *Brain* 2020.
33. Camdessanche JP, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barre syndrome. *Rev Neurol (Paris)* 2020;176:516-518.
34. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? *Lancet Neurol* 2020;19:383-384.

35. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. *Neurology* 2020.
36. Delamarre L, Gollion C, Grouteau G, et al. COVID-19-associated acute necrotising encephalopathy successfully treated with steroids and polyvalent immunoglobulin with unusual IgG targeting the cerebral fibre network. *J Neurol Neurosurg Psychiatry* 2020.
37. Reichard RR, Kashani KB, Boire NA, Constantopoulos E, Guo Y, Lucchinetti CF. Neuropathology of COVID-19: a spectrum of vascular and acute disseminated encephalomyelitis (ADEM)-like pathology. *Acta Neuropathol* 2020;140:1-6.
38. Benussi A, Pilotto A, Premi E, et al. Clinical characteristics and outcomes of inpatients with neurologic disease and COVID-19 in Brescia, Lombardy, Italy. *Neurology* 2020.
39. Kansagra AP, Goyal MS, Hamilton S, Albers GW. Collateral Effect of Covid-19 on Stroke Evaluation in the United States. *N Engl J Med* 2020.
40. de Havenon A, Ney J, Callaghan B, et al. A Rapid Decrease in Stroke, Acute Coronary Syndrome, and Corresponding Interventions at 65 United States Hospitals Following Emergence of COVID-19. *medRxiv* 2020.

ACCEPTED

**FIGURE LEGEND:**

**Figure 1:** Flow chart of patient inclusion and exclusion



ACCEPTED

**TABLES:****Table 1:** Prevalence of neurologic disorders among patients hospitalized with SARS-CoV-2 infection

<b>Variable</b>	<b>All COVID-19 Patients (N=4491)</b>
<b>Any new neurologic disorder—no./total no. (%)</b>	606/4491 (13.5%)
<b>Neurologic Disorders no./total no. (%)</b>	
Toxic/Metabolic Encephalopathy	309/4491 (6.8%)
Stroke (any type)	84/4491 (1.9%)
Ischemic/TIA	61/4491 (1.4%)
Intracerebral/Intraventricular hemorrhage	20/4491 (0.4%)
Spontaneous Subarachnoid hemorrhage	3/4491 (0.1%)
Seizure (clinical or electrographic)	74/4491 (1.6%)
Hypoxic/ischemic brain injury	65/4491 (1.4%)
Movement Disorder	41/4491 (0.9%)
Neuropathy	35/4491 (0.8%)
Myopathy	21/4491 (0.5%)
Guillain Barre Syndrome	3/4491 (0.1%)
Encephalitis/meningitis	0
Myelopathy/Myelitis	0

TIA=transient ischemic attack

**Table 2.** Cerebrospinal Fluid Findings Among COVID-19 Patients with Neurological

Disorders\* N=26 patients

CSF Variable	CSF Values
WBC count (per cubic mm)- median (IQR)	2 (1-4)
RBC count- median (IQR)	37 (3-656)
Glucose- median (IQR)	73 (59-92)
Protein- median (IQR)	61 (42-106)
Abnormal WBC Count <sup>#</sup> – no./total no. (%)	5/26 (19%)
Abnormal glucose– no./total no (%)	0
Abnormal protein <sup>^</sup> – no./total no (%)	20/26 (77%)
SARS-CoV-2 CSF PCR negative– no./total no (%)	18/18 (100%)

CSF=cerebrospinal fluid; WBC=white blood cells; RBC=red blood cells. Normal laboratory reference range for CSF: WBC<5 / per cubic mm; glucose 40-70 mg/dL or  $\geq 2/3$  of plasma glucose; protein 15-40 mg/dL

\*The CSF studies were normal among all four patients who had CSF collected but *no* new neurological disorder

#One patient with pleocytosis had a brain mass prior since 9/2019 prior to COVID-19 diagnosis; one patient had pleocytosis that was not present after correcting for RBCs; two patients with intracerebral and intraventricular hemorrhage had pleocytosis referable to the hemorrhage; and one patient had pleocytosis in the context of herpes encephalitis that pre-dated his COVID-19 symptom onset by 4 weeks. Repeat CSF studies during his COVID-19 admission showed improving pleocytosis.

<sup>^</sup>CSF protein was elevated in 3 patients with Guillain-Barre Syndrome and 17 patients with traumatic lumbar punctures with elevated RBCs

**Table 3.** Neurological disorders prior to or at the time of admission, compared to neurological disorders after admission among COVID-19 patients\*

	Neurologic Disorder Pre-admit or at time of admission (N=419)	Neurologic Disorder post-admission (N=180)	P
Days from admission to first neurologic symptom- median (IQR)	-0.8 (-3.5 to -0.5)	12.3 (5.2-21.2)	<0.001
<b>Demographics and Clinical Findings</b>			
Median Age (IQR)-yr	74 (62-83)	64 (57-72)	<0.001
Male sex-no./total no. (%)	248/419 (62%)	135/180 (75%)	0.002
Race (white vs other)- no./total no. (%)	268/419 (64%)	109/180 (61%)	0.429
Maximum SOFA score- median (IQR)	3 (0-4)	11 (4-14)	<0.001
Invasive mechanical ventilation- no./total no. (%)	97/419 (23%)	138/180 (77%)	<0.001
Acute renal failure- no./total no. (%)	84/419 (20%)	80/180 (44%)	<0.001
Comfort care status- no./total no. (%)	72/419 (17%)	39/180 (22%)	0.195
<b>Neurologic Disorder Type</b>			
Toxic/Metabolic Encephalopathy*	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 Barre Syndrome	3 (100%)	0	0.255
Encephalitis/meningitis	0	0	--
Myelopathy/Myelitis	0	0	--
<b>Outcomes</b>			
Discharged home— no./total no. (%)	161/219 (38%)	40/180 (22%)	0.001
Died in-hospital— no./total no. (%)	134/419 (32%)	72/180 (40%)	0.058

\*timing of neurologic disorders missing in 7 patients; ICH=intracerebral hemorrhage; IVH=intraventricular hemorrhage

**Table 4:** Demographic, Clinical and Hospital Outcomes among COVID-19 patients with and without neurologic disorders during hospitalization

<b>Characteristic</b>	<b>COVID-19 Positive with Neurologic Disorders (N=606)</b>	<b>COVID-19 Positive without Neurologic Disorders (N=3885)</b>	<b>P Value</b>
<b>Demographics</b>			
Median Age (IQR)-yr	71 (60-80)	63 (50-75)	<0.001
Male sex-no./total no. (%)	397/606 (66%)	2210/3885 (57%)	<0.001
Body Mass Index-median (IQR)	27 (24-31)	28 (25-33)	<0.001
Race- no./total no. (%)			<0.001
White	382/606 (63%)	1734/3885 (45%)	
Black	98/606 (16%)	606/3885 (16%)	
Asian	65/606 (11%)	248/3885 (6%)	
Other	61/606 (10%)	1297/3885 (33%)	
Past Medical History- no./total no. (%)			
Hypertension	287/606 (47%)	1425/3885 (37%)	<0.001
Diabetes	190/606 (31%)	986/3885 (25%)	0.002
Hyperlipidemia	190/606 (31%)	979/3885 (25%)	0.001
Chronic kidney disease	97/606 (16%)	400/3885 (10%)	<0.001
Obstructive Sleep Apnea	29/600 (5%)	156/3863 (4%)	0.363
Atrial Fibrillation	85/600 (14%)	322/3863 (8%)	<0.001
Venous thromboembolism	58/600 (10%)	217/3863 (6%)	<0.001
Past Neurologic History <sup>s</sup> - no./total no. (%)			
Ischemic Stroke	116/606 (19%)	275/3885 (7%)	<0.001
Seizure/epilepsy	89/606 (15%)	124/3885 (3%)	<0.001
Dementia	73/606 (12%)	143/3885 (4%)	<0.001
Neuropathy	38/606 (6%)	141/3885 (4%)	0.002
ICH/IVH	28/606 (5%)	25/3885 (1%)	<0.001
Movement disorder	20/606 (3%)	59/3885 (2%)	0.002
Traumatic brain injury	15/606 (3%)	36/3885 (1%)	0.003
Multiple sclerosis/demyelinating disease	5/606 (1%)	15/3885 (0.4%)	0.176
Myasthenia gravis	1/606 (0.2%)	5/3885 (0.1%)	0.581
Hydrocephalus	10/606 (2%)	9/3885 (0.2%)	<0.001
Brain Tumor	5/606 (1%)	6/3885 (0.2%)	0.010
<b>Clinical Findings</b>			
Intensive care unit vs. non-ICU unit- no./total no. (%)	242/600 (40%)	737/3852 (19%)	<0.001
Maximum SOFA score- median (IQR)	4 (3-9)	3 (0-4)	<0.001

Medications— no./total no. (%)			
Corticosteroids	146 (24%)	697 (18%)	<0.001
Hydroxychloroquine	445/606 (73%)	2570/3885 (66%)	<0.001
Azithromycin	380/606 (63%)	2295/3885 (59%)	0.090
Lopinavir/ritonavir	60/606 (10%)	254/3885 (7%)	0.003
Zinc	204/606 (34%)	1359/3885 (35%)	0.527
Ascorbic Acid (Vitamin C)	160/606 (26%)	918/3885 (24%)	0.137
Tocilizumab	81/606 (13%)	458/3885 (12%)	0.266
Remdesivir	1/606 (0.2%)	13/3885 (0.3%)	0.709
Therapeutic anticoagulation <sup>§</sup> (based on D-dimer)	176/606 (29%)	678/3885 (18%)	<0.001
Therapeutic anticoagulation <sup>§</sup> (clinical indication <sup>¥</sup> )	75/606 (12%)	216/3885 (6%)	<0.001
Acute renal failure- no./total no. (%)	167/606 (28%)	479/3885 (12%)	<0.001
Invasive mechanical ventilation- no./total no. (%)	241/602 (40%)	746/3885 (19%)	<0.001
Hospital length of stay (days)—median (IQR)	9.8 (4.9-22.6)	5.9 (3.0-10.7)	<0.001
Ventilator days <sup>†</sup> -- median (IQR)	11.8 (3.7-24.0)	5.0 (1.2-12.7)	<0.001
Comfort care status- no./total no. (%)	111/606 (18%)	156/3885 (4%)	<0.001
<b>Radiographic and Laboratory Findings</b>			
Head Computed Tomography-no./total no. (%)	510/606 (84%)	374/3885 (10%)	<0.001
Brain MRI- no./total no. (%)	89/606 (15%)	38/3885 (1%)	<0.001
Lumbar puncture- no./total no. (%)	26/606 (4%)	4/3885 (0.1%)	<0.001
Admission Interleukin-6 (pg/mL)*- median (IQR)	32 (14-66)	21 (10-52)	0.007
Admission C-reactive protein (mg/L)^- median (IQR)	93 (35-157)	107 (50-170)	0.001
Admission D-Dimer (ng/mL) <sup>‡</sup> - median (IQR)	532 (309-1112)	425 (272-791)	<0.001
Admission Ferritin (ng/mL) <sup>‡</sup> - median (IQR)	667 (317-1541)	677 (317-1387)	0.379
<b>Hospital Outcomes</b>			
Discharged home— no./total no. (%)	201/596 (34%)	2548/3803 (67%)	<0.001
Died in-hospital— no./total no. (%)	211/606 (35%)	751/3885 (19%)	<0.001
Other Discharge Dispositions, no./total no. (%)	187/596 (32%)	504/3803 (13%)	<0.001
Hospitalized	13/596 (2%)	27/3803 (1%)	<0.001
LTACH	14/596 (2%)	28/3803 (1%)	<0.001
Nursing home	122/596 (21%)	357/3803 (9%)	<0.001
Acute inpatient rehabilitation	32/596 (5%)	89/3803 (2%)	<0.001
Subacute rehabilitation	4/596 (1%)	3/3803 (0.1%)	0.001

ICH/IVH=intracerebral hemorrhage and/or intraventricular hemorrhage; SOFA=Sequential Organ Failure

Assessment; IQR=interquartile range; MRI=magnetic resonance imaging; LTACH=long term acute care hospital;

<sup>§</sup>Patients could have more than one past neurologic history diagnosis

<sup>§</sup> Includes therapeutic dosing of enoxaparin or heparin; <sup>¥</sup> Indications include atrial fibrillation, venous

thromboembolism or mechanical heart valve; <sup>†</sup>Includes only patients who received invasive mechanical ventilation

\*Data available in N=161 with neurologic disorders and N=841 without (normal range  $\leq 5$  pg/mL); ^ Data available in N=577 with neurologic disorders and N= 3466 without (normal range 0.0-3.0 mg/L); † Data available in N=492 with neurologic disorders and N=2993 without (normal range  $< 230$  ng/mL); ‡Data available in N=573 with neurologic disorders and N=3449 without (normal range 8.0-388.0 ng/mL)

ACCEPTED

## Appendix 1. Author Contributions

Name	Location	Contribution
Jennifer Frontera	NYU Langone Hospitals, NY, NY	Design, Data acquisition, data analysis and interpretation, drafted and devised manuscript
Sakinah Sabadia	NYU Langone Hospitals, NY, NY	Design, Data acquisition, revised the manuscript for intellectual content
Rebecca Lalchan	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Taolin Fang	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Brent Flusty	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Patricio Millar-Verneti	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Thomas Snyder	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Stephen Berger	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Dixon Yang	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Andre Granger	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Nicole Morgan	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Palak Patel	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Josef Gutman	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Kara Melmed	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Shashank Agarwal	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Matthew Bokhari	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Andres Andino	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Eduard Valdes	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Mirza Omari	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Alexandra Kvernland	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Kaitlyn Lillemoe	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content

Sherry Chou	UPMC, Pittsburgh, PA	Design, Data interpretation, revised the manuscript for intellectual content
Molly McNett	Ohio State University Columbus, OH	Design, Data interpretation, revised the manuscript for intellectual content
Raimund Helbok	Medical University of Innsbruck, Innsbruck Austria	Design, Data interpretation, revised the manuscript for intellectual content
Shraddha Mainali	Ohio State University Columbus, OH	Design, Data interpretation, revised the manuscript for intellectual content
Ericka Fink	UPMC, Pittsburgh, PA	Design, Data interpretation, revised the manuscript for intellectual content
Courtney Roberson	Johns Hopkins University, Baltimore, MD	Design, Data interpretation, revised the manuscript for intellectual content
Michelle Schober	University of Utah, Salt Lake City, UT	Design, Data interpretation, revised the manuscript for intellectual content
Jose Suarez	Johns Hopkins University, Baltimore, MD	Data interpretation, revised the manuscript for intellectual content
Wendy Ziai	Johns Hopkins University, Baltimore, MD	Data interpretation, revised the manuscript for intellectual content
David Menon	Cambridge University, Cambridge, England	Data interpretation, revised the manuscript for intellectual content
Daniel Friedman	NYU Langone Hospitals, NY, NY	Data acquisition and interpretation, revised the manuscript for intellectual content
David Friedman	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Manisha Holmes	NYU Langone Hospitals, NY, NY	Data acquisition and interpretation, revised the manuscript for intellectual content
Joshua Huang	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Sujata Thawani	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Jonathan Howard	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Nada Abou-Fayssal	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Penina Krieger	NYU Langone Hospitals, NY, NY	Data acquisition, revised the manuscript for intellectual content
Ariane Lewis	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Aaron Lord	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Ting Zhou	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
D. Ethan Kahn	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Barry Czeisler	NYU Langone Hospitals,	Data interpretation, revised the manuscript for

	NY, NY	intellectual content
Jose Torres	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Shadi Yaghi	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Koto Ishida	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Erica Scher	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Adam de Havenon	University of Utah, Salt Lake City, UT	Data interpretation, revised the manuscript for intellectual content
Dimitris Placatonakis	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Mengling Liu	NYU Langone Hospitals, NY, NY	Data analysis, revised the manuscript for intellectual content
Thomas Wisniewski	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Andrea Troxel	NYU Langone Hospitals, NY, NY	Data analysis, revised the manuscript for intellectual content
Laura Balcer	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content
Steven Galetta	NYU Langone Hospitals, NY, NY	Data interpretation, revised the manuscript for intellectual content

# Neurology®

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

Jennifer A. Frontera, Sakinah Sabadia, Rebecca Lalchan, et al.  
*Neurology* published online October 5, 2020  
DOI 10.1212/WNL.0000000000010979

**This information is current as of October 5, 2020**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://n.neurology.org/content/early/2020/10/05/WNL.0000000000010979.full">http://n.neurology.org/content/early/2020/10/05/WNL.0000000000010979.full</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Cohort studies</b> <a href="http://n.neurology.org/cgi/collection/cohort_studies">http://n.neurology.org/cgi/collection/cohort_studies</a> <b>COVID-19</b> <a href="http://n.neurology.org/cgi/collection/covid_19">http://n.neurology.org/cgi/collection/covid_19</a> <b>Critical care</b> <a href="http://n.neurology.org/cgi/collection/critical_care">http://n.neurology.org/cgi/collection/critical_care</a> <b>Prevalence studies</b> <a href="http://n.neurology.org/cgi/collection/prevalence_studies">http://n.neurology.org/cgi/collection/prevalence_studies</a> <b>Prognosis</b> <a href="http://n.neurology.org/cgi/collection/prognosis">http://n.neurology.org/cgi/collection/prognosis</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.neurology.org/about/about_the_journal#permissions">http://www.neurology.org/about/about_the_journal#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://n.neurology.org/subscribers/advertise">http://n.neurology.org/subscribers/advertise</a>

*Neurology*® is the official journal of the American Academy of Neurology. Published continuously since 1951, it is now a weekly with 48 issues per year. Copyright © 2020 American Academy of Neurology. All rights reserved. Print ISSN: 0028-3878. Online ISSN: 1526-632X.

