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Characteristics of a Diverse Cohort of Stroke Patients with SARS-CoV-2 and Outcome by Sex

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Background and Purpose: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is associated with stroke. The role of sex on stroke outcome has not been investigated. To objective of this paper is to describe the characteristics of a diverse cohort of acute stroke patients with COVID-19 disease and determine the role of sex on outcome. *Methods:* This is a retrospective study of patients with acute stroke and SARS-CoV-2 infection admitted between March 15 to May 15, 2020 to one of the six participating comprehensive stroke centers. Baseline characteristics, stroke subtype, workup, treatment and outcome are presented as total number and percentage or median and interquartile range. Outcome at discharge was determined by the modified Rankin Scale Score (mRS). Variables and outcomes were compared for males and females using univariate and multivariate analysis. *Results:* The study included 83 patients, 47% of which were Black, 28% Hispanics/Latinos, and 16% whites. Median age was 64 years. Approximately 89% had at least one preexisting vascular risk factor (VRF). The most common complications were respiratory failure (59%) and septic shock (34%). Compared with females, a higher proportion of males experienced severe SARS-CoV-2 symptoms requiring ICU hospitalization (73% vs. 49%; $p = 0.04$). When divided by stroke subtype, there were 77% ischemic, 19% intracerebral hemorrhage and 3% subarachnoid hemorrhage. The most common ischemic stroke etiologies were cryptogenic (39%) and cardioembolic (27%). Compared with females, males had higher mortality (38% vs. 13%; $p = 0.02$) and were less likely to be discharged home (12% vs. 33%; $p = 0.04$). After adjustment for age, race/ethnicity, and number of VRFs, mRS was higher in males than in females (OR = 1.47, 95% CI = 1.03–2.09). *Conclusion:* In this cohort of SARS-

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CoV-2 stroke patients, most had clinical evidence of coronavirus infection on admission and preexisting VRFs. Severe in-hospital complications and worse outcomes after ischemic strokes were higher in males, than females.

Key Words: COVID-19—Stroke—Outcome—Sex—Race

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Introduction

Coronavirus disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), usually presents as a respiratory illness. Neurological manifestations can be seen in 36.4% of patients.¹ Patients with vascular risk factors (VRFs), including history of stroke, tend to have worse prognosis.² COVID-19 triggers a robust inflammatory response which leads to hypercoagulability and thromboembolism.³ Reports of stroke in patients with COVID-19 are mostly limited to small case series or case reports of ischemic stroke (IS), though intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) have also been reported.^{4,5} Thus, our understanding of the relationship between SARS-CoV-2 and stroke is evolving. One key variable is sex. Data from observational studies and registries show that males with COVID-19 have a higher mortality rate than females.⁶ Pre-pandemic epidemiological studies, in contrast, have shown that stroke mortality is higher among females, particularly at older age.⁷ The effect of sex on stroke patients with SARS-CoV-2 infection has not been investigated. The aim of this study was to describe the stroke characteristics of patients with SARS-CoV-2 and the presence of sex-specific variations in stroke presentation, complications, and outcome.

Material and Methods

Study design and participants

This is a retrospective multi-center study of consecutive stroke patients admitted between March 15, 2020 and May 15, 2020 to one of the six comprehensive stroke centers in the Chicago area (Loyola University Medical Center, Northwestern Memorial Hospital, Rush University Medical Center, University of Chicago Medical Center, University of Illinois Health, or AMITA Health Alexian Brothers Hospital). The inclusion criteria were adult patients with confirmed diagnosis of SARS-CoV-2 infection and radiological evidence of stroke. The study was approved by the local Institutional Review Board at each participating institution and follows the guidelines set forth by the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Data collection

Baseline characteristics, laboratory and radiologic findings, in-hospital complications, treatments, and outcomes at hospital discharge were extracted from the electronic

health records. Laboratory data included blood and cerebrospinal fluid (CSF) studies. For blood values, we analyzed first and maximum values for the comprehensive metabolic panel, complete blood count, coagulation studies, antiphospholipid antibodies and inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, D-dimer, fibrinogen, ferritin, Interleukin-6, and lactate dehydrogenase levels). Data from head computed tomography (CT), computed tomographic angiography, brain magnetic resonance imaging (MRI), magnetic resonance angiography, conventional angiography, and transthoracic echocardiography or transesophageal echocardiography results were collected. SARS-CovV-2 was detected from nasopharyngeal or oropharyngeal swabs using Polymerase Chain Reaction. Patients were grouped based on clinical severity into 1) asymptomatic, 2) mild to moderate symptoms, and 3) severe symptoms, defined as those requiring intensive care unit (ICU) admission with or without mechanical ventilation.

Stroke assessment

Patients were subcategorized into IS, ICH or SAH based on radiographic findings. IS severity was assessed using the National Institutes of Health Stroke Scale score on admission. Stroke mechanism was classified using the TOAST criteria into 1) large-artery atherosclerosis, 2) cardioembolism, 3) small-vessel occlusion, 4) stroke of other determined etiology, and 5) cryptogenic stroke or stroke of undetermined etiology.⁸ ICH severity was assessed using the ICH score and the Glasgow coma scale score on admission. SAH grade was assessed with the Fisher scale and Hunt and Hess scores at presentation. Location was categorized into cortical, subcortical, infratentorial or mixed locations. Disposition and outcome, determined by the modified Rankin Scale (mRS) score at discharge, were reported for each stroke subtype.⁹

Statistical analysis

Results are presented as median and interquartile ranges (IQR) or total number (n) and percentage (%). Baseline characteristics and stroke subtypes were compared for males and females using Fisher's exact test or Pearson's Chi-Square for categorical variables and Mann-Whitney U test for continuous variables. The association between sex (with female being the reference category) and mRS at hospital discharge, was investigated using multivariate logistic regression analysis adjusting for age, race/ethnicity, and number of VRFs. Statistical analyses

were done using SPSS version 27 (SPSS Inc, Chicago, IL). All tests of significance were 2-tailed, with a threshold for significance of $p < 0.05$.

Results

Of the 83 patients included in the study, 53% were males. Median age for all patients was 64, and 75% were Hispanic or Black. [Table 1](#) depicts cohort characteristics. The most common VRF at baseline was arterial hypertension (75%) followed by diabetes mellitus (59%). Eighty nine percent had at least one VRF at baseline and 41% had three to four. Stroke as the presenting diagnosis was observed in 32 (39%) patients. Approximately 94% of the patients had symptoms of COVID-19 and 61% required ICU admission. The most frequent stroke subtype was IS (77%), followed by ICH (19%) and SAH (4%). Respiratory failure was the most common complication (59%). The rate of venous thromboembolic events was 25%. Echocardiographic information was available in 73% of cases. The most common cardiovascular abnormalities were reduced left ventricular ejection fraction (21%) followed by left atrial enlargement (15%), heart failure (11%), acute myocardial infarction (7%) and new onset atrial fibrillation/atrial flutter (6%). Head imaging was obtained in all patients, with majority having a non-contrast computed tomography (87%). MRI brain was available for 56% of patients and vascular imaging of the head or neck for 72%.

Initial median laboratory values on admission were elevated above normal ranges for LDH, D-dimer, high-sensitive cardiac troponin, serum ferritin, CRP, serum creatinine, blood urea nitrogen and IL-6 ([Supplemental Table I](#)). Throughout the hospital stay, all these laboratory values increased ([Supplemental Table II](#)). Anti-cardiolipin antibodies were obtained in 10 patients ([Supplemental Table III](#)). CSF studies were available in four patients, with a median protein level of 109 mg/dL and median red blood cell count of 138 number/ μ L. All CSF studies were negative for SARS-CoV-2.

Males and females had similar baseline characteristics. However, females had higher rates of mild to moderate COVID-19 symptoms while males had higher rates of severe symptoms requiring ICU admission. Males also had higher rates of decreased ejection fraction (33% vs 11%, $p = 0.03$) and higher levels of LDH, albumin, total bilirubin and BUN on admission compared with females.

Ischemic stroke characteristics

Approximately 77% of the patients had neuroimaging evidence of acute IS. Strokes were noted on admission in approximately half of the cases, and 72% were clinically symptomatic with a median NIHSS of 8. Infarcts were most often located cortically, and the most common etiology was stroke of undetermined etiology (39%) followed by cardioembolism (27%). A quarter of the patients had bilateral hemispheric infarction. The median time from

last known well to hospital presentation was 1 day. Eight percent were treated with tissue plasminogen activator (tPA) and 11% with endovascular thrombectomy. The mortality was 27% and the median mRS at discharge was 4. Withdrawal of care occurred in 7% of cases. No differences were observed in withdrawal of care among males (21%) and females (15%; $p = 0.74$). Among those who survived, the median mRS was 4. Males had higher case fatality, higher median mRS, and lower rates of good outcome than females ([Table 2](#)). Females, in turn, were more likely to be discharged home than males. In univariate analysis, males had increased mRS at hospital discharge than females (OR=1.5; 95% CI = 1.07–2.12). This difference remained statistically significant after adjustment for age, race/ethnicity, and number of VRFs (OR = 1.47, 95% CI = 1.03–2.09) ([Table 3](#)).

Hemorrhagic stroke characteristics

ICH was diagnosed in 19% of patients with 38% of cases discovered during hospitalization. Approximately 88% were clinically symptomatic with a median GCS score of 14 and ICH score of 2. The most common causes of ICH were spontaneous (44%) and anticoagulation-related (44%). Mortality rate was approximately 50% and the median mRS of those who survived was 2 ([Table 4](#)). In our cohort, there were three SAH. All cases were clinically severe with an average GCS of 6, Fisher scale score of 3 and Hunt and Hess grade of 4, and two of them expired.

Discussion

In this multicenter study of patients with stroke and SARS-CoV-2 infection admitted to comprehensive stroke centers in the Chicagoland area, males were more likely than females to have severe COVID-19 manifestations and worse ischemic stroke outcome at hospital discharge.

Approximately 77% of the strokes were ischemic, 19% ICH, and 4% SAH, which is similar to the general distribution of stroke subtypes reported in non-pandemic nationwide registries and population studies.⁷ Our current understanding of stroke in COVID-19 is modeled after small observational studies and select populations. The study published by Mao et al¹, for example, included 214 patients with coronavirus disease who exhibited neurologic involvement. Six were diagnosed with stroke, and five of these had severe COVID-19 disease. In our cohort, we observed that the presentation of stroke patients with SARS-CoV-2 was more pleomorphic with almost 40% of our cases having mild to moderate symptoms of COVID-19 or being asymptomatic at presentation. Males were more likely to have severe SARS-CoV-2 manifestations requiring ICU admission and mechanical ventilation, as well as higher levels of LDH at baseline and a trend for higher maximum levels of markers of inflammation. These observations are in agreement with cumulative data obtained from different countries that show that males

Table 1. Demographic and clinical characteristics of all stroke patients by sex

Variable	All N = 83	Male N = 44	Female N = 39	p value
Age*	64 (18)	63 (17)	68 (17)	0.60
Body Mass Index, (kg/m2)*	28 (11)	28 (7)	31 (13)	0.31
<i>Race</i>				
White [†]	13 (16)	7 (16)	6 (15)	0.99
Black [†]	39 (47)	17 (39)	22 (56)	0.08
Hispanic [†]	23 (28)	14 (32)	9 (23)	0.26
Other/Unknown [†]	8 (10)	6 (14)	2 (5)	0.18
<i>Social history</i>				
Smoking, n (%)	8 (10)	5 (11)	3 (8)	0.72
Alcohol use, n (%)	9 (11)	7 (16)	2 (5)	0.16
Illicit drug use, n (%)	5 (6)	2 (5)	3 (8)	0.66
<i>Prior medical history</i>				
Hypertension [†]	62 (75)	35 (80)	27 (69)	0.32
Diabetes mellitus [†]	49 (59)	29 (66)	20 (51)	0.19
Hyperlipidemia [†]	31 (37)	19 (43)	12 (31)	0.27
Coronary artery disease [†]	16 (19)	10 (23)	6 (15)	0.42
Atrial fibrillation/Atrial flutter [†]	8 (10)	5 (11)	3 (8)	0.72
Heart Failure [†]	11 (13)	7 (16)	4 (10)	0.53
Stroke [†]	13 (16)	5 (11)	8 (21)	0.37
Renal disease [†]	22 (27)	10 (23)	12 (31)	0.46
COPD/Chronic Asthma [†]	4 (5)	2 (5)	2 (5)	0.90
<i>Cumulative number of Vascular Risk Factors[§]</i>				
0 [†]	9 (11)	4 (9)	5 (13)	0.73
1-2 [†]	36 (43)	19 (43)	17 (44)	0.99
3-4 [†]	34 (41)	18 (41)	16 (41)	0.99
≥5 [†]	4 (5)	3 (7)	1 (3)	0.62
<i>Prior medication use</i>				
Antiplatelets-Single [†]	29 (35)	16 (36)	13 (33)	0.82
Antiplatelets-Double [†]	4 (5)	1 (3)	3 (8)	0.34
Anticoagulation-warfarin [†]	2 (2)	0	2 (5)	0.22
Direct oral anticoagulants [†]	11 (13)	8 (18)	3 (8)	0.20
ACEI or ARB [†]	18 (22)	12 (27)	6 (15)	0.29
Statins [†]	30 (36)	16 (36)	14 (36)	0.99
<i>SARS-COV-2 Clinical severity</i>				
Asymptomatic [†]	6 (7)	3 (7)	3 (8)	0.99
Mild to moderate [†]	26 (31)	9 (20)	17 (44)	0.03
Severe (ICU hospitalization) [†]	51 (61)	32 (73)	19 (49)	0.04
Severe (ICU hospitalization and mechanical ventilation) [†]	43 (52)	27 (61)	16 (41)	0.08
<i>In-hospital complications</i>				
Respiratory failure [†]	49 (59)	29 (66)	20 (51)	0.19
Septic shock [†]	28 (34)	18 (41)	10 (26)	0.17
Renal failure (dialysis) [†]	21 (25)	15 (34)	6 (15)	0.08
Liver failure [†]	7 (8)	4 (9)	3 (8)	0.99
Heart Failure [†]	9 (11)	7 (16)	2 (5)	0.16
New onset atrial fibrillation/atrial flutter [†]	5 (6)	3 (7)	2 (5)	0.99
Myocardial infarction [†]	6 (7)	3 (7)	3 (8)	0.99
Deep vein thrombosis [†]	17 (20)	8 (18)	9 (23)	0.59
Pulmonary embolism [†]	4 (5)	1 (3)	3 (8)	0.34
Systemic embolism [†]	5 (6)	3 (7)	2 (5)	0.99
<i>Echocardiographic findings</i>				
Echocardiogram done [†]	61 (73)	33 (75)	28 (72)	0.62
No abnormalities [†]	30 (49)	15 (45)	15 (54)	0.82
Left atrial enlargement [†]	9 (15)	4 (12)	5 (18)	0.72
Right ventricular enlargement [†]	7 (11)	5 (15)	2 (7)	0.43
Acute pulmonary hypertension [†]	4 (7)	1 (3)	3 (11)	0.33
Diffuse myocardial inhibition [†]	2 (3)	0	2 (7)	0.21
Left ventricular ejection fraction ≤50% [†]	14 (21)	11 (33)	3 (11)	0.03

ACEI: Angiotensin converting enzyme inhibitors ARB: Angiotensin II receptor type 1 blockers.

*median (IQR).

[†]n (%).

[§]Includes history of hypertension, diabetes mellitus, hypercholesterolemia, stroke, atrial fibrillation, chronic kidney disease and smoking.

Table 2. Characteristics of ischemic stroke patients

Variable	All N = 64	Male N = 34	Female N = 30	P value
Stroke Onset				
In-hospital [¶]	28 (44)	17 (50)	11 (37)	0.22
In the community [¶]	34 (53)	16 (47)	18 (60)	0.22
Cannot be determined [¶]	2 (3)	1 (3)	1 (3)	0.99
Symptomatic stroke [¶]	46 (72)	24 (71)	22 (73)	0.81
Incidentally found [¶]	18 (28)	10 (29)	8 (27)	0.81
LKW to symptom discovery, days*	0.4 (1.6)	0.4 (1.7)	0.5 (1.1)	0.78
LKW to hospital presentation, days*	0.6 (2.6)	0.5 (1.7)	1.0 (3.1)	0.16
NIHSS at admission*	8 (21)	10 (18)	4 (12)	0.08
Location				
Cortical [¶]	39 (61)	22 (65)	17 (57)	0.41
Subcortical, supratentorial [¶]	5 (8)	3 (9)	2 (7)	0.42
Infratentorial [¶]	5 (8)	0	5 (17)	0.02
Mixed [¶]	15 (23)	9 (26)	6 (20)	0.57
Mechanism				
Cryptogenic [¶]	25 (39)	10 (23)	15 (38)	0.20
Large-artery atherosclerosis [¶]	7 (11)	3 (7)	4 (10)	0.69
Cardioembolism [¶]	17 (27)	11 (25)	6 (15)	0.25
Lacunar [¶]	6 (9)	4 (9)	2 (5)	0.99
Stroke of other determined etiology [¶]	8 (9)	5 (11)	3 (8)	0.71
Treatment				
Tissue plasminogen activator [¶]	5 (8)	3 (7)	2 (5)	0.75
Mechanical thrombectomy [¶]	7 (11)	4 (9)	3 (8)	0.82
Disposition				
Home [¶]	14 (22)	4 (12)	10 (33)	0.04
Acute Rehabilitation [¶]	16 (25)	8 (24)	8 (27)	0.78
Other ^{¶,§}	16 (25)	9 (26)	7 (23)	0.77
Death [¶]	17 (27)	13 (38)	4 (13)	0.02
mRS (all patients)*	4.0 (3.0)	5.0 (2.0)	4.0 (3.0)	0.02
mRS (survivors)*	4.0 (2.0)	4.0 (2.0)	3.5 (3.0)	0.03

LKW: last known well; mRS: modified Rankin Scale; NIHSS: National Institute of Health Stroke Scale.

[¶]n (%).

*median (IQR).

[§]Includes skilled nursing facility, long-term acute care hospitals, and hospice.

with COVID-19 have a 1.7 times higher case fatality rate than females.⁶ It has been proposed that sex-specific differences in innate and adaptive immune mechanisms, by regulating the development of autoimmunity and the response to the viral infection may explain, at least in part, this phenomenon.⁶

In a cohort of 32 ischemic stroke patients with COVID-19 admitted to a New York Healthcare system, cryptogenic stroke accounted for approximately 66% of all the cases and large artery occlusion for 6.3%.¹⁰ In another single center study that included 31 acute ischemic cases, 52% of the patients had cryptogenic stroke, 42% cardioembolism, and 7% large artery atherosclerosis.¹¹ There were no lacunar infarctions in either study. In comparison, we observed that the frequency of cryptogenic stroke in our study was 39%, large artery atherosclerosis 11% and lacunar infarction 9%. A direct comparison among the studies is confounded in that our cohort included more Blacks and Hispanics, who in combination, accounted for 84% of all ischemic stroke cases. In

comparison, the other studies were largely enriched with whites. In addition, similar to a recent study that included 20 ischemic stroke patients,¹² our cohort had a higher prevalence of traditional VRFs which suggests a higher burden of atherosclerotic disease.

Incomplete stroke workup is likely to spuriously inflate the proportion of patients categorized as cryptogenic stroke. In addition, patients with severe COVID-19 who were hemodynamically unstable may have been deemed unsafe for diagnostic stroke studies. In one of the studies referenced above, almost a quarter of the strokes had incomplete evaluation.¹¹ Thus, it is plausible that center-specific variations in the availability of ancillary diagnostic tests could affect the rate of cryptogenic stroke reported in different studies.

Several observational studies have shown that myocardial injury is association with coronavirus infection.¹³ In a cohort of 21 patients with severe COVID-19, almost a third of them had newly diagnosed cardiomyopathy.¹⁴ In another study including 191 patients with COVID-19,

Table 3. Adjusted logistic regression analysis for mRS score and sex in ischemic stroke patients (dependent variable is sex with female being the reference category)

Variable	Adjusted OR (95% CI)	P value
Age, years	0.98 (0.93–1.03)	0.47
Race/Ethnicity		
White	Reference	
Black	1.26 (0.25–6.3)	0.78
Hispanic	2.7 (0.5–14.8)	0.25
Unknown	8.9 (0.6–126.5)	0.11
Vascular Risk Factors		
None	Reference	
1-2	1.49 (0.19–11.67)	0.71
3-4	1.46 (0.16–13.34)	0.74
≥ 5	n/a*	
mRS score [^]	1.47 (1.03–2.09) [£]	0.03

*low n, unable to compute.

[^]modified Rankin Scale score.[£]referred to any 1 point increase in mRS score.

23% had new or worsening heart failure.¹⁵ In our sample, the most frequently encountered echocardiographic abnormality was reduced left ventricular ejection fraction which, in univariate analysis, was more commonly seen in males than in females. Other abnormalities included left atrial or right ventricular enlargement, newly diagnosed arrhythmias, heart failure, or myocardial infarction. It is not clear from our study if these abnormalities were the cause of the stroke or contributed to outcome. However, our findings highlight the importance of cardiac screening and monitoring in patients with SARS-CoV-2 and stroke.

In relation to ischemic stroke, based on the hypercoagulable state associated with COVID-19 and the results obtained in select cohorts, it was proposed that elevated APL titers leading to procoagulability and large artery thrombosis is a common mechanism of cerebral ischemia in SARS-CoV-2.^{4,16} In our study, one of 10 patients had IgM anti-cardiolipin antibodies and three had both IgG

Table 4. Characteristics of patients with intracerebral hemorrhage

Variable	All N = 16	Male N = 9	Female N = 7	P value
Onset				
In-hospital [¶]	6 (38)	2 (22)	4 (57)	0.30
In the community [¶]	10 (63)	7 (78)	3 (43)	0.30
Symptomatic stroke [¶]	14 (88)	7 (78)	7 (100)	0.48
Incidentally found [¶]	2 (12)	2 (22)	0	0.48
Onset to presentation, hours*	5 (7)	7 (5)	6 (0.1)	0.70
Glasgow Coma Scale on admission*	14 (3)	13 (4)	14 (1)	0.25
ICH score*	2 (4)	2 (2)	2 (2)	0.65
Location				
Cortical [¶]	7 (41)	6 (67)	1 (14)	0.06
Subcortical, supratentorial [¶]	5 (29)	2 (22)	3 (43)	0.60
Infratentorial [¶]	3 (18)	1 (11)	2 (29)	0.55
Mixed [¶]	1 (6)	0	1 (14)	0.44
Mechanism				
Spontaneous [¶]	7 (44)	3 (33)	4 (57)	0.62
Traumatic [¶]	1 (6)	1 (6)	0	0.99
Anticoagulation related [¶]	7 (44)	5 (56)	2 (29)	0.36
Coagulopathy (Liver Failure) [¶]	1 (6)	0	1 (14)	0.44
Disposition				
Home [¶]	2 (13)	2 (22)	0	0.48
Acute Rehabilitation [¶]	2 (13)	1 (11)	1 (14)	0.99
Other ^{¶,§}	3 (19)	2 (22)	1 (14)	0.48
Death [¶]	8 (50)	4 (44)	4 (57)	0.99
Unknown [¶]	1 (6)	0	1 (14)	0.44
mRS (all patients) *	6 (4)	4 (5)	6 (1)	0.25
mRS (IQR) (survivors)*	2 (1)	1 (4)	3.5 (3)	0.41

ICH: intracerebral hemorrhage; mRS: modified Rankin scale.

*median (IQR).

[¶]n (%).[§]Includes skilled nursing facility, long-term acute care hospitals, and hospice.

and IgM anti-cardiolipin antibodies. The titers in these four cases were modestly elevated. We did not identify cases with elevated titers of anti- β 2-glycoprotein-1 antibodies. Though only a small number of patients had testing for APL, our results suggest that the development of APL in stroke patients with SARS-CoV-2 may not be as common as previously suggested.

SARS-CoV-2 RNA has been identified in the cerebrospinal fluid of a COVID-19 admitted with meningitis suggesting the possibility of a direct viral invasion of the brain.¹⁷ In our cohort, CSF analysis was done in only 4 patients. In all of them, the evaluation for SARS-CoV-2 was negative.

The rates of tPA in this study was almost half of our historical averages in our geographic area. In most cases, tPA was not offered due to late arrival to the hospital and unknown time of symptom onset. The mortality at hospital discharge, though elevated at 25%, was better than the 32% and 65% reported in other studies.^{10,11} Mortality and disability at hospital discharge were worse for males than females despite both groups having similar baseline characteristics. It is possible that the poor outcomes were influenced by more severe SARS-CoV-2 disease in males rather than stroke severity itself.

There is a paucity of information about hemorrhagic stroke in SARS-CoV-2 patients. In this study, we included 16 ICH and 3 SAH patients. A previous study including 33 COVID-19 patients with ICH suggested anticoagulation therapy may increase the risk of ICH.¹⁸ Our results are in agreement with this observation as anticoagulation-associated ICH was one of the leading causes of ICH. There is virtually no information about SAH in SARS-CoV-2 patients. Our three cases had high-grade SAH. In general, patients with ICH and SAH had a poor outcome with a mortality of approximately 50%.

Our study has several limitations. First, given the retrospective and observational nature of the study, the stroke workup was incomplete in some cases. Second, outcomes were limited to hospital discharge and long-term data are still lacking. Third, the sample size was small and thus limited our ability to perform subgroup analysis. Fourth, in this study we included patients with radiologic evidence of acute cerebrovascular injury. Though this approach enhances the accuracy of the diagnosis, we cannot exclude the possibility of missing stroke patients who were critically ill and unable to undergo brain imaging. Nonetheless, our study is the largest cohort of SARS-CoV-2 patients with stroke yet reported. Also, 75% of our cohort were Blacks and Hispanics which have been identified as populations disproportionately affected by COVID-19.¹⁹ Furthermore, given the geographic location of the multiple institutions that participated in this initiative, our findings are representative of an urban and near-suburban metropolitan area. In comparison, most papers that previously reported about stroke in COVID-19 patients were limited to one center or one health system.

In conclusion, we present the characteristics of stroke patients with proven SARS-CoV-2 infection. The large majority of our patients had pre-existing VRFs and manifested changes in laboratory markers of inflammation and coagulability. We identified males as more likely to develop severe COVID-19 syndrome and to have worse ischemic stroke outcomes at hospital discharge. Further studies are necessary to elucidate the mechanisms that explain these associations.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jstrokecerebrovasdis.2020.105314](https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.105314).

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