Stroke

CLINICAL AND POPULATION SCIENCES

Acute Cerebrovascular Events With COVID-19 Infection

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BACKGROUND AND PURPOSE: Coronavirus disease 2019 (COVID-19) has been associated with an increased incidence of thrombotic events, including stroke. However, characteristics and outcomes of COVID-19 patients with stroke are not well known.

METHODS: We conducted a retrospective observational study of risk factors, stroke characteristics, and short-term outcomes in a large health system in New York City. We included consecutively admitted patients with acute cerebrovascular events from March 1, 2020 through April 30, 2020. Data were stratified by COVID-19 status, and demographic variables, medical comorbidities, stroke characteristics, imaging results, and in-hospital outcomes were examined. Among COVID-19-positive patients, we also summarized laboratory test results.

RESULTS: Of 277 patients with stroke, 105 (38.0%) were COVID-19-positive. Compared with COVID-19-negative patients, COVID-19-positive patients were more likely to have a cryptogenic (51.8% versus 22.3%, $P<0.0001$) stroke cause and were more likely to suffer ischemic stroke in the temporal ($P=0.02$), parietal ($P=0.002$), occipital ($P=0.002$), and cerebellar ($P=0.028$) regions. In COVID-19-positive patients, mean coagulation markers were slightly elevated (prothrombin time 15.4±3.6 seconds, partial thromboplastin time 38.6±24.5 seconds, and international normalized ratio 1.4±1.3). Outcomes were worse among COVID-19-positive patients, including longer length of stay ($P<0.0001$), greater percentage requiring intensive care unit care ($P=0.017$), and greater rate of neurological worsening during admission ($P<0.0001$); additionally, more COVID-19-positive patients suffered in-hospital death (33% versus 12.9%, $P<0.0001$).

CONCLUSIONS: Baseline characteristics in patients with stroke were similar comparing those with and without COVID-19. However, COVID-19-positive patients were more likely to experience stroke in a lobar location, more commonly had a cryptogenic cause, and had worse outcomes.

Key Words: epidemiology ■ incidence ■ intracerebral hemorrhage ■ ischemic stroke ■ length of stay ■ risk factors ■ subarachnoid hemorrhage

On March 11, 2020, the World Health Organization declared coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) a global pandemic.[1] New York State quickly became the epicenter of the US outbreak. As of early August, the total number of cases in New York State accounted for more than one-fifth of the United States caseload and surpassed that of any country besides the United States, Brazil, and Russia.[2,3] Within New York City, ≈204 000 cases were confirmed, over 52 000 patients were hospitalized, and over 20 000 patients died.[3,4]

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
ICH	intracerebral hemorrhage
IS	ischemic stroke
MSHS	Mount Sinai Health System
SARS-CoV-2	severe acute respiratory syndrome coronavirus-2

COVID-19 has been associated with an increased incidence of thrombotic events, including severe cerebrovascular events in young patients.[5–7] However, some centers have reported a decline in acute cardiovascular and cerebrovascular cases and low rates of such events among hospitalized COVID-19 patients during the pandemic.[8–10] We sought to summarize the characteristics and short-term outcomes of patients admitted to a large multihospital health system in New York City with acute cerebrovascular disease during the COVID-19 pandemic. We hypothesized that patients with stroke and confirmed SARS-CoV-2 infection would have fewer traditional vascular risk factors, poorer outcomes, and an embolic or cryptogenic stroke cause more commonly than those without confirmed infection.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. We performed a retrospective observational study of consecutively admitted patients in the Mount Sinai Health System (MSHS) in New York, NY with discharge diagnosis of acute cerebrovascular events, including ischemic stroke (IS), transient ischemic attack, intracerebral hemorrhage (ICH), subarachnoid hemorrhage, and cerebral venous sinus thrombosis. MSHS serves a large and diverse population across New York City. MSHS comprises one Comprehensive Stroke Center with neurosurgical services and 5 Primary Stroke Centers, 3 of which offer 24/7 acute endovascular therapies and 2 of which also offer neurosurgical services, linked by a robust intrasystem transfer process for patients requiring acute stroke intervention and higher-level medical support. The Comprehensive Stroke Center and endovascular therapy–capable sites also receive referral transfers from several community hospitals throughout New York City and its greater metropolitan area. Of the 175 patients transferred for endovascular therapy evaluation with emergent large vessel occlusion in 2019, 103 underwent intervention, making up just over 47% of total MSHS endovascular therapy volumes.

In this study, we included patients admitted from March 1, 2020 through April 30, 2020. We routinely collect data for quality control purposes on all admitted patients with stroke in our health system as part of the Mount Sinai Stroke Registry, including stroke subtype and discharge disposition as defined below. For the purposes of this study, we expanded the data collection to gather additional data of interest during this study time period, under the approval of the Icahn School of Medicine at Mount Sinai Institutional Review Board, which waived the need for informed consent. In addition, to be able to calculate the proportion of admitted COVID-19 patients with stroke, we used our institutional data warehouse to identify all adult patients with COVID-19 hospitalized between March 1, 2020 and April 30, 2020. Patients were diagnosed with COVID-19 if they had at least one positive result for SARS-CoV-2 by nasopharyngeal swab, tracheal, or bronchial polymerase chain reaction during the hospitalization. In cases where clinical suspicion was high for COVID-19 and the initial test negative, polymerase chain reaction was routinely repeated to confirm clinical suspicion. If a patient had multiple nasopharyngeal polymerase chain reaction tests performed during the hospitalization, the patient was considered positive if at least one sample was positive for SARS-CoV-2 infection during hospitalization. In most cases, neurological assessment for acute stroke presentations was performed before reporting of COVID-19 testing.

All data (including demographic information, baseline comorbidities, baseline medications, medication administration during the hospitalization, all provider notes, all laboratory and diagnostic study results from the care provided during the hospitalization) were recorded systematically by clinically trained data abstractors after review of the entire record of the inpatient hospitalization available in the electronic health record. Standard forms based on modified Behavioral Risk Factor Surveillance System forms[11] were used to capture comorbidities. Trained vascular neurologists validated data entry by reviewing a random sample of patients.

Stroke subtype was categorized into IS, ICH, subarachnoid hemorrhage, transient ischemic attack, or cerebral venous sinus thrombosis. IS was further subtyped by mechanism based on modified TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria[12]: small-vessel, large artery atherosclerosis, cardioembolic, cryptogenic, and other known cause. The subtype was determined after review of risk factor profiles, clinical features, and results of diagnostic tests, including computed tomography scan, magnetic resonance imaging, vascular imaging, ECG, echocardiography, and assessment of prothrombotic syndromes as relevant. Cryptogenic subtype was determined after excluding the subtypes of small-vessel, large artery atherosclerosis, cardioembolic, and other known cause. In cases with missing diagnostic information or conflicting stroke mechanisms, data review was performed by at least 2 vascular neurologists for adjudication. Vital signs and laboratory results closest to the time of stroke discovery were recorded, as were acute stroke treatments or interventions. Reperfusion outcomes following mechanical thrombectomy were reported according to scores on the Thrombolysis in Cerebral Infarction scale.

Findings from noncontrast head computed tomography, computed tomography angiogram of the head and neck, brain magnetic resonance imaging, and magnetic resonance angiogram of the head and neck were recorded using standardized forms summarizing reports read by trained attending neuroradiologists. Location of acute infarct or hemorrhage was recorded and stenosis or occlusion of intracranial or extracranial cervical vessels. Other treatments were summarized, including medical treatments related to COVID-19. Of note, at the beginning of the COVID-19 surge in New York City, our health system introduced a COVID-19 anticoagulation algorithm that recommended consideration of treatment-dose anticoagulation for

patients with moderate or severe COVID-19. Patients were considered high risk based on oxygen requirement or elevations in D-dimer, creatinine, or C-reactive protein.

In-hospital outcomes were recorded, including neurological worsening (defined as an increase in neurological deficits according to recorded examinations by a neurologist), new IS or ICH (reported on follow up imaging), one of the following medical complications documented by the primary team: deep venous thrombosis, pulmonary embolism, myocardial infarction, intensive care unit admission, cardiac arrhythmia, hemodialysis, mechanical ventilation, tracheostomy, shock requiring vasoactive medications, goals of care decisions, and discharge disposition (home, in-hospital death, transfer to acute rehabilitation, transfer to subacute rehabilitation, discharge to hospice, or transfer to another hospital or inpatient ward).

Statistical Analysis

Using our institutional data warehouse data, we calculated the number of adults admitted to MSHS with COVID-19 and used the total number of patients with stroke from our stroke dataset to calculate the proportion of admitted COVID-19 patients with acute cerebrovascular disease. Using the stroke dataset, we summarized characteristics of consecutively admitted patients with stroke, reporting means and SDs for continuous variables, and frequencies and percentages for categorical variables. We examined demographic variables, medical comorbidities, stroke characteristics, imaging results, laboratory test results (including coagulation, hematologic, inflammatory, and autoimmune markers), in-hospital treatments, and outcomes among patients with stroke, stratifying by COVID-19 status and assessing significant differences in variable distributions between COVID-19-positive and COVID-19-negative using *t*-tests for continuous variables and χ^2 tests for categorical variables. Finally, using MSHS Stroke Registry data, we performed comparisons of stroke subtype and discharge disposition between the COVID-19 positive group and (1) stroke admissions during the same time period 1 year prior (March 1, 2019 through April 30, 2019) and (2) stroke admissions during 2019 (January 1 through December 31). For this comparison, we defined stroke subtype and discharge disposition based upon available data in the Stroke Registry. Using data from the entire year 2019, we calculated the average daily number of admissions and multiplied by 61 to calculate the expected number of stroke admissions from March 1, 2019 through April 30, 2019. All analyses were performed in SAS version 9.4 using a significance threshold of α=0.05.

RESULTS

During the study period, 277 patients were diagnosed with stroke, of whom 38.0% (n=105) were COVID-19-positive. This represents 1.9% of the 5469 patients admitted to MSHS with COVID-19 during the study period. Table 1 lists baseline characteristics stratified by COVID-19 infection status. A total of 24.6% of the cohort did not receive SARS-CoV-2 testing, predominantly during the first 2 weeks of the study period, after which almost all admitted patients with stroke received testing. There were no significant differences in age, race-ethnicity, or major cardiovascular risk factors between patients with or without COVID-19. However, significantly more patients in the COVID-19-negative

Table 1. Baseline Characteristics, Stratified by COVID-19 Infection Status*

	COVID-19 positive (n=105)	COVID-19 negative (n=172)	*P* value
Age, y, mean (SD)	65.9 (14.3)	66.7 (15.5)	0.66
Female	41 (39.1)	91 (53.9)	0.038
Race			0.16
Asian or Pacific Islander	11 (10.5)	11 (6.6)	
Black participant	23 (21.9)	36 (21.4)	
White participant	17 (16.2)	49 (29.2)	
Other/not reported	54 (51.4)	72 (42.9)	
Ethnicity			0.13
Hispanic or Latino	26 (24.8)	27 (15.9)	
Not Hispanic or Latino	53 (50.5)	87 (51.2)	
Not reported	26 (24.8)	56 (32.9)	
Hypertension	82 (78.1)	131 (76.6)	0.78
Hypercholesterolemia	47 (45.6)	78 (46.2)	0.93
Diabetes			
Type 1	4 (3.8)	4 (2.3)	0.47
Type 2	39 (37.1)	58 (33.7)	0.56
Obesity	37 (35.6)	46 (27.4)	0.15
Atrial fibrillation or flutter	11 (10.7)	22 (13.0)	0.57
Smoking, current or past	26 (28.3)	74 (47.1)	0.014
Coronary artery disease	20 (19.2)	46 (27.4)	0.13
Myocardial infarction	3 (3.0)	15 (8.9)	0.06
Congestive heart failure	13 (12.6)	24 (14.2)	0.7
Carotid stenosis	65(4.9)	12 (7.2)	0.44
Prior cerebrovascular disease			
Ischemic stroke	13 (12.4)	35 (20.4)	0.09
Transient ischemic attack	9 (8.6)	9 (5.2)	0.27
Intracerebral hemorrhage	3 (2.9)	5 (2.9)	0.98
Subarachnoid hemorrhage	0	2 (1.2)	0.27
Renal dysfunction	16 (15.4)	25 (14.9)	0.19
Liver disease	8 (7.6)	8 (4.7)	0.8
Deep venous thrombosis	7 (6.7)	7 (4.1)	0.35
Cancer			0.30
Active	4 (3.9)	9 (5.3)	
Inactive	4 (3.9)	14 (8.2)	
Immunodeficiency syndrome	0	3 (1.8)	0.18
Taking any full-dose anticoagulant at admission	89 (84.8)	151 (87.8)	0.47
Taking any full-dose anticoagulant at stroke onset	72 (68.6)	156 (90.7)	<0.0001
Taking antiplatelet medication	69 (65.7)	102 (59.3)	0.29
Take immunosuppressant medication	2 (2.0)	5 (2.9)	0.63

COVID-19 indicates coronavirus disease 2019.

*Number and percent for categorical variables; mean and SD for continuous variables.

cohort had a history of smoking (47.1% versus 28.3%, *P*=0.014) and were taking a full-dose anticoagulant at stroke onset (90.7% versus 68.6%, *P*<0.0001).

Initial stroke severity was higher among those with COVID-19 (mean National Institutes of Health Stroke Scale of 15.5 versus 9.6 among those without COVID-19, Table 2). Although the distribution of stroke subtypes was similar between the COVID-19 and non-COVID-19 cohorts (*P*=0.45), IS cause differed between cohorts (Table 2). For 51.8% (n=43) of COVID-19-positive patients, etiologic subtype was cryptogenic, compared with only 22.3% (n=27) for the COVID-19-negative cohort (*P*<0.0001). Additionally, only 6.0% (n=5) of COVID-19 patients suffered small-vessel IS and 28.9% (n=24) cardioembolic IS, compared with 17.4% (n=21) and 42.2% (n=51) among non-COVID-19 patients, respectively. IS occurred more commonly in the temporal (*P*=0.04), parietal (*P*=0.002), occipital (*P*=0.002), and cerebellar (*P*=0.027) regions among COVID-19-positive patients compared with COVID-negative patients. ICH location did not differ between groups. Receipt of intravenous thrombolysis and mechanical thrombectomy were similar regardless of COVID-19 status. Prevalence of arterial stenosis and occlusion was similar between groups, and there was no difference in Thrombolysis in Cerebral Infarction score in patients treated with thrombectomy. Pulmonary ground-glass opacities were seen on computed tomography angiogram in 67.7% (n=44) of COVID-19-positive patients with stroke, compared with only 8.8% of COVID-negative patients (*P*<0.0001).

Table 3 summarizes laboratory test results comparing COVID-19-positive patients to COVID-19-negative patients and proportions of COVID-19 patients with abnormal values. At the time closest to stroke discovery, mean coagulation markers were mildly elevated compared with normal values (prothrombin time 15.4±3.7 seconds, partial thromboplastin time 38.9±24.8 seconds, and international normalized ratio 1.4±1.3). White blood cells, hemoglobin, and hematocrit were each abnormal in around half of the COVID-19 patients; white blood cells and platelets were higher among COVID-19-positive patients compared with COVID-negative, and hemoglobin and hematocrit were lower. Elevated peak troponin levels were seen in 62.9% of COVID-19 patients (mean 0.80±2.0 ng/mL), and 97.0% had elevated peak D-dimer levels (mean 8.6±7.5 ng/mL). Peak inflammatory markers were most frequently elevated in COVID-19 patients, including C-reactive protein, erythrocyte sedimentation rates, and interleukin-6 levels. Forty-five percent (n=48) of COVID-19-positive patients with stroke were treated with systemic anticoagulation, compared with only 1.2% (n=2) of COVID-19-negative patients with stroke (*P*<0.0001).

Outcomes were worse among COVID-19-positive patients with stroke compared with COVID-19-negative patients with stroke (Table 4). Mean length of stay for the COVID-19 cohort was 17.4±14.8 days compared with 8.0±6.4 days for the non-COVID-19 cohort (*P*<0.0001), and 58.7% (n=61) of the COVID-19 cohort required intensive care unit admission, compared with 44.7% of non-COVID-19 cohort (*P*=0.025). Half of COVID-19-positive patients with stroke experienced neurological worsening during admission, compared with only 21% of the COVID-19-negative cohort (*P*<0.0001). Additionally, 37.2% (n=35) of COVID-19-positive patients with stroke developed acute respiratory distress syndrome and 45.2% (n=47) required mechanical ventilation, compared with only 2.6% (n=4) and 19.4% (n=33) of COVID-19-negative patients with stroke, respectively (*P*<0.0001 for each). Only 29.8% (n=14) of intubated COVID-19-positive patients were extubated, compared with 75.8% (n=25) of COVID-19-negative patients. In-hospital death occurred in 33% (n=35) of COVID-19-positive patients with stroke, compared with 12.9% (n=22) among COVID-19-negative patients. Only 22.9% (n=24) of the COVID-19-positive patients were discharged home compared with 49.4% (n=84) in the COVID-19-negative cohort.

Finally, there was a higher proportion of IS and ICH and lower proportion of subarachnoid hemorrhage and transient ischemic attack among COVID-19-positive patients with stroke compared with COVID-19 negative patients admitted during the same period 1 year prior (Table 5). Among IS, cryptogenic cause was more than twice as common among COVID-19 positive patients as COVID-19 negative patients in all comparison groups. One-third of COVID-19 patients with stroke died in hospital, compared with much lower proportions in all comparison groups. There were fewer overall MSHS stroke admissions during the pandemic (277) compared with the same period 1 year prior (312) and to the expected number of admissions during a 61-day period based on a daily average of admissions in 2019 (332).

DISCUSSION

In this large, multihospital retrospective observational study located in the epicenter of the COVID-19 pandemic in the United States, we found that 38% of all admitted strokes occurred in COVID-19-positive patients from March 1, 2020 through April 30, 2020. The COVID-19-positive cohort had more severe strokes and a higher prevalence of cryptogenic stroke mechanism and lobar stroke location. COVID-19-positive patients with stroke had mild coagulopathy, but the majority had elevated inflammatory markers. Most significantly, outcomes were much worse in the COVID-19-positive cohort compared with the COVID-19-negative cohort, and 33.3% suffered in-hospital death. The number of stroke admissions overall were reduced during the pandemic.

Substantial evidence has suggested that infection with COVID-19 may predispose to venous and arterial

Table 2. Stroke Characteristics, Including Subtypes and Imaging, Stratified by COVID-19 Infection Status

	COVID-19 positive	COVID-19 negative	*P* value
Total N	105	172	…
Stroke subtype			0.45
Ischemic	83 (79.1)	121 (70.4)	
Intracerebral hemorrhage	16 (15.2)	33 (19.2)	
Subarachnoid hemorrhage	4 (3.8)	9 (5.2)	
Transient ischemic attack	2 (1.9)	7 (4.1)	
Cerebral venous sinus thrombosis	0	2 (1.2)	
NIHSS score on presentation, mean (SD)	15.5 (10.7)	9.6 (9.5)	<0.0001
modified Rankin Scale score ≤1 before presentation	51 (81.0)	83 (78.3)	0.68
Ischemic stroke			
Ischemic stroke subtype			<0.0001
Small vessel	5 (6.0)	21 (17.4)	
Large artery atherosclerosis	5 (6.0)	17 (14.1)	
Cardioembolic	24 (28.9)	51 (42.2)	
Cryptogenic	43 (51.8)	27 (22.3)	
Other known cause	6 (7.2)	5 (4.1)	
Location			
Frontal lobe	38 (34.9)	51 (29.7)	0.26
Temporal lobe	30 (28.6)	31 (18.0)	0.04
Parietal lobe	46 (43.8)	45 (26.2)	0.002
Occipital lobe	28 (26.7)	21 (12.2)	0.002
Basal ganglia	10 (9.5)	32 (18.6)	0.041
Centrum semiovale	8 (7.6)	20 (11.6)	0.28
Midbrain	2 (1.9)	0	0.07
Pons	4 (3.8)	10 (5.8)	0.46
Cerebellum	21 (20.0)	18 (10.5)	0.027
Medulla	3 (2.9)	3 (1.7)	0.54
Vermis	1 (1.0)	0	0.20
Received intravenous thrombolysis	8 (7.7)	25 (14.5)	0.09
Received mechanical thrombectomy	13 (12.5)	18 (10.5)	0.60
TICI score			0.34
2A	1 (7.7)	3 (18.8)	
2B	5 (38.5)	4 (25.0)	
2C	5 (38.5)	3 (18.8	
3	2 (15.4)	6 (37.5)	
Artery stenosis			
Anterior cerebral	3 (2.9)	2 (1.2)	0.30
Common carotid	3 (2.9)	6 (3.5)	0.77
Internal carotid	9 (8.6)	27 (15.7)	0.087
Middle cerebral, M1	4 (3.8)	13 (7.6)	0.21
Middle cerebral, M2	5 (4.8)	10 (5.8)	0.71
Middle cerebral, M3	3 (2.9)	4 (2.3)	0.78
Posterior cerebral	6 (5.7)	8 (4.7)	0.70
Vertebral	12 (11.4)	17 (9.9)	0.68
Basilar	4 (5.9)	8 (5.7)	0.99
Artery occlusion			
Anterior cerebral	2 (1.9)	1 (0.6)	0.30
Common carotid	2 (1.9)	2 (1.2)	0.62
Internal carotid	11 (10.5)	10 (5.8)	0.16
Middle cerebral, M1	13 (12.4)	16 (9.3)	0.42
Middle cerebral, M2	9 (8.6)	13 (7.6)	0.76
Middle cerebral, M3	6 (5.7)	4 (2.3)	0.14
Posterior cerebral	2 (1.9)	3 (1.7)	0.92
Vertebral	2 (1.9)	7 (4.1)	0.32
Basilar	1 (1.5)	2 (1.3)	0.96
Intracerebral hemorrhage			
Location			
Frontal lobe	9 (56.3)	14 (41.2)	0.90
Temporal lobe	4 (25.0)	5 (14.7)	0.68
Parietal lobe	5 (31.2)	9 (26.5)	0.86
Occipital lobe	4 (25.0)	3 (8.8)	0.29
Basal ganglia	5 (31.2)	15 (44.1)	0.22
Midbrain	0	1 (2.9)	0.43
Pons	0	1 (2.9)	0.43
Cerebellum	1 (6.3)	5 (14.7)	0.28
Medulla	1 (6.3)	0	0.20
Lung ground-glass opacities on CT angiogram	44 (67.7)	12 (8.8)	<0.0001

COVID-19 indicates coronavirus disease 2019; CT, computed tomography; NIHSS, National Institutes of Health Stroke Scale; and TICI, Thrombolysis in Cerebral Infarction.

thromboembolism, to a greater degree with worse disease severity.[13,14] However, overall IS incidence during the COVID-19 pandemic appeared to have decreased, perhaps because people avoided seeking health care for more minor symptoms or symptoms went unrecognized in hospitalized patients whose deficits may have been masked by other sequelae of critical illness or sedation.[9,15,16] Prior studies have provided evidence for a prevalence of acute cerebrovascular disease, most commonly acute IS, of 2% to 6%, with greater prevalence in critically ill patients with worsened COVID-19 disease severity.[14,17–20] However, one recent study estimated that the prevalence may be <1%.[10] We found that 1.9% of COVID-19 patients admitted to MSHS had acute stroke, and overall admissions for stroke were reduced during the pandemic. This may have been because of the selective presentation of patients to medical attention. If patients with less debilitating symptoms did not seek health care during the pandemic, this would decrease the number of admissions for acute cerebrovascular events and increase the observed severity of strokes and associated morbidity and mortality during this period.

Table 3. Laboratory Test Results

Laboratory test	Normal range	COVID-19-positive			COVID-19-negative			*P* value
		N	Mean (SD)	Number (%) abnormal	N	Mean (SD)	Number (%) abnormal	
Coagulation function closest to time of stroke discovery								
Prothrombin time, s	12.3–14.9	97	15.4 (3.7)	47 (48.5)	162	14.6 (4.4)	45 (27.8)	0.1225
Partial thromboplastin time, s	25.4–34.9	100	38.9 (24.8)	48 (48.0)	158	31.1 (13.4)	66 (41.8)	0.0013
International normalized ratio, unitless	≤1.1	97	1.4 (1.3)	54 (55.7)	163	1.46 (2.58)	45 (27.6)	0.80
Hematologic blood function closest to time of stroke discovery								
White blood cells, $\times 10^3$/uL	4.5–11.0	104	11.7 (5.9)	50 (48.1)	171	9.9 (6.0)	56 (32.8)	0.0159
Hemoglobin, g/dL	11.7–15.0	104	11.7 (2.6)	54 (51.9)	172	13.0 (2.4)	77 (44.8)	<0.0001
Hematocrit, %	34.0–47.0	104	35.5 (8)	50 (48.1)	172	39.5 (6.9)	56 (32.6)	<0.0001
Platelets, $\times 10^3$/uL	150–450	104	293.2 (146.5)	29 (28.2)	172	234.0 (88.4)	27 (15.7)	<0.0001
Peak troponin levels, ng/mL	0.0–0.03	97	0.8 (2)	61 (62.9)	156	0.33 (1.53)	54 (34.6)	0.0406
Peak inflammatory markers								
D-dimer level, ug/mL	0.00–0.50	101	8.6 (7.5)	98 (97.0)	39	36.7 (126.8)	37 (94.9)	0.0277
Fibrinogen level, mg/dL	175–450	82	550.3 (237)	62 (75.6)	24	466.3 (180.3)	12 (50.0)	0.1118
C-reactive protein level, mg/L	0.0–5.0	100	153 (122.6)	97 (97.0)	45	63.5 (101.4)	30 (66.7)	<0.0001
Erythrocyte sedimentation rate: MM/HR	0–15	43	68.9 (38.4)	38 (88.4)	29	35.0 (32.1)	20 (69.0)	0.0002
Interleukin-6, pg/mL	0.0–5.0	60	410.5 (842.8)	57 (95.0)	9	42.0 (76.0)	5 (55.6)	0.197
Procalcitonin level, ng/mL	<0.49	84	7.9 (37.2)	30 (35.7)	29	11.7 (38.0)	10 (34.5)	0.6389
Lactate dehydrogenase levels, U/L	100–220	89	664 (502)	84 (97.7)	35	469.2 (684.4)	29 (82.9)	0.0891

COVID-19 indicates coronavirus disease 2019; HR, hour; and MM, millimeter.

Most studies describing the occurrence of acute cerebrovascular disease in COVID-19 patients have been relatively small retrospective cohorts or case series.[7,21–25] Consequently, data on the incidence, cause, and outcomes of COVID-19-associated cerebrovascular events are lacking. In addition to traditional cerebrovascular risk factors, risk factors for cerebrovascular disease in the setting of COVID-19 infection have been thought to include hypercoagulability, whether secondary to the systemic inflammatory response to infection, or a COVID-19-specific cytokine storm and endothelial inflammation.[26–30] Coagulopathy, often evidenced by elevated D-dimer, and a history of cerebrovascular disease have been found to be associated with increased disease severity and mortality.[26,31,32] We, too, found traditional cerebrovascular risk factors to be present in the COVID-19-positive cohort, although not more common compared with the COVID-19-negative cohort. Additionally, a major behavioral cerebrovascular risk factor, smoking, was significantly less common in the COVID-19-positive cohort, but it is possible that behavioral risk factors such as smoking may be inaccurately recorded in the medical record among those in poorer health on admission. We also found evidence of a mild coagulopathy among COVID-19 patients. While we did not examine the association between coagulopathy and mortality, outcomes were significantly worse in the COVID-19-positive cohort. Others, including colleagues in Italy and New York City, have reported poorer outcomes in their COVID-19 patients with stroke as well.[10,16,26]

One of the largest studies comparing stroke between COVID-19 and non-COVID-19 patients during the pandemic came from Italy.[26] Of their 111 patients with cerebrovascular disease, a similar percentage to ours tested positive for COVID-19 (38.7%) and they found significant elevations in inflammatory markers; however, they reported a lower percentage of ICH (7.0%) compared with ours (15.2%). Notably, they did not describe patterns of treatment with anticoagulation, which represents a significant difference from our study given that 45.7% of our COVID-19-positive patients with stroke were treated with anticoagulation. The higher rate of treatment with anticoagulation among our COVID-19-patients with stroke may reflect an overall difference in approach to prevention of thrombotic events in COVID-19-positive patients, which may also explain the higher prevalence of ICH in our population. We report a mortality rate among COVID-19-positive patients with stroke of 33.3%, which is similar to the Italian cohort. However, that study did not comment on cause of stroke or provide details on stroke location and medical complications among COVID-19-positive patients with stroke.

A smaller study from New York City compared COVID-19 patients with stroke to concurrent and historical controls.[10] In this study of 32 COVID-19-positive patients with stroke, cryptogenic stroke occurred in 65.6% (compared with 52% observed in our study), and there were elevations in troponin and inflammatory markers in the COVID-19-positive patients. A larger percentage (78.1%) were treated with systemic anticoagulation. Notably, the in-hospital death rate was higher

Table 4. Treatments and Outcomes Among Patients With Stroke, Stratified by COVID-19 Infection Status

	COVID-19 positive	COVID-19 negative	*P* value
COVID-related treatments received			
Steroids	32 (30.5)	0	<0.0001
Hydroxychloroquine	79 (75.2)	0	<0.0001
Systemic anticoagulation	48 (45.7)	2 (1.2)	<0.0001
Antiviral medication	5 (4.8)	1 (0.6)	0.0204
Azithromycin	63 (60.0)	2 (1.2)	<0.0001
Monoclonal antibody	7 (6.4)	0	<0.0001
Other	15 (14.3)	0	<0.0001
Length of stay, d, mean (SD)	17.4 (14.8)	8.0 (6.4)	<0.0001
Intensive care unit admission	61 (58.7)	76 (44.7)	0.025
Discharge NIHSS among survivors, mean (SD)	6.7 (8.0)	5.2 (6.0)	0.26
Neurological worsening	54 (51.9)	35 (21.0)	<0.0001
Deep venous thrombosis during hospitalization	6 (6.1)	3 (1.8)	0.058
Pulmonary embolism during hospitalization	6 (6.1)	3 (1.8)	0.058
Acute respiratory distress syndrome	35 (37.2)	4 (2.6)	<0.0001
New cardiac arrhythmia	13 (13.4)	15 (9.0)	0.26
Need for dialysis/continuous renal replacement therapy	18 (18.4)	5 (3.0)	<0.0001
Need for mechanical ventilation	47 (45.2)	33 (19.4)	<0.0001
Ventilator outcome			0.0002
Extubated	14 (29.8)	25 (75.8)	
Tracheostomy	16 (34.0)	3 (9.1)	
Expired on ventilator	17 (36.2)	5 (15.2)	
Shock requiring pressors	33 (34.7)	13 (8.1)	<0.0001
Goals of care decisions			
Do not resuscitate	31 (29.5)	21 (12.2)	0.003
Do not intubate	23 (21.9)	16 (9.3)	0.001
Comfort measures	20 (19.1)	12 (7.0)	0.002
Disposition			<0.0001
Home	24 (22.9)	84 (49.4)	
Acute rehabilitation	11 (10.5)	21 (12.4)	
Subacute rehabilitation	21 (20.0)	36 (21.2)	
Hospice	3 (2.9)	3 (1.8)	
Transfer to another hospital or inpatient ward	11 (10.5)	4 (2.4)	
In-hospital death	35 (33.3)	22 (12.9)	
Cause of death			0.29
Comfort measures	11 (31.4)	11 (50.0)	
Brain death	4 (11.4)	3 (13.6)	
Cardiac death	20 (57.1)	8 (36.4)	

COVID-19 indicates coronavirus disease 2019; and NIHSS, National Institutes of Health Stroke Scale.

in their study (63.6%). This study also had limited detail about stroke location and medical complications among COVID-19-positive patients with stroke.

Results from whole blood analysis and thromboelastography with SARS-CoV-2 have revealed an underlying state of hypercoagulability, distinct from disseminated intravascular coagulation, associated with elevated levels of fibrinogen, Factor VIII, Protein C, von Willebrand Factor, C-reactive protein, and D-dimer.[33] Case reports have revealed a number of individuals found to have antibody profiles similar to those of the antiphospholipid syndrome with elevated anticardiolipin and β-2 glycoprotein I antibodies.[34] Each of these findings suggests dysregulation in the setting of a cytokine-mediated inflammatory response. A generalized inflammatory state may cause clotting factor dysfunction that is nonspecific and may be seen in other disease entities such as influenza.[35] Viral translation through ACE-2 receptors expressed in vessel walls may cause endotheliitis.[36] Along with this mechanism, metalloproteinase activation and procoagulant gene expression may contribute to thrombus formation and may explain the phenomenon of intramural thrombi and large vessel occlusions, which seem to be more common in infected patients of varying disease severity.[7,36] In addition, the SARS-CoV strain that caused the 2003 SARS epidemic has been implicated in increased stroke risk, possibly through the transcription of procoagulant genes.[37]

There are several strengths of this study, including the large sample size from a multihospital health system caring for patients in the epicenter of the US pandemic. We used an existing infrastructure of data collection that we expanded with rigorous and standardized data collection and end point adjudication by vascular neurologists. Limitations of this study include lack of data on cerebrovascular events occurring outside of the MSHS inpatient setting. Furthermore, this was an observational study, and we cannot comment on efficacy of particular treatments for COVID-19-related cerebrovascular disease. Regarding the comparison of stroke admissions with stroke admissions during all of 2019, this may represent an overestimation of expected number of stroke admissions since it includes winter months; the other comparison group involving admissions from March 1 through April 30, 2019 may represent a more accurate comparison. Last, the small sample sizes in our cohorts may have limited our ability to detect differences that actually exist. Also, due to the small number of events, we could not reliably run multivariable models due to the risk of overfitting the model, which would have resulted in inaccurate and biased results.

Future research will include ongoing collection of clinical and diagnostic characteristics of patients admitted to our health system with cerebrovascular disease and COVID-19, allowing longitudinal outcome collection, in-depth neuroimaging, and granular neurocognitive testing to elucidate the long-term

Table 5. Comparisons Between COVID-19-Positive Group and Contemporary and Historical COVID-19-Negative Groups

Group	COVID-19 positive group	COVID-19 negative comparison groups					
Date range	March 1, 2020 through April 30, 2020	March 1, 2020 through April 30, 2020		March 1, 2019 through April 30, 2019		January 1, 2019 through December 31, 2019	
Total N	105	172		312		1985	
			P value*		*P* value*		*P* value*
Stroke subtype			0.45		0.019		0.074
Ischemic	83 (79.1)	121 (70.4)		227 (72.8)		1442 (72.6)	
Intracerebral hemorrhage	16 (15.2)	33 (19.2)		32 (10.3)		221 (11.1)	
Subarachnoid hemorrhage	4 (3.8)	9 (5.2)		21 (6.7)		112 (5.6)	
Transient ischemic attack	2 (1.9)	7 (4.1)		32 (10.3)		207 (10.4)	
Ischemic stroke subtype			<0.0001		<0.0001		<0.0001
Small vessel	5 (6.0)	21 (17.4)		60 (27.9)		389 (29.7)	
Large artery atherosclerosis	5 (6.0)	17 (14.1)		27 (12.6)		160 (12.2)	
Cardioembolic	24 (28.9)	51 (42.2)		63 (29.3)		426 (32.5)	
Cryptogenic	43 (51.8)	27 (22.3)		51 (23.7)		257 (19.6)	
Other known cause	6 (7.2)	5 (4.1)		14 (6.5)		78 (6.0)	
Discharge disposition			<0.0001		<0.0001		<0.0001
Home	24 (22.9)	84 (49.4)		162 (51.9)		989 (49.9)	
Acute rehabilitation or transfer to another hospital	22 (21.0)	25 (14.5)		18 (5.8)		101 (5.1)	
Subacute rehabilitation	21 (20.0)	36 (21.2)		101 (32.4)		662 (33.4)	
Hospice	3 (2.9)	3 (1.8)		10 (3.2)		61 (3.1)	
In-hospital death	35 (33.3)	22 (12.9)		15 (4.8)		131 (6.6)	

COVID-19 indicates coronavirus disease 2019.
**P* value for comparison between listed COVID-19 negative comparison group and the COVID-19 positive group.

effects and outcomes of COVID-19 infection after stroke.

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APPENDIX

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