

ORIGINAL CONTRIBUTION

SARS2-CoV-2 and Stroke in a New York Healthcare System

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BACKGROUND AND PURPOSE: With the spread of coronavirus disease 2019 (COVID-19) during the current worldwide pandemic, there is mounting evidence that patients affected by the illness may develop clinically significant coagulopathy with thromboembolic complications including ischemic stroke. However, there is limited data on the clinical characteristics, stroke mechanism, and outcomes of patients who have a stroke and COVID-19.

METHODS: We conducted a retrospective cohort study of consecutive patients with ischemic stroke who were hospitalized between March 15, 2020, and April 19, 2020, within a major health system in New York, the current global epicenter of the pandemic. We compared the clinical characteristics of stroke patients with a concurrent diagnosis of COVID-19 to stroke patients without COVID-19 (contemporary controls). In addition, we compared patients to a historical cohort of patients with ischemic stroke discharged from our hospital system between March 15, 2019, and April 15, 2019 (historical controls).

RESULTS: During the study period in 2020, out of 3556 hospitalized patients with diagnosis of COVID-19 infection, 32 patients (0.9%) had imaging proven ischemic stroke. Cryptogenic stroke was more common in patients with COVID-19 (65.6%) as compared to contemporary controls (30.4%, $P=0.003$) and historical controls (25.0%, $P<0.001$). When compared with contemporary controls, COVID-19 positive patients had higher admission National Institutes of Health Stroke Scale score and higher peak D-dimer levels. When compared with historical controls, COVID-19 positive patients were more likely to be younger men with elevated troponin, higher admission National Institutes of Health Stroke Scale score, and higher erythrocyte sedimentation rate. Patients with COVID-19 and stroke had significantly higher mortality than historical and contemporary controls.

CONCLUSIONS: We observed a low rate of imaging-confirmed ischemic stroke in hospitalized patients with COVID-19. Most strokes were cryptogenic, possibly related to an acquired hypercoagulability, and mortality was increased. Studies are needed to determine the utility of therapeutic anticoagulation for stroke and other thrombotic event prevention in patients with COVID-19.

Key Words: coronavirus ■ COVID-19 ■ diagnosis ■ pandemic ■ troponin

Coronavirus disease 2019 (COVID-19), the illness caused by the severe acute respiratory syndrome CoV-2 coronavirus, has an unclear impact on the cerebrovascular system. With over 200 000 confirmed cases as of April 15, 2020, New York State currently accounts for ≈10% of all confirmed cases worldwide. Given early reports of an association between COVID-19

and cerebrovascular disease, there is a critical, unmet need to define associations and outcomes of patients with cerebrovascular disease and COVID-19.

Understanding factors associated with stroke in patients with COVID-19 will aid in the diagnosis, treatment, and prevention of COVID-19 associated cerebrovascular disease as well as potentially identify underlying

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
IQR	interquartile range
NIHSS	National Institutes of Health Stroke Scale
OR	odds ratio

mechanisms. In this study, we aim to characterize ischemic stroke in patients with COVID-19 from a large healthcare system with a diverse patient population in the New York metropolitan area and compare these characteristics to those of contemporary and historical ischemic stroke controls without COVID-19.

METHODS

Study Population

We obtained institutional review board approval from NYU Langone Health to perform the study, and informed consent was waived by the institutional review board. Data from the study are available for sharing upon reasonable request to the corresponding author. This is a retrospective observational study including patients admitted to one of 3 comprehensive stroke centers in the New York metropolitan area (NYU Langone Manhattan, NYU Langone Brooklyn in Sunset Park, Brooklyn, and NYU Langone Winthrop in Mineola, Long Island) with acute ischemic stroke hospitalized between March 15, 2020, and April 19, 2020. All consecutive patients with radiological confirmation of acute ischemic stroke during this time frame were included. In addition, we included consecutive patients from 2 of our facilities (NYU Langone Brooklyn and NYU Langone Manhattan) with a discharge diagnosis of ischemic stroke between March 15, 2019, and April 15, 2019, as a historical comparator group (historical control).

Stroke Assessment and Classification

In general, patients underwent a standard diagnostic evaluation, including brain imaging, intracranial and extracranial vascular imaging, and cardiac evaluation, including ECG, in-house continuous cardiac telemetry for at least 24 hours, and transthoracic echocardiography per institutional protocol. Stroke subtype was classified based on the Trial of ORG 10172 in Acute Stroke Treatment classification.¹ Large artery atherosclerosis was defined as 50% or more narrowing in an artery supplying the ischemic infarct territory, small vessel disease was defined as a small (≤ 1.5 cm on head computed tomography or ≤ 2 cm on diffusion-weighted imaging sequence) subcortical infarct in patients with risk factors for small vessel disease, cardioembolic was defined as the presence of a major cardioembolic source, such as atrial fibrillation, endocarditis, or ejection fraction $\leq 30\%$, and other was defined as an alternative mechanism such as dissection or known hypercoagulability, excluding de novo hypercoagulability in the setting of a COVID-19. Cryptogenic was defined as cases not meeting criteria for any of the above stroke subtypes, including those with incomplete workup or with multiple competing high-risk mechanisms.¹

In addition, we defined embolic stroke of undetermined source according to the criteria proposed by the Cryptogenic Stroke/Embolic Stroke of Undetermined Source International Working Group.² Finally, we also classified strokes based on the ASCOD criteria (atherosclerosis, small-vessel disease, cardiac pathology, other cause, and dissection).³

Study Variables

The following variables were abstracted from the medical records of patients:

1. Demographic variables: age, sex, and race/ethnicity.
2. Clinical variables: History of hypertension, history of diabetes mellitus, history of hyperlipidemia, history of coronary artery disease, history of congestive heart failure, history of atrial fibrillation, history of prior stroke or transient ischemic attack; active smoking; admission National Institutes of Health Stroke Scale (NIHSS) score; date of stroke determined as date of stroke symptom onset and if not available, it was based on the date the stroke likely occur based on the abstractors clinical judgment.
3. Laboratory variables: cardiac troponin level (closest to the time of the stroke), C-reactive protein (closest to the time of the stroke), erythrocyte sedimentation rate (closest to the time of the stroke), and D-dimer level (highest level and closest to the time of the stroke).
4. Imaging variables: infarct pattern (multiple vascular territories versus single vascular territory) and proximal large artery occlusion (defined as occlusion of the intracranial internal carotid artery, M1, and M2 segments of the middle cerebral artery, basilar artery, or P1 segment of the posterior cerebral artery).
5. In-hospital treatments: alteplase, mechanical thrombectomy, anticoagulation therapy, mechanical ventilation, hydroxychloroquine, and other novel investigational treatments.
6. Discharge outcomes: discharge disposition (home, acute rehab, nursing facility, or death/hospice), and in-hospital mortality.

COVID-19 Screening and Diagnosis

Screening for COVID-19 was performed at first provider contact and included evaluation for recent COVID-19 exposure, history of fever or respiratory symptoms, or chest radiographic findings. In general, patients with a negative screen do not undergo COVID-19 testing. A positive screen would trigger testing, and this is generally the case when screening could not be completed. Assays for COVID-19 were performed in accordance with standards established by the World Health Organization. A reverse-transcriptase polymerase chain reaction study was performed in each center's laboratory using a sample obtained via a nasopharyngeal swab. The primary variable of interest was COVID-19 status (positive versus negative).

Statistical Analysis

No sample-size calculations were performed. All patients (cases and control groups) were divided into 3 groups: group 1 included patients with ischemic stroke and COVID-19 (cases), group 2 included contemporary patients with ischemic stroke without COVID-19 (contemporary controls), and

Table 1. Characteristics of COVID-19 Positive Imaging Proven Ischemic Stroke Patients

	Demographics Risk Factors	COVID-19 Symptoms and Severity	Days From COVID-19 Symptoms to Stroke and Any COVID-19 Treatment Before Stroke	Laboratory Values Closest to Time of Stroke	Stroke Subtype*	Treatment	Outcome
Patient 1	50s black with HTN	Cough	6 d	CRP 11	Cryptogenic	Alteplase	Discharged to rehabilitation
				D-dimer >10 000	A2 S0 C9 O1 D0	Thrombectomy	
					Aspirin		
Patient 2	60s white with HTN, DM2, HLPD, AF, CHF, and CAD	Cough, fever, hypoxia	1 d	CRP 31.6	Large artery atherosclerosis (basilar stenosis)	Aspirin, clopidogrel	Death
				D-dimer 342			
				IL-6 level 5	A1 S3 C1 O0 D0		
Patient 3	70s white with HTN, DM2, AF, HLPD, and prior stroke	Fever, cough, hypoxia	5 d	CRP 72	Cardioembolic	Alteplase	Death
				D-dimer 3247	A3 S0 C1 O2 D0	Thrombectomy	
				IL-6 level 14			
Patient 4	70s white with HTN and HLPD	Cough, hypoxia	8 d	CRP 111	Cryptogenic	Anticoagulation	Death
				D-dimer >10 000	A9 S0 C1 O1 D9		
				Troponin 18.1			
Patient 5	70s Asian with HTN	Fever, cough, hypoxia	5 d	CRP 63.8	Cryptogenic	Anticoagulation	Death
				D-dimer >10 000	A9 S0 C9 O1 D9		
				Troponin 0.23			
Patient 6	50s white with HTN, DM2, and HLPD	No symptoms	No symptoms prior	NA	Large artery atherosclerosis (M1 segment stenosis)	Aspirin	Discharged home
						Clopidogrel	
					A1 S3 C9 O0 D0		
Patient 7	40s black with HTN, DM2, and HLPD	Hypoxia	No symptoms prior	CRP 16.7	Cardioembolic (EF 26%)	Thrombectomy	Discharged to rehabilitation
				D-dimer 769	A0 S0 C1 O0 D0	Aspirin	
Patient 8	40s Asian without known medical history	Fever, cough, hypoxia	14 d	CRP 170	Cryptogenic	Anticoagulation	Death
			Hydroxychloroquine	D-dimer >10 000	A9 S0 C0 O2 D9		
				Troponin 0.837			
Patient 9	60s white with HTN and AF	No symptoms	1 d	CRP 6.9	Cardioembolic	Anticoagulation	Home
					A0 S3 C1 O2 D0		
Patient 10	50s white with HTN, DM2, and HLPD	Fever, cough, hypoxia	5 d	CRP 101.1	Cryptogenic	Anticoagulation	Death
				D-dimer 319	A9 S0 C1 O2 D9		
				IL-6 <5			
Patient 11	60s white with HLPD	Fever, cough, hypoxia	18 d	CRP 214.3	Cryptogenic	Anticoagulation	Critically ill
				D-dimer 4841	A9 S3 C3 O1 D9		
				IL-6 264			
Patient 12	70s white with HTN and AF	Cough, hypoxia	10 d	CRP 94.4	Cardioembolic new onset AF after stroke	Alteplase Thrombectomy Anticoagulation	Critically ill
			Hydroxychloroquine	D-dimer >10 000			
					IL-6 870		
Patient 13	60s white with HTN and HLPD	Fever, cough, hypoxia	15 d	CRP 154.4	Cryptogenic	Alteplase Thrombectomy Anticoagulation	Death
				D-dimer 4102	A3 S0 C0 O1 D0		
Patient 14	40s black with no past medical history	Cough	No symptoms prior	CRP 141.8	Cryptogenic	Anticoagulation	Death
				D-dimer >10 000	A1 S3 C0 O1 D0		
				Troponin 0.34			
Patient 15	40s white with DM2 and HLPD	Hypoxia	3 d	CRP 38.8	Cryptogenic	Anticoagulation	Discharged to rehabilitation
				D-dimer >10 000	A0 S0 C0 O1 D0		
				IL-6 <5			
Patient 16	70s white with HTN, HLPD, and AF	Fever, cough, hypoxia	24 d	CRP 76	Cardioembolic	Anticoagulation	Death
			Hydroxychloroquine	D-dimer 3723	A9 S3 C1 O1 D9		
				Tocilizumab			

(Continued)

Table 1. Continued

	Demographics Risk Factors	COVID-19 Symptoms and Severity	Days From COVID-19 Symptoms to Stroke and Any COVID-19 Treatment Before Stroke	Laboratory Values Closest to Time of Stroke	Stroke Subtype*	Treatment	Outcome	
Patient 17	40s white with HTN, HLPD, DM2, and CAD	Fever, cough, hypoxia	No symptoms prior	CRP 17	Cardioembolic (EF=30%) A0 S0 C0 O1 D0	Aspirin	Death	
				D-dimer 2004				
				Troponin 4.5				
Patient 18	60s white with HTN, DM2, HLPD, CAD, and AF	Fever, cough	Unknown	CRP 108	Cardioembolic A3 S3 C1 O2 D9	Anticoagulation	Discharged to rehabilitation	
				D-dimer 226				
				IL-6 30				
Patient 19	70s white with HTN and HLPD	Fever, cough	6 d	CRP 60.3	Cryptogenic A3 S3 C0 O2 D9	Aspirin	Discharged to rehabilitation	
				D-dimer 662				
				Troponin 0.2				
Patient 20	60s black with DM2 and HLPD	Fever, cough, hypoxia	5 d	CRP 70	Cryptogenic A3 S3 C9 O1 D9	Anticoagulation	Death	
				Hydroxychloroquine				D-dimer 4786
				Troponin 0.1				
Patient 21	60s white with HTN, HLPD, and CAD	Fever, cough, hypoxia	27 d	CRP 248	Cryptogenic A9 S3 C3 O1 D9	Anticoagulation	Death	
				Hydroxychloroquine				D-dimer 5870
				Troponin 0.2				
				IL-6 125				
Patient 22	60s with no known medical history	Fever, cough, hypoxia	16 d	CRP 323.73	Cryptogenic A0 S0 C3 O2 D0	Anticoagulation	Death	
				Hydroxychloroquine				D-dimer 3081
Patient 23	40s black with HTN	No COVID-19 symptoms	No symptoms prior	CRP 11.9	Cryptogenic A0 S0 C0 O1 D0	Thrombectomy	Critically ill	
				D-dimer 2735		Anticoagulation		
Patient 24	70s white with DM2	Fever, cough, hypoxia	27 d	CRP 142.1	Cryptogenic A0 S0 C3 O1 D0	Anticoagulation	Death	
				Hydroxychloroquine				D-dimer 2814
				Lopinavir-Ritonavir				
Patient 25	50s white without known medical history	Fever, cough, hypoxia	7 d	CRP 9.9	Cryptogenic A9 S0 C2 O1 D9	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer 3248
Patient 26	60s Asian with HLPD	Fever, cough, hypoxia	10 d	CRP 297	Cryptogenic A3 S3 C2 O1 D0	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer >10000
Patient 27	60s white without known medical history	Fever, cough, hypoxia	17 d	CRP 314.5	Cryptogenic A0 S3 C3 O1 D0	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer 2703
				Tocilizumab				Troponin 0.89
Patient 28	70s white with DM2 and CAD	Fever, cough, hypoxia	3 d	CRP 366.5	Watershed from hypotension A3 S3 C3 O1 D0	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer >10000
				Troponin 0.52				
Patient 29	40s black with HTN, HLPD, and CHF	Fever, cough, hypoxia	15 d	CRP 235	Watershed from hypotension A3 S3 C1 O1 D0	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer 2087
				Troponin 1.42				
Patient 30	50s white with no known medical history	Fever, cough, hypoxia	22 d	CRP 210.78	Cryptogenic A0 S0 C0 O1 D0	Anticoagulation	Discharged to rehabilitation	
				D-dimer 6933				
				Troponin 0.7				
Patient 31	50s with no known medical history	Fever, cough, hypoxia	Unknown	CRP 284.91	Cryptogenic A9 S0 C0 O1 D9	Anticoagulation	Critically ill	
				D-dimer >10000				
				Troponin 1.3				
Patient 32	60s white with HLPD	Fever, cough, hypoxia	15 d	CRP 83.03	Cryptogenic A9 S0 C9 O1 D9	Anticoagulation	Critically ill	
				Hydroxychloroquine				D-dimer 3058
				Troponin 0.7				

D-dimer is in ng/mL, troponin level is in mg/dL, and IL-6 is in pg/mL. AF indicates atrial fibrillation; CAD, coronary artery disease; CHF, congestive heart failure; COVID-19, coronavirus disease 2019; CRP, C-reactive protein measured in ng/mL; DM2, type II diabetes mellitus; EF, ejection fraction; HLPD, hyperlipidemia; HTN, hypertension; IL-6, interleukin 6; and NA, not available.

*Stroke subtype performed using Trial of ORG 10172 in Acute Stroke Treatment criteria and using ASCOD criteria (atherosclerosis, small-vessel disease, cardiac pathology, other cause, and dissection).

group 3 included historical patients with ischemic stroke without COVID-19 over the same time frame (historical controls). We compared baseline characteristics and stroke subtypes between the groups, using the Fischer exact test for categorical variables and nonparametric test for continuous variables. We then performed binary logistic regression analyses to determine baseline characteristics and laboratory values associated with stroke in the setting of COVID-19 compared with historical and contemporary controls. In these models, we included variables with a 2-sided $P < 0.05$ on univariate models. In addition, we performed binary logistic regression analyses to determine the association between COVID-19 related stroke and in-hospital mortality adjusting for age and admission NIHSS score. Analysis was performed using SPSS version 25.0 (Chicago, IL), and a 2-sided $P < 0.05$ was considered significant.

RESULTS

Characteristics of Patients With COVID-19 and Stroke

Out of 3556 patients hospitalized with COVID-19 infection during the study period, we identified a total of 32

patients (0.9%) who had radiologically proven ischemic stroke. Among contemporary controls, 70% (32/46) underwent the COVID-19 test and the rest screened negative and were not tested.

Of the 32 patients (Table 1), stroke was the reason for admission in 43.8%, and COVID-19 symptoms were the reason for admission in 56.2%, with index stroke occurring during the hospital stay. The number of strokes in hospitalized patients with COVID-19 in our health care system, all COVID-19 new hospitalizations in our health care system, and all COVID-19 new hospitalizations in New York City are shown in Figure 1. Among the 32 patients with COVID-19 and stroke, the median (interquartile range [IQR]) age was 62.5 (52.0–69.25) years and 71.9% (23/32) were men; 70.0% (21/30) were white, 20.0% (6/30) were black, 10.0% (3/30) were Asian, 13.3% (4/30) were Hispanic; 65.6% (21/32) were of cryptogenic subtype and 34.4% (11/32) met the criteria for embolic stroke of undetermined source. The median (IQR) time from first COVID-19 symptoms to identification of stroke was 10 (5–16.5) days. The most prominent clinical features were cough (84.4%),

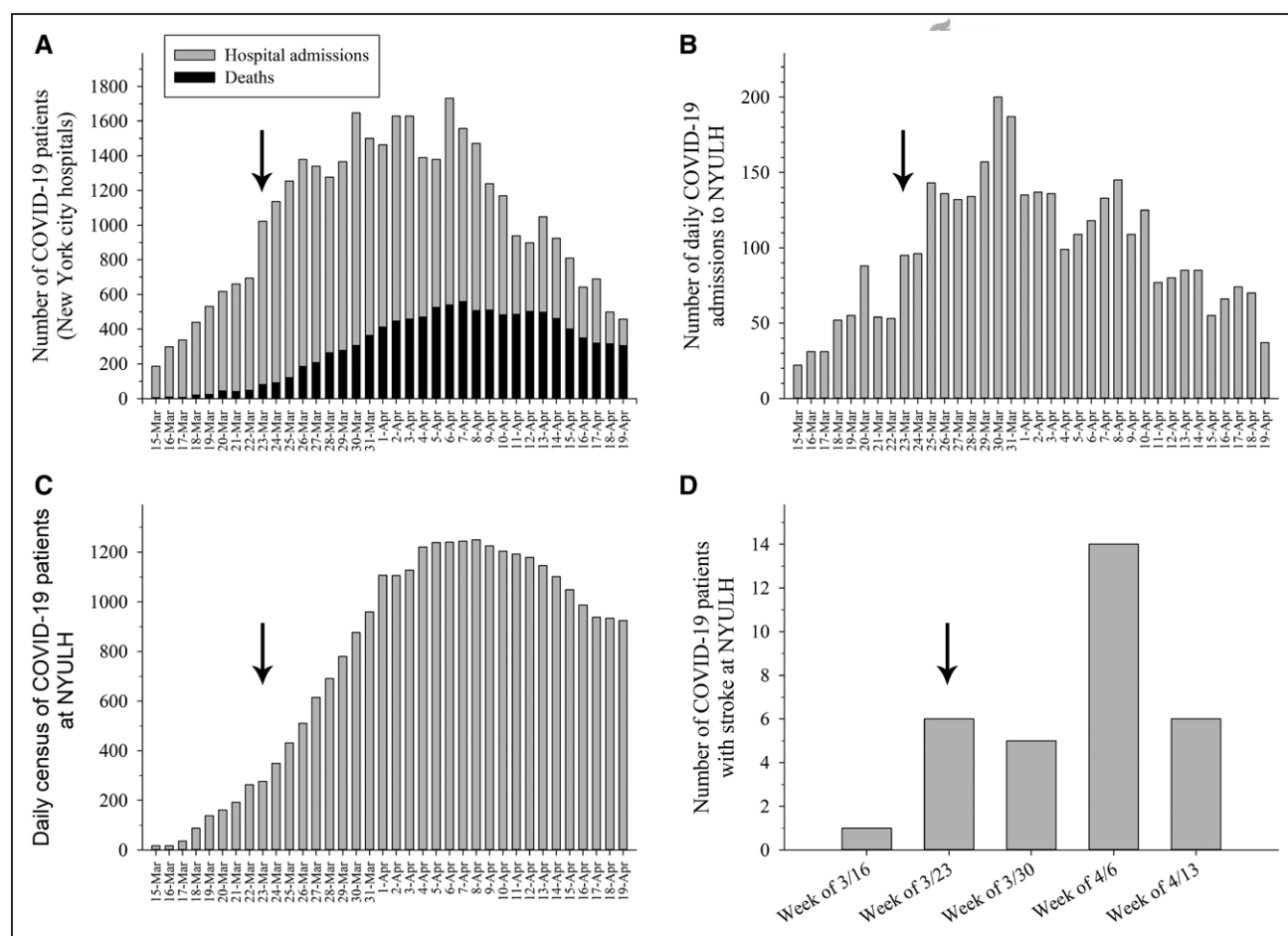


Figure 1. The number of coronavirus disease 2019 (COVID-19) related hospitalizations and ischemic strokes during the study period are shown.

A, COVID-19 hospitalizations (gray bars) and COVID-19 related deaths (black bars) in New York City over the study period. **B**, All COVID-19 admissions to New York University Langone Health (NYULH) during the study period. **C**, Number of in-house COVID-19 positive patients per day. **D**, COVID-19 hospitalizations with imaging proven ischemic stroke. Arrows indicate when the stay at home order was issued (March 22, 2020 at 8 PM).



Figure 2. These images are from 2 patients with ischemic stroke in the setting of coronavirus disease 2019 (COVID-19).

The **left** shows chest imaging (CT or x-ray) and the **right** shows brain imaging of 2 patients with cryptogenic stroke and COVID-19 infection in our patient cohort.

fever (71.9%), and hypoxia (78.1%). At last follow-up, 81.3% (26/32) met the criteria for severe disease; 75.0% (24/32) were dead or critically ill. The median (IQR) D-dimer level closest to the time of the stroke was 3913 ng/mL (2549–10 000), and the median (IQR) C-reactive protein level was 101.1 ng/mL (38.8–214.3). Figure 2 shows brain and chest imaging of 2 patients with COVID-19 and cryptogenic stroke subtype. Treatments before stroke symptoms/diagnosis included hydroxychloroquine (40.6%, n=13), lopinavir-ritonavir (3.1%, n=1), and tocilizumab (6.3%, n=2).

Univariate Analyses

When compared with contemporary stroke controls, patients with COVID-19 and stroke were younger

(median [IQR] in years: 63 [17] versus 70 [18], $P=0.001$), had higher admission NIHSS score (median [IQR] NIHSS score: 19 [23] versus 8 [12], $P=0.007$), had higher peak D-dimer level (median [IQR] in ng/mL: >10 000 [7427] versus 525 [2871], $P=0.011$), were more likely to be treated with anticoagulation (78.1% versus 23.9%, $P<0.001$), more likely to have a cryptogenic stroke subtype (65.6% versus 30.4%, $P=0.003$), and higher inpatient mortality (63.6% versus 9.3%, $P<0.001$; Table 2).

When compared with historical stroke controls, patients with COVID-19 and stroke were more likely to be men (71.9% versus 45.0%, $P=0.012$), had higher admission NIHSS score (median [IQR] NIHSS score: 19 [23] versus 3 [12], $P=0.001$), had higher erythrocyte sedimentation rate level (median [IQR]: 79 [53] versus 41 [52], $P=0.001$), were more likely to have positive troponin

Table 2. Demographic and Clinical Characteristics of Patients With COVID-19 and Stroke Versus Contemporary and Historical Ischemic Stroke Controls

	COVID-19 Positive (A) (n=32)	COVID-19 Negative (B)* (n=46)	Historical Controls (C) (n=80)	P Value (A vs B)	P Value (A vs C)	P Value (B vs C)
Age, median (IQR)	63 (17)	70 (18)	68.5 (23)	0.001	0.078	0.881
Sex (% men)	71.9% (23)	52.2% (24)	45.0% (36)	0.102	0.012	0.464
Hypertension (%)	56.3% (18)	76.1% (35)	80.0% (64)	0.086	0.017	0.655
Diabetes mellitus (%)	34.4% (11)	28.3% (13)	30.0% (24)	0.623	0.658	1.000
Hyperlipidemia (%)	56.3% (18)	50.0% (23)	42.5% (34)	0.649	0.213	0.460
Congestive heart failure (%)	6.3% (2)	10.9% (5)	5.0% (4)	0.694	1.000	0.285
Coronary artery disease (%)	15.6% (5)	26.1% (12)	20.0% (16)	0.404	0.790	0.506
Atrial fibrillation (%)	18.8% (6)	21.7% (10)	25.0% (20)	0.784	0.622	0.829
History of stroke or TIA (%)	3.1% (1)	13.0% (6)	25.0% (20)	0.230	0.007	0.169
Active smoking (%)	0% (0)	4.3% (2)	12.8% (10/78)	0.513	0.059	0.207
NIHSS score, median (IQR)	19 (23)	8 (12)	3 (12)	0.007	0.001	0.071
D-dimer level (ng/mL) closest to stroke diagnosis, median (IQR)	3913 (7451)	526 (2752)	NA	0.023	NA	NA
Highest D-dimer (ng/mL) level during hospitalization, median (IQR)	>10,000 (7427)	525 (2871)	NA	0.011	NA	NA
CRP level, median (IQR), ng/mL	101.1 (175.5)	37.2 (130.7)	NA	0.208	NA	NA
ESR level, median (IQR)	79 (53)	40 (86)	41 (52)	0.172	0.001	0.860
Troponin level ≥ 0.1 mg/dL	45.2% (14/31)	23.1% (9/39)	8.1% (6/74)	0.073	<0.001	0.039
Large vessel occlusion (%)	45.5% (10/22)	27.9% (12/43)	20.3% (16/79)	0.318	0.026	0.372
Alteplase (%)	12.5% (4)	10.9% (5)	7.5% (6)	1.000	0.468	0.528
Thrombectomy (%)	18.8% (6)	17.4% (8)	13.8% (11)	1.000	0.563	0.612
Anticoagulation (%)	78.1% (25)	23.9% (11)	25.0% (20)	<0.001	<0.001	1.000
Stroke subtype				0.011	0.001	0.365
Cardioembolic	21.9% (7)	21.7% (10)	35.0% (28)			
Large vessel disease	6.3% (2)	17.4% (8)	21.3% (17)			
Small vessel disease	0% (0)	13.0% (6)	10.0% (8)			
Cryptogenic	65.6% (21)	30.4% (14)	25.0% (20)			
Other defined mechanisms	6.3% (2)	17.4% (8)	8.8% (7)			
Cryptogenic stroke (vs other mechanism) (%)	65.6% (21)	30.4% (14)	25.0% (20)	0.003	<0.001	0.537
Embolic stroke of undetermined source (vs other mechanism)* (%)	50.0% (11/22)	25.0% (11/44)	24.1% (19/79)	0.055	0.033	1.000
In-hospital death (%)	63.6% (14/22)	9.3% (4/43)	6.3% (5)	<0.001	<0.001	0.718

COVID-19 indicates coronavirus disease 2019; CRP, C-reactive protein measured in ng/mL; ESR, erythrocyte sedimentation rate measure in mm/h; IQR, interquartile range; NA, not available; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Patients with incomplete diagnostic evaluation were excluded, +one patient with cryptogenic stroke excluded due to upper respiratory in the week before admission but no COVID testing performed.

levels (45.2% versus 8.1%, $P < 0.001$), were more likely to have proximal large vessel occlusion (45.5% versus 20.3%, $P = 0.026$), were more likely to be treated with anticoagulation (78.1% versus 25.0%, $P < 0.001$), were more likely to have a cryptogenic stroke subtype (65.6% versus 25.0%, $P < 0.001$), and higher inpatient mortality (63.6% versus 6.3%, $P < 0.001$; Table 2). Conversely, patients with COVID-19 and stroke were less likely to have hypertension (56.3% versus 80.0%, $P = 0.017$) and history of prior stroke or transient ischemic attack (3.1% versus 25.0%, $P = 0.007$).

Among patients with ischemic stroke and COVID-19, cryptogenic stroke subtype was associated with a trend

towards higher d-dimer median (IQR) level in ng/mL at the time of the stroke (4841 [7064] versus 2087 [6306], $P = 0.109$) but not with a significantly higher median (IQR) C-reactive protein level ng/mL (141.8 [169.1] versus 74 [122.8], $P = 0.303$).

Binary Logistic Regression Analyses

In binary logistic regression models (Table 3), when compared with contemporary controls, patients with COVID-19 had non-significantly higher admission NIHSS score (odds ratio [OR] per point increase 1.14 [95% CI, 0.99–1.31], $P = 0.079$) and higher peak d-dimer

Table 3. Binary Logistic Regressions Analyses Showing Clinical and Laboratory Factors Associated With COVID-19 Positivity ($P<0.05$) Compared With Contemporary Controls (Model 1) and Historical Controls (Model 2)

	Adjusted Odds Ratio (95% CI)	P Value
Model 1 (n=36 patients included)		
Age per year increase	0.98 (0.91–1.04)	0.446
NIHSS score per unit increase	1.14 (0.99–1.31)	0.079
Highest fibrinogen per 100 unit increase	1.02 (1.00–1.05)	0.114
Model 2* (n=53 patients included)		
Age per year increase	0.89 (0.78–1.01)	0.062
Male sex	13.48 (0.91–200.27)	0.059
NIHSS per unit increase	1.23 (1.05–1.44)	0.010
History of hypertension	0.57 (0.05–6.87)	0.656
Positive troponin	17.25 (0.58–510.35)	0.099
ESR per unit increase	1.03 (1.00–1.06)	0.041

COVID-19 indicates coronavirus disease 2019; ESR, erythrocyte sedimentation rate measured in mm/h; and NIHSS, National Institutes of Health Stroke Scale.

*History of stroke or transient ischemic attack could not be included in the model due to the <2 occurrences in one of the cells.

level (OR per 100 ng/mL increase 1.02 [95% CI, 1.00–1.05], $P=0.114$). In addition, when adjusting for age and NIHSS score, patients with COVID-19 and stroke had a significantly higher in-hospital mortality than contemporary controls (adjusted OR 64.87 [95% CI, 4.44–987.28], $P=0.002$).

In binary logistic regression models (Table 3), when compared with historical controls, COVID-19 positive patients were non-significantly more likely to be younger (OR per year increase 0.89 [95% CI, 0.78–1.01], $P=0.062$), be men (OR 13.48 [95% CI, 0.91–200.27], $P=0.059$), have elevated troponin levels (OR 17.25 [95% CI, 0.58–510.35], $P=0.099$), a significantly higher admission NIHSS score (OR per point increase 1.23 [95% CI, 1.05–1.44], $P=0.010$), and a significantly higher erythrocyte sedimentation rate level (OR per 1 unit increase 1.03 [95% CI, 1.00–1.06], $P=0.041$). In addition, when adjusting for age and NIHSS score, patients with COVID-19 and stroke had a significantly higher in-hospital mortality than historical controls (adjusted OR 40.27 [95% CI, 5.44–298.01], $P<0.001$).

DISCUSSION

Main Findings

In this multi-ethnic study, we report key demographic and clinical characteristics of patients who develop ischemic stroke associated with acute severe acute respiratory syndrome CoV-2 coronavirus infection. The observed rate of imaging-confirmed acute ischemic stroke in hospitalized patients with COVID-19 of 0.9% was lower

compared with prior reports from Chinese COVID-19 studies. Reasons for difference are unknown but could possibly be related to differences in the patient population studied in our patient population as compared to the other studies and other studies including hemorrhagic stroke and venous sinus thrombosis patients. In addition, the rate of ischemic stroke in our study may be an underestimate as the detection of ischemic stroke symptoms is challenging in those critically ill with COVID-19 infection who are intubated and sedated.

When classified according to the Trial of ORG 10172 in Acute Stroke Treatment criteria,¹ a majority (65.6%) of these patients were classified as cryptogenic stroke and 34.4% met embolic stroke of undetermined source criteria. In contrast, 30.4% of the contemporary COVID negative control group and 25.0% of the historical control group were classified as cryptogenic stroke, in keeping with other modern stroke cohorts.⁴ Patients with COVID-19 and stroke were very ill as a group; 68.8% of patients required mechanical ventilation and 81.3% had severe illness graded according to the American Thoracic Society/Infectious Diseases Society of America Criteria for pneumonia severity.⁵ Our findings are congruent with other studies which reported an increased prevalence of neurological disorders in those with more severe infection.⁶

Our study also shows that the number of COVID-19 positive ischemic strokes has increased initially but seems to have peaked and then decreased. This finding may be related to the overall reduction in COVID-19 admissions, likely due to social distancing and stay at home order (Figure 1). In addition, a therapeutic anticoagulation protocol was instated in our institution the week of April sixth, 2020, which suggests the use of therapeutic anticoagulation in patients with high D-dimer levels. This may have led to a lower rate to thrombotic complications including ischemic stroke in hospitalized COVID-19 positive patients.

Furthermore, the number of patients with stroke hospitalized in the study period were less than historical controls. This witnessed low volume of acute emergencies during the COVID-19 pandemic has been observed in other institutions as well.⁷ The reasons for this are unclear but possibly that patients with stroke and mild symptoms are staying at home and not presenting to the emergency department for stroke treatment.

Mechanisms of Associations

There are multiple, not mutually exclusive, possible mechanisms associating COVID-19 with ischemic stroke. In patients with COVID-19 requiring invasive respiratory support, the median duration of mechanical ventilation has been reported 11 days,⁸ which renders them vulnerable to complications associated with critical illness and a prolonged intensive care unit stay including the risk

for (1) hypotension and inadequate cerebral perfusion; (2) relative hypertension leading to posterior reversible encephalopathy syndrome; (3) septic embolization in the case of superimposed bacterial infection; (4) stress cardiomyopathy and an attendant reduction in left ventricular ejection fraction; and (5) atrial fibrillation with or without a rapid ventricular response.

Additionally, severe COVID-19 has been associated with a hyperinflammatory state (cytokine storm⁹) and hyperviscosity. Progression to disseminated intravascular coagulation is more common in COVID-19 than in other forms of critical illness; one case series reported an incidence of 8.7% with associated 94% mortality.¹⁰ Mortality is associated with higher fibrin-degradation product levels and prolonged prothrombin and activated partial thromboplastin times.¹¹ D-dimer was elevated in 36% of patients with COVID-19 in Wuhan,¹² which was associated with a higher risk of mortality,¹³ an association suggested to be driven at least partially by increased thrombotic complications. Preliminary reports from China describe patients with COVID-19 who developed multiple, bilateral ischemic cerebral infarcts, antiphospholipid antibodies, and hematologic indices suggestive of an acquired thrombophilia.¹⁴ During the first SARS outbreak in the early 2000s, postmortem studies demonstrated a florid vasculitis in multiple arterial beds,¹⁵ and it is not known whether this disease pattern occurs with severe acute respiratory syndrome CoV-2 coronavirus infection.

Potential Therapeutic Implications

There are 2 main implications for clinical care that arise from our data. First, many institutions are currently attempting to balance the benefits of rapid, structured neurological evaluations for patients with COVID-19 exhibiting new neurological symptoms with the risks of exposing multiple team members to infection.¹⁶ As centers develop protocols for the prompt triage and assessment of patients with COVID-19, the co-occurrence of stroke and COVID-19 should be considered when weighing these risks. Second, stroke in the setting of COVID-19 could be a manifestation of systemic hypercoagulability as shown in our patient population with higher D-dimer levels when compared with contemporary controls. Further study is required whether therapeutic anticoagulation in this setting mitigates ischemic stroke risk. In fact, PROTECT COVID (A Randomized Trial of Anticoagulation Strategies in COVID-19) is an ongoing randomized clinical trial testing the safety and efficacy of therapeutic versus prophylactic anticoagulation in patients with COVID-19 infection and mild to moderate elevation in D-dimer level (URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT04359277).

Strengths and Limitations

Our study reports the clinical characteristics of a diverse patient population with ischemic stroke in the setting of COVID-19. We report subject level data, including key clinical variables, markers of disease severity, and diagnostic workup for ischemic stroke.

Our findings should be interpreted with caution in the context of a number of important limitations. First, our study was a relatively small, retrospective, observational study with potential for selection bias. Second, we did not have outcome data on all patients as some are still admitted receiving active clinical care. Third, we do not have complete laboratory investigations or diagnostic imaging for all study subjects, and therefore, some cryptogenic strokes may be related to another undiagnosed mechanism. This likely contributed to an increased prevalence of cryptogenic stroke subtype in patients with COVID-19 infection. Fourth, our study may not be fully representative of all patients with stroke in our healthcare system; patients who are critically ill may not be diagnosed with stroke due to impaired consciousness, confounding systemic illness, or withdrawal of life-sustaining therapies. Fifth, since this report focused on ischemic stroke, we did not provide information on hemorrhagic stroke and venous sinus thrombosis occurring in patients with COVID-19. These complications in the setting of COVID-19 need further study. Finally, since not all patients were tested for COVID-19, it is possible that some asymptomatic patients with stroke may have been COVID positive but were included in the control group.

Conclusions

We observed a relatively low rate of imaging proven ischemic stroke in hospitalized patients with COVID-19 infection. In patients with COVID-19 and ischemic stroke, a majority of strokes were classified as cryptogenic, possibly related to an acquired hypercoagulability, and were associated with increased mortality. Ongoing studies are testing the utility of therapeutic anticoagulation for stroke and other thrombotic event prevention, in select patients with COVID-19 and laboratory evidence suggestive of hypercoagulability.

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REFERENCES

- Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41. doi: 10.1161/01.str.24.1.35
- Hart RG, Diener HC, Coutris SB, Easton JD, Granger CB, O'Donnell MJ, Sacco RL, Connolly SJ; Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014;13:429–438. doi: 10.1016/S1474-4422(13)70310-7
- Sirimarco G, Lavallée PC, Labreuche J, Meseguer E, Cabrejo L, Guidoux C, Klein IF, Olivot JM, Abboud H, Adraï V, et al. Overlap of diseases underlying ischemic stroke: the ASCOD phenotyping. *Stroke*. 2013;44:2427–2433. doi: 10.1161/STROKEAHA.113.001363
- Ornello R, Degan D, Tiseo C, Di Carmine C, Perciballi L, Pistoia F, Carolei A, Sacco S. Distribution and temporal trends from 1993 to 2015 of ischemic stroke subtypes: a systematic review and meta-analysis. *Stroke*. 2018;49:814–819. doi: 10.1161/STROKEAHA.117.020031
- Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, et al; Infectious Diseases Society of America; American Thoracic Society. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27–S72. doi: 10.1086/511159
- Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, Chang J, Hong C, Zhou Y, Wang D, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China [published online April 10, 2020]. *JAMA Neurol*. 2020. <https://jamanetwork.com/journals/jamaneurology/fullarticle/2764549>. Accessed April 15, 2020. doi: 10.1001/jamaneuro.2020.1127
- Garcia S, Albaghdadi MS, Meraj PM, Schmidt C, Garberich R, Jaffer FA, Dixon S, Rade JJ, Tannenbaum M, Chambers J, et al. Reduction in ST-segment elevation cardiac catheterization laboratory activations in the United States during COVID-19 pandemic [published online April 7, 2020]. *J Am Coll Cardiol*. 2020. <http://www.onlinejacc.org/content/early/2020/04/07/jacc.2020.04.011>. Accessed April 15, 2020. doi: 10.1016/j.jacc.2020.04.011
- Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, Greninger AL, Pipavath S, Wurfel MM, Evans L, et al. Covid-19 in critically ill patients in the seattle region - case series [published online March 30, 2020]. *N Engl J Med*. 2020. <https://www.nejm.org/doi/full/10.1056/NEJMoa2004500>. Accessed April 15, 2020. doi: 10.1056/NEJMoa2004500
- Chen G, Wu D, Guo W, Cao Y, Huang D, Wang H, Wang T, Zhang X, Chen H, Yu H, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620–2629.
- Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. *J Thromb Haemost*. 2020;18:844–847. doi: 10.1111/jth.14768
- Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China [published online March 13, 2020]. *JAMA Intern Med*. 2020. <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184>. Accessed April 15, 2020. doi: 10.1001/jamainternmed.2020.0994
- Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta*. 2020;505:190–191. doi: 10.1016/j.cca.2020.03.004
- Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054–1062. doi: 10.1016/S0140-6736(20)30566-3
- Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, Chen H, Ding X, Zhao H, Zhang H, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. *N Engl J Med*. 2020;382(17):e38.
- Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, Cai J, Li X, Kang W, Weng D, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. *J Pathol*. 2003;200:282–289. doi: 10.1002/path.1440
- Majersik JJ, Reddy VK. Acute neurology during the COVID-19 pandemic: supporting the front line [published online April 13, 2020]. *Neurology*. 2020. <https://n.neurology.org/content/early/2020/04/13/WNL.0000000000009564>. Accessed April 15, 2020. doi: 10.1212/WNL.0000000000009564