

# UCSF

## UC San Francisco Previously Published Works

### Title

Risk Factors for New Neurologic Diagnoses in Hospitalized Patients With COVID-19: A Case-Control Study in New York City.

### Permalink

<https://escholarship.org/uc/item/72n4x643>

### Journal

Neurology: Clinical Practice, 12(4)

### ISSN

2163-0402

### Authors

Thakur, Kiran

Chu, Victoria

Hughes, Christine

et al.

### Publication Date

2022-08-01

### DOI

10.1212/CPJ.0000000000200006

Peer reviewed

# Risk Factors for New Neurologic Diagnoses in Hospitalized Patients With COVID-19

A Case-Control Study in New York City

Kiran T. Thakur, MD, Victoria T. Chu, MD, Christine Hughes, MPH, Carla Y. Kim, BA, Shannon Fleck-Derderian, PhD, Catherine E. Barrett, PhD, Elizabeth Matthews, MD, Alanna Balbi, MD, Amanda Bilski, MD, Mashina Chomba, MBChB, MMed, Ori Lieberman, MD, PhD, Samuel D. Jacobson, MD, Sachin Agarwal, MD, David Roh, MD, Soojin Park, MD, Vivian Ssonko, MBBS, Wendy G. Silver, MD, Wendy D. Vargas, MD, Andrew Geneslaw, MD, Michelle Bell, MD, Brandon Waters, MD, Agam Rao, MD, Jan Claassen, MD, Amelia Boehme, PhD, Joshua Z. Willey, MD, Mitchell S.V. Elkind, MD, Magdalena E. Sobieszczyk, MD, Jason Zucker, MD, Andrea McCollum, PhD, and James Sejvar, MD

**Correspondence**  
Dr. Thakur  
ktt2115@cumc.columbia.edu

*Neurology: Clinical Practice* August 2022 vol. 12 no. 4 e66-e74 doi:10.1212/CPJ.000000000200006

## Abstract

### Background and Objectives

There have been numerous reports of neurologic manifestations identified in hospitalized patients infected with SARS-CoV-2, the virus that causes COVID-19. Here, we identify the spectrum of associated neurologic symptoms and diagnoses, define the time course of their development, and examine readmission rates and mortality risk posthospitalization in a multiethnic urban cohort.

### Methods

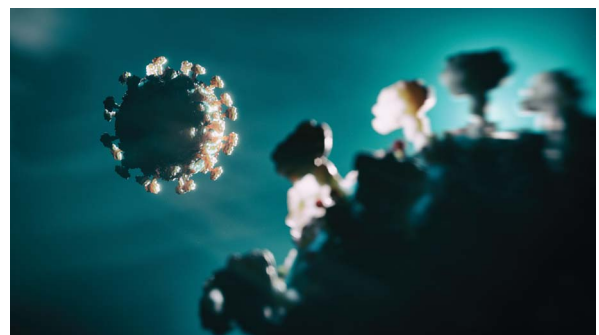
We identify the occurrence of new neurologic diagnoses among patients with laboratory-confirmed SARS-CoV-2 infection in New York City. A retrospective cohort study was performed on 532 cases (hospitalized patients with new neurologic diagnoses within 6 weeks of positive SARS-CoV-2 laboratory results between March 1, 2020, and August 31, 2020). We compare demographic and clinical features of the 532 cases with 532 controls (hospitalized COVID-19 patients without neurologic diagnoses) in a case-control study with one-to-one matching and examine hospital-related data and outcomes of death and readmission up to 6 months after acute hospitalization in a secondary case-only analysis.

### Results

Among the 532 cases, the most common new neurologic diagnoses included encephalopathy (478, 89.8%), stroke (66, 12.4%), and seizures (38, 7.1%). In the case-control study, cases were more likely than controls to be male (58.6% vs 52.8%,  $p = 0.05$ ), had baseline neurologic comorbidities (36.3% vs 13.0%,  $p < 0.0001$ ), and were to be treated in an intensive care unit (62.0% vs 9.6%,  $p < 0.0001$ ). Of the 394 (74.1%) cases who survived acute hospitalization, more than half (220 of 394, 55.8%) were readmitted within 6 months, with a mortality rate of 23.2% during readmission.

### Discussion

Hospitalized patients with SARS-CoV-2 and new neurologic diagnoses have significant morbidity and mortality postdischarge. Further research is needed to define the effect of neurologic diagnoses during acute hospitalization on longitudinal post-COVID-19-related symptoms including neurocognitive impairment.



#### MORE ONLINE

#### COVID-19 Resources

For the latest articles, invited commentaries, and blogs from physicians around the world

[NPub.org/COVID19](https://www.npub.org/COVID19)

Department of Neurology (KTT, CYK, EM, A. Balbi, A. Bilski, MC, OL, SDJ, SA, DR, SP, VS, WGS, WDV, AG, MB, BW, JC, A. Boehme, JZW, MSVE), Columbia University Irving Medical Center-New York Presbyterian Hospital; United States Centers for Disease Control and Prevention (VTC, CH, SF-D, CEB, AR, AM, JS), Atlanta, GA; Department of Pediatrics (AG), Columbia University Irving Medical Center-New York Presbyterian Hospital; and Division of Infectious Diseases, Department of Internal Medicine, Columbia University Irving Medical Center-New York Presbyterian Hospital (MES, JZ), New York.

Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

Neurologic symptoms and conditions are seen across the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease continuum including the early prodromal and acute phase and are being increasingly reported in the postinfectious period.<sup>1</sup> Estimates of the effect of SARS-CoV-2 on those with underlying neurologic conditions and those who develop new neurologic manifestations in the context of acute SARS-CoV-2 infection are significant despite being varied across studies.<sup>2-5</sup> Differences in methodology including case definitions and case ascertainment have contributed to variable reporting of hospital-based data on neurologic conditions.<sup>6,7</sup> As worldwide coronavirus disease 2019 (COVID-19) cases continue to rise and novel variants emerge, a more comprehensive clinical understanding of short-term and long-term complications remains crucial. In this study, we identify the occurrence of neurologic diagnoses among patients with laboratory-confirmed SARS-CoV-2 infection in New York City comprising a large proportion of medically underserved persons, which was the epicenter of the first surge of the COVID-19 pandemic in the United States. We compare demographic and clinical features of patients with COVID-19 with neurologic diagnoses during hospitalization with those without neurologic diagnoses in a retrospective case-control study and examine hospital-related data and outcomes of death and readmission up to 6 months after acute hospitalization among cases alone.

## Methods

### Neurologic COVID-19 Patient Identification

We retrospectively reviewed electronic medical records (EMRs) of patients hospitalized with COVID-19 during March 1, 2020, and August 30, 2020, at Columbia University Irving Medical Center-New York Presbyterian Hospital (CUIMC/NYP) in New York City, encompassing Milstein Hospital, Morgan Stanley Children's Hospital of New York (CHONY), and Allen Hospital. Only laboratory-confirmed SARS-CoV-2–infected patients, defined by a positive nasopharyngeal swab SARS-CoV-2 reverse transcriptase PCR (RT-PCR) test result, were included in this study. Clinical data were collected both through manual EMR review and data extracted from the CUIMC COVID-CARES database, which is a hospital system wide database of all patients tested for COVID-19, including hospitalized patients with positive SARS-CoV-2 RT-PCR results admitted to CUIMC-NYP, Allen-NYP, and CHONY-NYP.

Cases were defined as hospitalized patients who developed new neurologic diagnoses within 6 weeks of their first positive SARS-CoV-2 RT-PCR result. To identify cases, 2,318 patients from all neurology services were reviewed for new-onset neurologic signs/symptoms from the vascular and general neurology units, neurologic intensive care unit, neurology consult lists, and epilepsy monitoring unit. In addition, patients with any neuroimaging, EEG, and/or lumbar puncture (LP) results were reviewed. Altogether, 574

patients with new-onset neurologic signs, symptoms, and diagnoses were identified (Figure 1). In addition, every 10th patient among 3,635 patients from the COVID-CARES database was reviewed for specified new neurologic diagnoses to address selection bias for those with severe neurologic conditions who are typically managed by neurology services. A total of 75 additional cases were identified from the COVID-CARES database (Figure 1). Continuous EEG data were categorized by the presence of sporadic epileptiform discharges, periodic epileptiform discharges, electrographic seizures, and electroclinical seizures, upon review by epilepsy specialists (M.B. and B.W.). All neurologic diagnoses were made by the clinical team based on established clinical practice parameters. All neurologic diagnoses represented in these cases were based on diagnosis by the clinical team and included using established criteria for diagnosis of encephalopathy: disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to environment) AND disturbance develops over a short period of time (hours to days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day AND an additional disturbance in cognition (memory deficit, disorientation, language, visuospatial ability, and perception).<sup>8</sup> From a total of 649 identified neurologic cases, 31 cases with only SARS-CoV-2 serology positivity and 86 cases who presented with neurologic signs and symptoms but were discharged without formal neurologic diagnoses were excluded, leaving 532 that met the case definition.

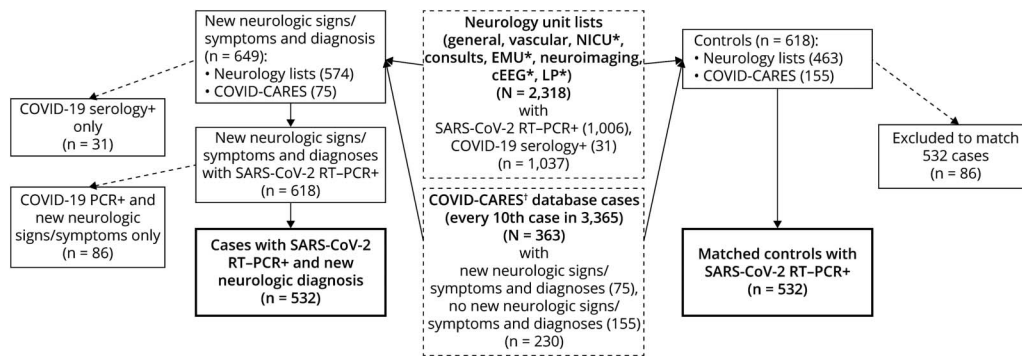
### Descriptive Case Analysis

We analyzed the distribution and timing of neurologic diagnoses, clinical characteristics, and outcome measures. Neurologic diagnoses and presenting COVID-19 symptoms were stratified by age categories. Timing of neurologic diagnosis was calculated as the number of days between neurologic diagnosis and first RT-PCR–positive SARS-CoV-2 test result. Hospital-related data including length of stay (LOS), intensive care unit (ICU) admission, ICU LOS, and oxygen requirement and outcome measures of limiting treatments to comfort measures only, hospice admission, mortality during acute hospitalization, and readmission to an NYP hospital within 6 months of COVID-19 hospitalization were further described. Data analysis was performed using SAS v9.4 (SAS Institute, Cary NC).

### Case-Control Population

A case-control study was conducted to assess differences in patients with COVID-19 with and without neurologic diagnoses. Controls were defined as patients hospitalized with laboratory-confirmed SARS-CoV-2 infection by RT-PCR and without new neurologic diagnoses or neurologic signs/symptoms, as listed in Table 1. Potential controls were identified from the COVID-CARES database and matched one-to-one to cases based on calendar time ( $\pm 5$  days of hospital admission date). Descriptive analyses of

**Figure 1** Case Inclusion



Central boxes with dashed lines represent sources from which cases and controls were identified, including all Neurology units and the COVID-CARES database established at CUIMC/NYP. The workflow on the left details exclusion process for cases; the right side details exclusion process for controls. Bold outlined boxes indicate final sample size for cases and controls. cEEG = continuous electroencephalography; COVID-19 = coronavirus disease 2019; COVID-CARES = Comprehensive database of COVID-19 infectious cases at CUIMC; EMU = epilepsy monitoring unit; LP = lumbar puncture; NICU = neurologic intensive care unit; RT-PCR = reverse transcriptase PCR; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

sociodemographic information and medical history were performed to compare cases and controls. Basic frequencies were calculated, and categorical data were compared using the Pearson  $\chi^2$  test and Fisher exact test as appropriate. The two-sample Student *t*-test was used to compare continuous variables, and the Wilcoxon rank sum test was used when sample size was small ( $n < 5$ ). Unmatched logistic regression models were used to assess differences in medical history between cases and controls in adjusted models, controlling for age as a continuous variable and sex. Data analysis was performed using SAS v9.4 (SAS Institute, Cary, NC).

### Standard Protocol Approvals, Registrations, and Patient Consents

This activity was reviewed by Centers for Disease Control and Prevention (CDC) and was conducted in a manner consistent with applicable federal law and CDC policy (45 C.F.R. part 46.102(l) (2), 21 C.F.R. part 56; 42 U.S.C. §241(d); 5 U.S.C. §552a; 44 U.S.C. §3501 et seq.) as a public health nonresearch project. This study received approval from CUIMC institutional review board with a waiver of written informed consent for retrospective analysis.

### Data Availability

Data supporting the findings of this study are available from the corresponding author (K.T.) upon request. All supplementary data will be made available upon request with further anonymized data available to qualified investigators upon request to the corresponding author.

## Results

### Description of Cases

Of the 2,681 patients (2,318 from neurologic services and 363 from the CARES database) reviewed, 532 (20.4%) met the case definition of laboratory-confirmed acute SARS-CoV-2 infection and new neurologic diagnoses at hospital presentation and/or during

hospitalization (Figure 1). The mean (SD) age was 65 years (17.8), with 303 (57.0%) being 65 years and older. Three hundred twelve (58.6%) were male and 242 (45.5%) self-identified as Hispanic/Latino ethnicity. One hundred forty-one (26.5%) self-identified as White, 112 (21.1%) as Black, 13 (2.4%) as Asian, and 154 (28.9%) as other/multiracial (Table 1). There were no significant differences in age between Hispanic/Latino and non-Hispanic/Latino cases. No significant differences were observed in death, hospice, readmission, or death during readmission between the 2 groups (eTable 6, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)).

Encephalopathy was the most common new neurologic diagnosis (478, 89.8%), followed by ischemic stroke (66, 12.4%), seizures (38, 7.1%), intracranial hemorrhage (ICH) (33, 6.2%), critical illness myopathy (19, 3.6%), critical illness neuropathy (9, 1.7%), and posterior reversible encephalopathy syndrome (3, 0.6%) (Table 2). Cases with encephalopathy were significantly more likely to be of older age ( $p = 0.02$ ) and have preexisting neurologic disorders (181, 37.9% vs 12, 22.2%;  $p = 0.02$ ) when compared with cases without encephalopathy (eTable 1, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). Seizure diagnosis was significantly associated with age ( $p < 0.0001$ ), with most seizures (23 of 38, 60.5%) occurring in age groups younger than 65 years (Table 2). Although not significant, both ischemic stroke (25 of 66, 17.4%) and ICH (14 of 33, 9.7%) were more prevalent in cases aged 50–64 years when compared with other age groups (Table 2). Common neurologic sign/symptoms reported include confusion (257, 48.3%), reduced consciousness (125, 23.5%), and psychiatric manifestations defined as new symptoms of depressed mood, anxiety, and/or mania (53, 10%) (eTable 2, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)).

A new neurologic diagnosis was established on initial hospital presentation in 29% (110 of 376 with diagnosis dates noted) of cases: 75 of 297 (25.3%) cases of encephalopathy, 15 of 53 (28.3%) cases of ischemic stroke, and 13 of 31 (41.9%) cases



**Table 1** Demographic Characteristics of Hospitalized Patients With COVID-19 With and Without New Neurologic Diagnoses

	Cases <sup>a</sup> (n = 532)		Controls <sup>b</sup> (n = 532)		$\chi^2$ p value <sup>c</sup>
<b>Age: mean (SD), y</b>	65.0 (17.8)		58.7 (21.3)		<0.0001
<b>Age category, y</b>					
<b>Younger than 18</b>	15	2.8%	19	3.6%	<0.0001
<b>18–49</b>	69	13.0%	143	26.9%	
<b>50–64</b>	144	27.1%	131	24.6%	
<b>65–79</b>	203	38.2%	150	28.2%	
<b>Older than 80</b>	100	18.8%	89	16.7%	
<b>Unknown<sup>d</sup></b>	1	0.2%	0	0.0%	
<b>Sex</b>					
<b>Male</b>	312	58.6%	281	52.8%	0.05
<b>Female</b>	219	41.2%	251	47.2%	
<b>Unknown<sup>d</sup></b>	1	0.2%	0	0.0%	
<b>Ethnicity</b>					
<b>Hispanic/Latino</b>	242	45.5%	280	52.6%	0.002
<b>Non-Hispanic/Latino</b>	174	32.7%	127	23.9%	
<b>Others</b>	11	2.1%	20	3.8%	
<b>Declined/unknown</b>	105	19.7%	105	19.7%	
<b>Race</b>					
<b>White</b>	141	26.5%	122	22.9%	0.36
<b>Black</b>	112	21.1%	99	18.6%	
<b>Asian</b>	13	2.4%	12	2.3%	
<b>Other/multiracial</b>	154	28.9%	170	32.0%	
<b>Declined/unknown</b>	112	21.1%	129	24.2%	
<b>Medical history</b>					
<b>None</b>	37	7.0%	110	20.7%	<0.0001
<b>Chronic lung disease</b>	96	18.0%	86	16.2%	0.42
<b>Cardiac disease</b>	383	72.0%	296	55.6%	<0.0001
<b>Diabetes mellitus</b>	232	43.6%	170	32.0%	<0.0001
<b>History of neurologic disease</b>	193	36.3%	69	13.0%	<0.0001
<b>Renal disease</b>	99	18.6%	64	12.0%	0.003
<b>Liver disease</b>	18	3.4%	16	3.0%	0.73
<b>Immune disorder</b>	63	11.8%	58	10.9%	0.63
<b>Immunocompromising medications</b>	31	5.8%	15	2.8%	0.02
<b>Pregnant</b>	1	0.5%	32	12.8%	<0.0001

**Table 1** Demographic Characteristics of Hospitalized Patients With COVID-19 With and Without New Neurologic Diagnoses (*continued*)

	Cases <sup>a</sup> (n = 532)		Controls <sup>b</sup> (n = 532)		$\chi^2$ p value <sup>c</sup>
<b>ICU Admission</b>	330	62.0%	51	9.6%	<0.0001

<sup>a</sup> Cases defined as patients hospitalized between March and August 2020 in the New York Presbyterian system who are diagnosed with a new neurologic condition within 6 wk of RT-PCR positivity.  
<sup>b</sup> Controls defined as patients hospitalized between March and August 2020 in the New York Presbyterian system who are SARS-CoV-2 RT-PCR+ with no new neurologic diagnosis within 6 wk of RT-PCR positivity.  
<sup>c</sup> Chi-square p-value.  
<sup>d</sup> The age and sex for one case was missing from the electronic medical record.

of seizure (Figure 2). Cases, on average, had a neurologic diagnosis 10 days after the first positive SARS-CoV-2 RT-PCR test (median = 4.9 days, interquartile range = –0.5 to 19.2 days, range: –32.1 to 69.5 days) (Figure 2).

The average length of hospital stay was 30.2 days (SD = 32.2) for cases, with 330 (62%) cases admitted to the ICU (eFigure 1A, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). The average LOS in the ICU was 26 days; 237 cases (44.5%) stayed in the ICU for more than 10 days, of which 22 (9.3%) cases had ICU stays of more than 60 days (eFigure 1B, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). Two hundred seventy-eight cases (52.3%) were intubated, 104 (19.5%) received renal replacement therapy, and 6 (1.1%) were placed on extracorporeal membrane oxygenation (Table 3). Fifteen percent (80 of 532) of the cases had thrombotic complications including 60 (11.1%) with deep vein thromboses and 21 (3.9%) with pulmonary embolism (eTable 4, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). Outcome measures of cases with neurologic diagnoses included provision of comfort care only (111, 20.9%), death during initial hospitalization (138, 25.9%), readmission to an NYP hospital within 6 months (220, 55.8%), and death during hospital readmission (51, 9.6%) (Table 3).

### Case-Control Study

There were 532 controls matched to cases based on hospitalization date. Cases with new neurologic diagnoses were older compared with controls (mean 65.0 years [SD: 17.8] vs 58.7 years [SD: 21.3];  $p < 0.0001$ ) with more than half of the cases (303, 57.0%) being 65 years and older (Table 1). Cases were more likely to be male (58.6% vs 52.8%,  $p < 0.05$ ) and have a medical history of hypertension (66.7% vs 48.7%), hyperlipidemia (33.1% vs 23.1%), diabetes mellitus type I or II (43.6% vs 32.0%), chronic kidney disease (13.9% vs 7.5%), dementia (14.5% vs 4.3%), stroke (13% vs 3.6%), or seizures (8.6% vs 1.7%) when compared with controls ( $p < 0.0001$ ) (eTable 3, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). Controls were more likely to have no medical history than cases (20.7% vs 7.0%,  $p < 0.0001$ ), and cases were more likely to be admitted to the ICU when compared with controls (62.0% vs 9.6%,  $p < 0.0001$ ) (eTable 3, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)).

**Table 2** New Neurological Diagnosis for Hospitalized Patients With COVID-19

Neurologic diagnosis <sup>a</sup>	All cases (n = 532) <sup>b</sup>		Younger than 18 y (n = 15)		18–49 y (n = 69)		50–64 y (n = 144)		65–79 y (n = 203)		Older than 80 y (n = 100)		$\chi^2$ p value <sup>c</sup> Na
	n	%	n	%	n	%	n	%	n	%	n	%	
<b>Encephalopathy</b>	478	89.8	11	73.3	59	85.5	127	88.2	184	90.6	97	97.0	0.02
<b>Ischemic stroke</b>	66	12.4	1	6.7	6	8.7	25	17.4	23	11.3	10	10.0	0.25
<b>Seizures</b>	38	7.1	7	46.7	5	7.2	11	7.6	12	5.9	3	3.0	<0.0001
<b>Intracranial hemorrhage</b>	33	6.2	1	6.7	3	4.3	14	9.7	12	5.9	2	2.0	0.15
<b>Critical illness myopathy</b>	19	3.6	0	0.0	5	7.2	8	5.6	6	3.0	0	0.0	0.05 <sup>d</sup>
<b>Critical illness neuropathy</b>	9	1.7	0	0.0	2	2.9	4	2.8	3	1.5	0	0.0	0.43 <sup>d</sup>
<b>Posterior reversible encephalopathy syndrome</b>	3	0.6	0	0.0	2	2.9	1	0.7	0	0.0	0	0.0	0.1 <sup>d</sup>
<b>Acute disseminated encephalomyelitis</b>	1	0.2	0	0.0	1	1.5	0	0.0	0	0.0	0	0.0	0.16 <sup>d</sup>
<b>Mononeuritis multiplex</b>	1	0.2	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0	1 <sup>d</sup>
<b>Meralgia paresthetica</b>	1	0.2	0	0.0	1	1.5	0	0.0	0	0.0	0	0.0	0.16 <sup>d</sup>
<b>Myelitis</b>	1	0.2	0	0.0	1	1.5	0	0.0	0	0.0	0	0.0	0.16 <sup>d</sup>

<sup>a</sup> Clinical diagnoses established by EMR search term review for diagnoses in chart.

<sup>b</sup> 1 case was missing age information and not included in age-stratified table.

<sup>c</sup> Chi-square p value with 4 degrees of freedom.

<sup>d</sup> Exact test.

When controlling for age and sex in an adjusted model, preexisting neurologic conditions which included a history of seizure (adjusted OR 6.23; 95% confidence interval [CI] 2.97, 13.09;  $p < 0.0001$ ), stroke (adjusted OR 3.48; 95% CI 2.05, 5.90;  $p < 0.0001$ ), or dementia (adjusted OR 3.15; 95% CI 1.90, 5.23;  $p < 0.0001$ ) remained more prevalent in cases compared with controls, as did comorbidities of hypertension (adjusted OR 1.77; 95% CI 1.33, 2.34;  $p < 0.0001$ ), hyperlipidemia (adjusted OR 1.37; 95% CI 1.03, 1.82;  $p < 0.0001$ ), diabetes (adjusted OR 1.45; 95% CI 1.12, 1.88;  $p < 0.0001$ ), and renal disease (adjusted OR 1.48; 95% CI 1.05, 2.09;  $p < 0.0001$ ) (eFigure 2, links.lww.com/CPJ/A357).

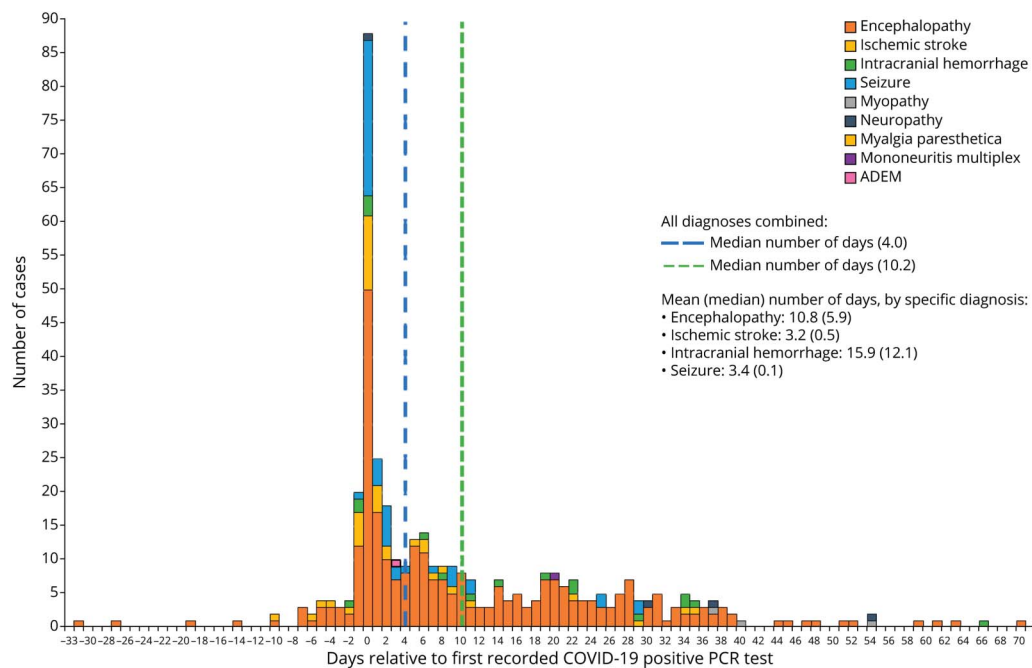
## Discussion

In our hospitalized COVID-19 population in New York City, new neurologic diagnoses were commonly found. Our study documents neurologic presentations and manifestations among minority populations affected significantly by the COVID-19 pandemic in the United States. A significant portion of our hospitalized cohort were critically ill and died or were made comfort care during hospitalization. In a prior NYC-based study,<sup>9</sup> the highest incidence, hospitalization rates, and mortality were among Black/African American and Hispanic/Latino persons, as well as those who were living in neighborhoods with high poverty including our local Northern Manhattan community, aged 75 years and older, and with underlying medical conditions.

Our study found that COVID-19–infected patients with new neurologic diagnoses had substantial rates of readmission and death up to 6 months after discharge. Overall, early data from other studies have shown that readmission and mortality among COVID-19 survivors are common.<sup>10,11</sup> In a national cohort of patients in the Veterans Administration system, 27% of survivors of COVID-19 hospitalization were readmitted or died by 60 days after discharge, and in another CDC-based study, among 106,543 (85%) surviving patients, 9% (9,504) were readmitted to the same hospital within 2 months of discharge through August 2020.<sup>10,11</sup> Few studies have assessed readmission and mortality after acute hospitalization in patients with COVID-19 with neurologic diagnoses. One study published in a posthospitalized cohort showed that patients with neurologic complications due to acute COVID-19 infection had worse 6-month Modified Rankin Scale score (median score 4 vs 3 among controls, adjusted OR 1.98, 95% CI 1.23–3.48,  $p = 0.02$ ), poorer activities of daily living (adjusted OR 0.38, 95% CI 0.29–0.74,  $p = 0.01$ ), and a lower likelihood of returning to work than those hospitalized with acute COVID-19 without neurologic complications (41% vs 64%,  $p = 0.04$ ).<sup>12</sup>

Other studies have found a similar association between neurologic diagnosis and severity of COVID-19 infection, particularly among adults older than 60 years.<sup>13</sup> The relationship between COVID-19 severity and neurologic manifestations is likely bidirectional because severely ill patients seem to be more likely to develop neurologic complications related to severe systemic illness effects, and those

**Figure 2** Time of First Recorded COVID RT-PCR-Positive Test to First Neurologic Diagnosis



Cases with neurologic diagnoses established on the same day of their first positive COVID PCR test (usually coinciding with day of presentation to hospital) are indicated by the bar at zero days. Cases with established primary neurologic diagnoses before their first COVID PCR positivity result are represented by units to the left of zero days. Cases with established primary neurologic diagnoses after their first COVID-positive PCR test are indicated to the right of zero days. All cases are color coded by diagnosis. The blue and green dashed lines indicate median and mean number of days between first COVID-positive PCR test and primary neurologic diagnosis, respectively. RT-PCR = reverse transcriptase PCR.

predisposed with underlying neurologic may be predisposed to more severe COVID-19 illness. Similar to other hospital-based populations, the most commonly identified neurologic diagnoses included encephalopathy, followed by ischemic stroke.<sup>14</sup> Many neurologic conditions during acute COVID-19 are seen in other systemic infectious diseases, including sepsis-associated encephalopathy, which is seen in up to 70% of patients, and in COVID-19 acute respiratory distress syndrome, which is associated with significant neurodisability both in the acute and postacute period.<sup>15</sup> Consistent with other hospital-based studies, patients with COVID-19 with neurologic diagnoses, most commonly encephalopathy, were older with more than half of the cases being 65 years and older.<sup>4</sup> Delirium is significantly more common in older people who have COVID-19, with data from a recent meta-analysis and systematic review demonstrating 1 in 3 hospitalized older patients with COVID-19 are affected (pooled prevalence 34%), compared with 5% in young adults aged 18–34 years and 12% for all ages.<sup>13</sup> Importantly, delirium in older hospitalized patients has previously been demonstrated to be an independent risk factor for mortality and cognitive impairment.<sup>6</sup> Unique to our cohort, we identified that approximately one-third of neurologic conditions, including encephalopathy, stroke, and new onset seizures, were diagnosed at the time of initial hospital presentation, emphasizing that neurologic conditions are commonly presenting features in the acute phase of COVID-19 infection and may mask systemic symptoms.

Careful review of the EMR did not reveal any cases of meningoencephalitis, and although there has been conflicting evidence around whether SARS-CoV-2 may have neurotropic potential, data from several neuropathologic studies suggest this to be less likely.<sup>16–20</sup> Whether novel variants may lead to varied neurologic presentations and possibly alter the neuroinvasive potential of viruses requires further analysis as our data captured cases from the first surge of the pandemic.

This study has several limitations. We focus our study on hospitalized patients with COVID-19 in one hospital system and do not identify neurologic manifestations in those with asymptomatic or mild disease. We conducted our study during the first major surge of the COVID-19 pandemic when SARS-CoV-2 RT-PCR testing was not readily available at times. Our demographic data including race and ethnicity relied on chart review data, which was not available in many charts. Given the retrospective nature of our study, we relied on chart review to identify clinical data, and thus, there is likely an underreporting of neurologic symptoms, signs, and conditions. To define new neurologic diagnoses, we relied on diagnoses by clinical teams, often lacking formal neurologic consultation, although we did attempt to use ancillary studies (neuroimaging, EEG, and LP results) to confirm clinical diagnosis (eTable 5, [links.lww.com/CPJ/A357](https://links.lww.com/CPJ/A357)). During our first surge of the pandemic, many neurologic assessments were performed through phone/video consultation limiting the interpretation of findings and many patients presented in

**Table 3** Clinical Characteristics and Outcomes of Hospitalized Patients With COVID-19 With New Neurologic Diagnoses

	Cases (n = 532)	
	n	%
<b>Overall</b>		
<b>Highest oxygen requirement</b>		
Room air	46	8.6
Nasal cannula	66	12.4
Nonbreather mask	79	14.8
Noninvasive ventilation	6	1.1
Intubation	278	52.3
<b>Outcomes</b>		
Renal replacement	104	19.5
Extracorporeal membrane oxygenation (ECMO)	6	1.1
Comfort care	111	20.9
Do not resuscitate/do not intubate	250	47.0
<b>Discharge status</b>		
Survived	394	74.1
Hospice	31	5.8
Death	138	26.0
<b>Postdischarge status</b>		
Survived (including in hospice)	n = 394	
Readmission <sup>a</sup> within 6 mo	220/394	55.8
Death (after readmission)	51/220	23.2

<sup>a</sup> Readmission to Columbia University Irving Medical Center (CUIMC), Children's Hospital of New York (CHONY) or Allen Hospital in New York Presbyterian (NYP) system.

acute respiratory distress, and thus, there are limited data regarding early prodromal symptoms/signs. Thus, there is likely a significant underrepresentation of neurologic diagnoses which would be obtained by detailed bedside neurologic evaluations, including peripheral neuropathy and myopathies. Strengths of our study include the use of cases and controls with definitive SARS-CoV-2 by laboratory testing. Although we included some patients who were drawn from services other than neurology in our sample, most came from the neurology services, and so our findings may not apply or be generalizable to other patient groups. We evaluated a large number of patients in a multiethnic population and performed detailed and extensive chart reviews to obtain data. We evaluated 6-month posthospitalization-related data including readmission and mortality-related data. Because of our reliance on EMR data, we were only able to capture those who were readmitted to our NYP hospital system, thus likely underestimating readmission and mortality rates in the early post-SARS-CoV-2 period.

## TAKE-HOME POINTS

- Many patients hospitalized with acute COVID-19 had new neurologic diagnoses, most frequently encephalopathy.
- There was a significant association of new neurologic diagnoses with severity of illness, including ICU admission.
- Those with new neurologic diagnoses had a high risk of readmission and mortality during readmission. Further research is needed to define the effect of neurologic diagnoses during acute hospitalization on longitudinal post-COVID-19-related symptoms including neurocognitive impairment.

In this urban study with a substantial number of Hispanic/Latino patients hospitalized with laboratory-confirmed SARS-CoV-2 infection, we found that many had new neurologic diagnoses, most frequently encephalopathy. There was a significant association of new neurologic diagnoses with ICU admission. Concerningly, those with new neurologic diagnoses had a high risk of readmission and mortality during readmission. Quantifying the burden of neurologic events during the acute phase of illness will shed light on potential risk factors and mechanisms of post-COVID-19 neuropsychiatric conditions increasingly reported in survivors.<sup>2,21-24</sup> Several questions remain regarding the implications of the timing and severity of neurologic manifestations on post-acute COVID-19 recovery. Well-designed cohorts in the acute COVID-19 period are needed to define risk factors associated with poor outcomes in the posthospitalization period, especially among multiethnic cohorts who were affected significantly by the pandemic.

## Study Funding

Supported by the Centers for Disease Control and Prevention (contract 75D30120C07986 to Westat), F30 MH114390 to OJL.

## Disclosure

Dr. Elkind receives royalties from UpToDate for a chapter on COVID-19 and neurologic disease. Dr. Sobieszczyk was funded by a COVID supplement to the National Institute of Allergy and Infectious Diseases of the NIH under Award Number UM1AI06947. The other authors report no disclosures relevant to the manuscript. Full disclosure form information provided by the authors is available with the full text of this article at [Neurology.org/cp](https://www.neurology.org/cp).

## Publication History

Received by *Neurology: Clinical Practice* February 22, 2022. Accepted in final form April 26, 2022.



## Appendix Authors

Name	Location	Contribution
<b>Kiran T. Thakur, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
<b>Victoria T. Chu, MD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design
<b>Christine Hughes, MPH</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data
<b>Carla Y. Kim, BA</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
<b>Shannon Fleck-Derderian, PhD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Catherine E. Barrett, PhD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Elizabeth Matthews, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Alanna Balbi, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Amanda Bilski, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Mashina Chomba, MBChB MMed</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Ori Lieberman, MD, PhD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data

## Appendix *(continued)*

Name	Location	Contribution
<b>Samuel D. Jacobson, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Sachin Agarwal, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>David Roh, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Soojin Park, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Vivian Ssonko, MBBS</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Wendy G. Silver, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Wendy D. Vargas, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Andrew Geneslaw, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data
<b>Michelle Bell, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
<b>Brandon Waters, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data
<b>Agam Rao, MD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content

Continued

## Appendix (continued)

Name	Location	Contribution
<b>Jan Claassen, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Amelia Boehme, PhD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
<b>Joshua Z. Willey, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Mitchell S.V. Elkind, MD</b>	Department of Neurology, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, New York	Drafting/revision of the manuscript for content, including medical writing for content
<b>Magdalena E. Sobieszcyk, MD</b>	Department of Pediatrics, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content
<b>Jason Zucker, MD</b>	Department of Pediatrics, Columbia University Irving Medical Center-New York Presbyterian Hospital, New York, NY	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design
<b>Andrea McCollum, PhD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data
<b>James Sejvar, MD</b>	United States Centers for Disease Control and Prevention, Atlanta, GA	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data

## References

1. Yassin A, Nawaiseh M, Shaban A, et al. Neurological manifestations and complications of coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *BMC Neurol*. 2021;21(1):138.
2. Harb AA, Chen R, Chase HS, Natarajan K, Noble JM. Clinical features and outcomes of patients with dementia compared to an aging cohort hospitalized during the initial New York city COVID-19 wave. *J Alzheimers Dis*. 2021;81(2):679-690.
3. Liotta EM, Batra A, Clark JR, et al. Frequent neurologic manifestations and encephalopathy-associated morbidity in Covid-19 patients. *Ann Clin Translational Neurol*. 2020;7(11):2221-2230.
4. Frontera JA, Melmed K, Fang T, et al. Toxic metabolic encephalopathy in hospitalized patients with COVID-19. *Neurocrit Care*. 2021;35(3):693-706.
5. Chomba M, Schiess N, Seeher K, et al. Pre-existing neurological conditions and COVID-19 risk: a commissioned rapid review. 2021. Accessed December 1, 2021. [ssrn.com/abstract=3907265](https://www.ssrn.com/abstract=3907265).
6. Kennedy M, Helfand BK, Gou RY, et al. Delirium in older patients with COVID-19 presenting to the emergency department. *JAMA Netw Open*. 2020;3(11):e2029540.
7. Ellul MVA, Varatharaj A, Pollak TA, et al; CoroNerve Steering Committee. Defining causality in COVID-19 and neurological disorders. *J Neurol Neurosurg Psychiatry*. 2020;91(8):811-812.
8. Ball RHN, Braun MM, Moulton LH, et al. Development of case definitions for acute encephalopathy, encephalitis, and multiple sclerosis reports to the vaccine: adverse event reporting system. *J Clin Epidemiol*. 2002;55(8):819-824.
9. Thompson CNBJ, Baumgartner J, Pichardo C, et al. COVID-19 outbreak—New York city, February 29–June 1, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(46):1725-1729.
10. Donnelly JPWX, Iwashyna TJ, Prescott HC. Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. *JAMA*. 2021;325(3):304-306.
11. Lavery AMPL, Preston LE, Chevinsky JR, et al. Characteristics of hospitalized COVID-19 patients discharged and experiencing same-hospital readmission—United States, March–August 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(45):1695-1699.
12. Frontera JAYD, Yang D, Patel P, et al. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci*. 2021;426:117486.
13. Misra S, Kolappa K, Prasad M, et al. Frequency of neurological manifestations in COVID-19: a systematic review and meta-analysis of 350 studies. *Neurology*. 2021;97(23):e2269-e2281.
14. Frontera JA, Sabadia S, Lalchan R, et al. A prospective study of neurologic disorders in hospitalized patients with COVID-19 in New York city. *Neurology*. 2021;96(4):e575-e586.
15. Goffon T, Young G. Sepsis-associated encephalopathy. *Nat Rev Neurol*. 2012;8(10):557-566.
16. Mukerji SSSI, Solomon IH. What can we learn from brain autopsies in COVID-19? *Neurosci Lett*. 2021;742:135528.
17. Huang YH, Jiang D, Huang JT. SARS-CoV-2 detected in cerebrospinal fluid by PCR in a case of COVID-19 encephalitis. *Brain Behav Immun*. 2020;87:149.
18. Lou JJ, Movassaghi M, Gordy D, et al. Neuropathology of COVID-19 (neuro-COVID): clinicopathological update. *Free Neuropathol*. 2021;2:2.
19. Al-Sarraj S, Troakes C, Hanley B, et al. Invited Review: the spectrum of neuropathology in COVID-19. *Neuropathol Appl Neurobiol*. 2021;47(1):3-16.
20. Matschke J, Lütgehetmann M, Hagel C, et al. Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. *Lancet Neurol*. 2020;19(11):919-929.
21. Salahuddin H, Afreen E, Sheikh IS, et al. Neurological predictors of clinical outcomes in hospitalized patients with COVID-19. *Front Neurol*. 2020;11:585944.
22. Qin C, Zhou L, Hu Z, et al. Clinical characteristics and outcomes of COVID-19 patients with a history of stroke in Wuhan, China. *Stroke*. 2020;51(7):2219-2223.
23. Eskandar EN, Altschul DJ, de la Garza Ramos R, et al. Neurologic syndromes predict higher in-hospital mortality in COVID-19. *Neurology*. 2021;96(11):e1527-e1538.
24. Dhillon PS, Dineen RA, Morris H, et al. Neurological disorders associated with COVID-19 hospital admissions: experience of a single tertiary healthcare center. *Front Neurol*. 2021;12:640017.