JVIN | Journal of Vascular and Interventional Neurology

OFFICIAL JOURNAL OF ZEENAT QURESHI STROKE INSTITUTE

Concurrent SARS-CoV-2 Infection is Associated with Higher Rates of Death or Disability at 90 Days in Stroke Patients – Analysis from a US Comprehensive Stroke Center

Nour Abdelhamid, MD[1], Alan Pan, MS[1], Salman Farooq, MD[2,*], Mohamed Fahmy[3], Ahmed Eid[4], Tanu Garg, MD[1], John Volpi, MD[1], David Chiu, MD[1], Vivek Misra, MD[1], Yi Zhang, MD[5], Danish Kherani, MD[1], Syed Gillani, MD[1], Charles McCane, CCRC[1], Jason Lee, BS, RN[1], Ken Ling, MD[1], Jennifer Meeks, MS[1], Farhaan Vahidy, PhD[1], Rajan Gadhia, MD[1]

[1] *Stanley H Appel Department of Neurology, Eddy Scurlock Stroke Center, Houston Methodist Hospital*

[2] *Department of Neurology, Medical College of Wisconsin*

[3] *Department of Pulmonary Critical Care, University of Texas Medical Branch at Galveston*

[4] *Department of Internal Medicine, OhioHealth*

[5] *Department of Neurosurgery, Houston Methodist Hospital*

Abstract

Background— Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection is associated with cerebrovascular events. Given the novelty of this viral illness, there is paucity of data regarding this association. We aim to provide further evidence by reporting risk factors, clinical course and outcome in patients with SARS-CoV-2 infection presenting at our institute with cerebrovascular complications.

Methods— We extracted a cross-sectional analysis of data from our institutional HOPES stroke registry to identify patients with SARS-CoV-2 infection who had cerebrovascular events. We analyzed the data and compared demographics, laboratory, and clinical presentations across all stroke patients during the peak pandemic period.

Results— 22 patients with SARS-CoV-2 infection were treated at our medical center between March 2020 and October 2020. Majority of these patient (~80%) suffered acute ischemic strokes while ~20% experienced intracranial hemorrhage (ICH). We found that the majority of our cohort presented with neurological manifestations (77%) prior to the respiratory illness, yet the cause of mortality was largely secondary to the pulmonary complications of COVID-19 (56%). Patients with SARS-CoV-2 infection who suffered cerebrovascular events had a worse 90-day outcome, as defined by the modified Rankin Scale score. Additionally, patients with SARS-CoV-2 infection who received chemical or mechanical thrombolysis had higher rate of intracranial bleeding, with 5 of the 7 (71%) treated patients dying during their hospitalization.

Conclusions— Neurological outcome appears to be worse in patients with SARS-CoV-2 infection when compared to patients without SARS-CoV-2 infection experiencing cerebrovascular events.

Keywords— Acute stroke; COVID-19; Stroke outcome; Infectious disease.

BACKGROUND

Viral syndrome resulting from the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), coronavirus disease 2019 (COVID-19), has spread globally since its first reported case in Wuhan, China in December 2019 and has resulted in more than 1.5 million deaths worldwide. While the hallmark of COVID-19 is respiratory insufficiency, up to 36% of patients with SARS-CoV-2 infection were reported to have various neurological manifestations, including cerebrovascular complication seen in up to 6% of these patients.[1] Exact mechanism of these complication has not been established yet, however, available data suggests

Vol.12, No. 2, pp. 51-62, Published December, 2021.

***Corresponding Author:** Salman Farooq, MD.,9200 W. Wisconsin Ave, Milwaukee, WI 53226,E-mail: salmanfarooq196@gmail.com.

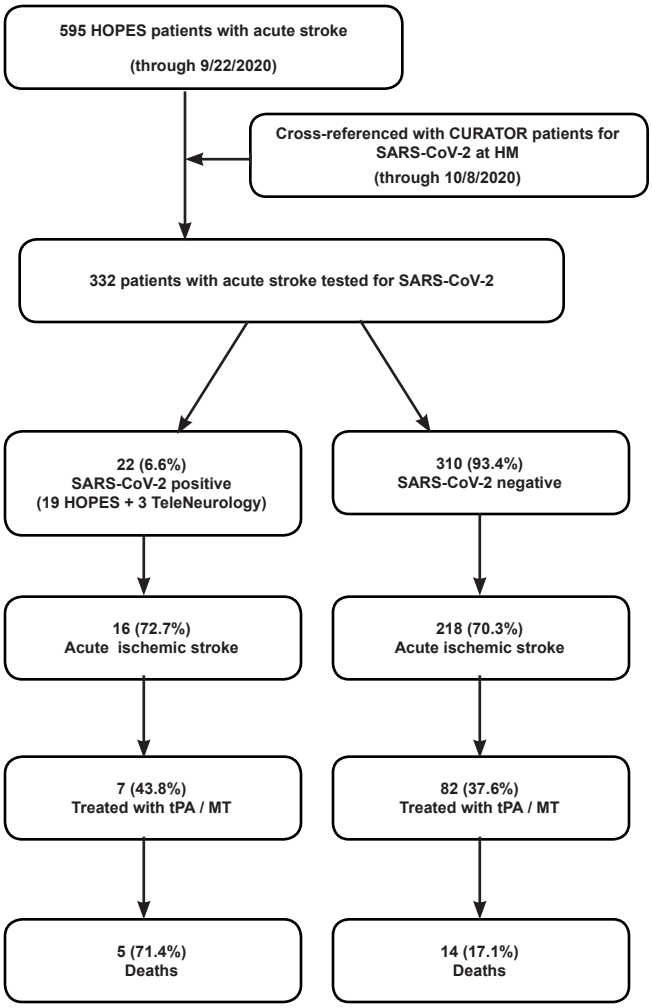

FIGURE 1: Phenotype of stroke patients.

hypoxia, inflammation, and diffuse intravascular coagulation leading to thromboembolic and intrinsic vascular disease.[2-4]

Stroke is a significant cause of morbidity and mortality in the United States and worldwide.[5] Thus far, there is paucity of data pertaining to risk and severity of cerebrovascular complications in patients with SARS-CoV-2 infection. Also, there is no reliable data available on the safety and efficacy of chemical-use pharmacological thrombolysis or mechanical thrombolysis-use thrombectomy in patients with SARS-CoV-2 infection presenting with acute ischemic stroke, especially when theoretically reported hemostatic abnormalities[6] in patients with moderate to severe COVID could pose additional safety concerns with thrombolysis.[7, 8]

We managed 22 stroke patients with SARS-CoV-2 infection in our comprehensive stroke center between March 2020 and October 2020. In this study, we compare the demographics, clinical characteristics, management approaches and outcomes of stroke between patients with SARS-CoV-2 infection and patients without SARS-CoV-2 infection at our comprehensive stroke center during this time period.

METHODS

Study Setting and Design

We conducted a cross-sectional analysis of data extracted from two patient registries at Houston Methodist Hospital; the Houston Methodist Hospital Outcomes-based Prospective Endpoints in Stroke (HOPES) registry and the COVID-19 Surveillance and Outcomes Registry (CURATOR). HOPES is a validated data warehouse for detailed phenotypic data on all stroke patients (Acute Ischemic Stroke, Transient Ischemic Attack, Intracranial Hemorrhage and Subarachnoid Hemorrhage) treated across Houston Methodist Hospital.[9] Additionally, HOPES captures 90-day functional outcome assessments for all stroke patients, regardless of stroke subtype and treatment. HOPES data is populated from electronic health records and is validated by a medical chart review process conducted by vascular neurologists and trained stroke research staff. Functional outcome data at 90 days is collected by trained staff using modified Rankin Scale assessments.[10] The CURATOR captures demographic, comorbidities, medication history, physiological assessments, COVID-19 treatment, and outcomes data for all individuals tested for SARS-CoV-2 at all Houston Methodist facilities. The CURATOR platform comprises of a validated data warehouse and a rapid bio-informatics analytical pipeline to provide quick and validated insights across several aspects of COVID-19 research.[11] Approval for this project was obtained by HM Institutional Review Board.

Cohort identification, Stroke Treatment, and Outcomes

Clinically and/or radiologically confirmed stroke patients from the HOPES registry who were tested for SARS-CoV-2 pathogen at Houston Methodist between March 21 and October 8, 2020 were included in this study. SARS-CoV-2 positivity was determined by laboratory confirmation of SARS-CoV-2 RNA by polymerase chain reaction (PCR) tests. Data on thrombolytic therapies (intravenous alteplase or mechanical thrombectomy) was obtained from HOPES and further validated via manual chart review. Radiological evidence of intracranial hemorrhage following intravenous alteplase or mechanical thrombectomy was obtained by evaluation of neuroimaging by a vascular neurologist utilizing published methods.[12] Further chart reviews were conducted for COVID-19 and treated stroke patients to ascertain a pre-morbid modified Rankin score based on published methods.[13] Patients with a 90-day modified Rankin score of 5 (severe disability) or 6 (death) or whose admission encounter resulted in in-hospital mortality were flagged as having experienced a poor outcome.

Other Covariates

Other variables of interest included demographics (age, sex, race, ethnicity), socio-economic measures (insurance, geo-mapped area deprivation indices, and zip code-based Census estimates for median income, population density, and poverty level), and comorbidity burden (defined by the Charlson Comorbidity Index).[14] Vital signs, laboratory tests, hospital course treatments, and utilization of high-acuity hospital

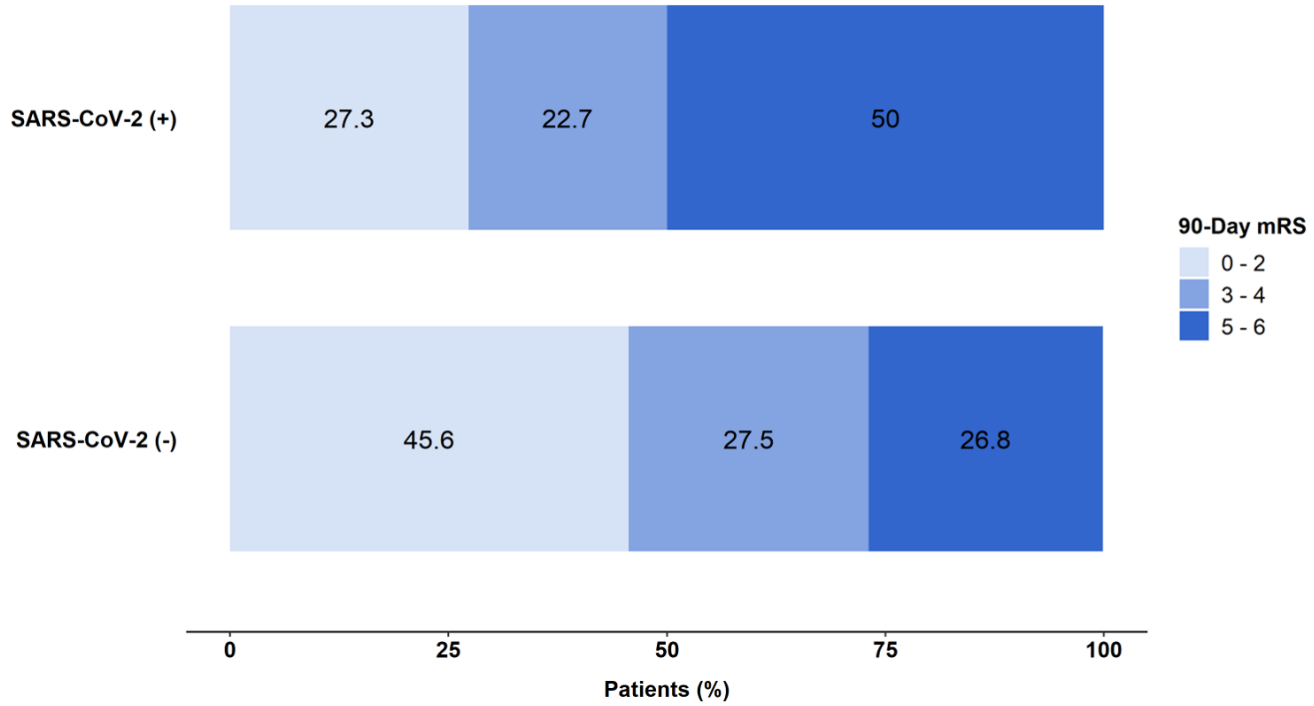

FIGURE 2: Outcome characteristics of ischemic stroke patients treated with intravenous alteplase and / or mechanical thrombectomy.

resources (intensive care and mechanical ventilation) were also included.

Statistical Analysis

Descriptive statistics (means, standard deviations, medians, interquartile ranges, proportions) were used to summarize and compare various subgroups of patients with SARS-CoV-2 infection and patients without SARS-CoV-2 infection who did or did not receive thrombolysis. Univariable analyses utilizing t-test and chi-square tests were performed to explore the association of socio-demographic, comorbidity and clinical parameters with SARS-CoV-2 infectivity and severe COVID-19 related outcomes. Unadjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) are reported. Bivariable comparisons of SARS-CoV-2/COVID-19 outcomes among patients treated with intravenous alteplase and/or mechanical thrombectomy were conducted, with statistical significances reported for proportional and median differences. Data preparation and analyses were performed using R statistical software (version 3.6.1; The R Foundation).

RESULTS

A total of 332 patients were admitted to our medical center with stroke between March 21 and October 8, 2020. Twenty two of these 332 patients (6.6%) tested positive for SARS-CoV-2 infection, out of which 11 (50%) subsequently experienced severe disability or death at 90 days. Of the 332 patients, 234 patients had acute ischemic stroke which included 16 patients with SARS-CoV-2 infection. Of the 234 acute ischemic stroke patients, thrombolysis with intravenous alteplase and/or mechanical thrombectomy was performed in 82 patients without SARS-CoV-2 infection and 7 patients with SARS-CoV-2 infection. The proportions of SARS-CoV-2 infectivity and COVID-19 outcomes among all acute stroke patients as well as the subset of ischemic stroke patients treated with intravenous alteplase and/or mechanical thrombectomy are presented in Figure 1.

Socio-Demographic, Clinical, and Outcome Characteristics of Acute Stroke Patients With SARS-CoV-2 Infection

The demographic profiles were statistically similar for patients with SARS-CoV-2 infection, regardless of result status (Table 1). Patients with SARS-CoV-2 infection experienced relatively higher proportions of particular comorbidities, although statistical significance was not demonstrated in this sample size. Across both comparison groups, patients more frequently experienced acute ischemic stroke than intracranial hemorrhage: n (%), AIS–16 (72.7) vs 218 (70.3), ICH–3 (13.6) vs 49 (15.8). Outcome measures, as assessed by the 90-day modified Rankin score, was more favorable in patients without SARS-CoV-2 infection, with modified Rankin score 0–2 observed in 45.6% (131/287) of patients without SARS-CoV-2 infection and 27.3% (6/22) of patients without SARS-CoV-2 infection. Conversely, modified Rankin score 5–6 was observed in 50.0% (11/22) of patients with SARS-CoV-2 infection, compared to 26.8% (77/287) of patients without SARS-CoV-2 infection. The 90-day modified Rankin score outcome trends are depicted in Figure 2. Among patients who experienced ischemic stroke, treatment with intravenous alteplase and/or mechanical thrombectomy varied, with 18.8% (3/16) of patients with SARS-CoV-2 infection (vs 29.40% of patients without SARS-CoV-2 infection) receiving

TABLE 1: Socio-Demographic, Clinical, and Outcome Characteristics among Acute Stroke Patients from HOPES Tested for SARS-CoV-2 at Houston Methodist through October 8th, 2020.

	SARS-CoV-2 Positive (n = 22)	SARS-CoV-2 Negative (n = 310)	OR (95% CI)[a] P-value
Demographic and Social Characteristics – n (%)			
Age – Mean (SD)	66.4 (18.6)	67.4 (14.8)	1.00 (0.97 – 1.03), P=0.763
Female (vs. Male)	13 (59.1)	147 (47.4)	2.40 (0.92 – 6.99), P=0.084
Race			
White	14 (63.6)	186 (60.0)	Reference
Black	6 (27.3)	96 (31.0)	0.83 (0.29 – 2.14), P=0.712
Asian	1 (4.5)	13 (4.2)	1.02 (0.05 – 5.74), P=0.984
Other / Mixed / Not Reported	1 (4.5)	15 (4.8)	0.89 (0.05 – 4.90), P=0.910
Hispanic (vs. Non-Hispanic)	5 (22.7)	49 (15.8)	1.89 (0.59 – 5.19), P=0.243
Insurance Type			
Commercial	4 (18.2)	67 (21.6)	Reference
Medicare	11 (50.0)	174 (56.1)	1.06 (0.35 – 3.92), P=0.924
Medicaid	0 (0)	17 (5.5)	-
Self-Pay	4 (19.2)	33 (10.6)	2.03 (0.45 – 9.08), P=0.338
Other	3 (13.6)	19 (6.1)	2.64 (0.49 – 13.03), P=0.228
Area Deprivation Index			
State Rank, Median (IQR)	4.5 (2.3 – 8.5)	4.0 (2.0 – 7.0)	1.05 (0.90 – 1.22)P=0.518
1 – 2	6 (27.3)	97 (31.3)	-
3 – 5	5 (22.7)	91 (29.4)	-
6 – 8	5 (22.7)	83 (26.8)	-
9 – 10	6 (27.3)	36 (11.6)	-
National Rank, Median (IQR)	53.5 (29.8 – 88.3)	54.0 (27.5 – 76.5)	1.00 (0.99 – 1.02)P=0.607
1 – 25	4 (18.2)	73 (23.5)	-
26 – 50	7 (31.8)	66 (21.3)	-
51 – 75	4 (18.2)	87 (28.1)	-
76 – 100	7 (31.8)	81 (26.1)	-
Household Income, Median (IQR)	66,363 (52,898 – 76,527)	60,309 (46,676 – 82,133)	1.00 (1.00 – 1.00), P=0.972
Poverty %, Median (IQR)	13.2 (11.0 – 17.2)	13.6 (7.4 – 20.5)	0.98 (0.93 – 1.04), P=0.555
Population Density (pop/mi^2), Median (IQR)	2,648 (1,416 – 3,767)	3,142 (1,504 – 4,988)	1.00 (1.00 – 1.00), P=0.130
Comorbidities – n (%)			
Charlson Comorbidity Index, Median (IQR)	7 (4 – 11.8)	8.0 (5.0 – 11.0)	0.98 (0.88 – 1.08), P=0.665
Myocardial Infarction	8 (36.4)	89 (28.7)	1.42 (0.55 – 3.43), P=0.447
Congestive Heart Failure	9 (40.9)	113 (36.5)	1.21 (0.48 – 2.89), P=0.676
Peripheral Vascular Disease	7 (31.8)	97 (31.3)	1.02 (0.38 – 2.51), P=0.959
Dementia	4 (18.2)	44 (14.2)	1.34 (0.37 – 3.80), P=0.608
Chronic Obstructive Pulmonary Disease	7 (31.8)	73 (23.5)	1.52 (0.56 – 3.74), P=0.384
Connective Tissue Disease	1 (4.5)	25 (8.1)	0.54 (0.03 – 2.77), P=0.559
Peptic Ulcer	1 (4.5)	20 (6.5)	0.69 (0.04 – 3.58), P=0.724
Liver Disease (Mild)	2 (9.1)	38 (12.3)	0.72 (0.11 – 2.59), P=0.661
Liver Disease (Moderate to Severe)	0 (0)	11 (3.5)	-
Diabetes w/o Complications	8 (36.4)	146 (47.1)	0.64 (0.25 – 1.54), P=0.333
Diabetes with Complications	6 (27.3)	82 (26.5)	1.04 (0.36 – 2.63), P=0.933
Chronic Kidney Disease (Mild to Moderate)	5 (22.7)	31 (10.0)	2.65 (0.83 – 7.23), P=0.073
Solid Tumor (Localized)	3 (13.6)	44 (14.2)	0.95 (0.22 – 2.95), P=0.942
Solid Tumor (Metastatic)	3 (13.6)	41 (13.2)	1.04 (0.24 – 3.21), P=0.956
AIDS	0 (0)	4 (1.3)	-

TABLE 1: (continued)

	SARS-CoV-2 Positive (n = 22)	SARS-CoV-2 Negative (n = 310)	OR (95% CI)[a] P-value
Stroke Assessments and Outcomes – n (%)			
Stroke Type			
Acute Ischemic Stroke (AIS)	16 (72.7)	218 (70.3)	P=0.999
Intracerebral Hemorrhage (ICH)	3 (13.6)	49 (15.8)	P=0.999
Subarachnoid Hemorrhage (SAH)	1 (4.5)	18 (5.8)	P=0.999
Transient Ischemic Attack (TIA)	2 (9.1)	25 (8.1)	P=0.999
NIHSS Total, Median (IQR)	7.5 (0 – 18.8)	6 (1 – 15.3)	P=0.667
90-Day Modified Rankin Scale (mRS)			
0 – 2	6 (27.3)	131/287 (45.6)	P=0.147
0	3 (13.6)	49 (17.1)	
1	0 (0)	37 (12.9)	
2	3 (13.6)	45 (15.7)	
3 – 4	5 (22.7)	79/287 (27.5)	P=0.811
3	5 (22.7)	37 (12.9)	
4	0 (0)	42 (14.6)	
5 – 6	11 (50.0)	77/287 (26.8)	P=0.038
5	2 (9.1)	34 (11.8)	
6	9 (40.9)	43 (15.0)	
NA	-	23/310 (7.4)	-
90-Day mRS among Ischemic Stroke Patients Treated with tPA / MT			
tPA only	2 (9.1)	33 (10.6)	P=0.999
0 – 2	2	20	
3 – 4	0	8	
5 – 6	0	1	
MT only	1 (4.5)	31 (10.3)	P=0.613
0 – 2	0	8	
3 – 4	0	9	
5 – 6	1	13	
tPA + MT	4 (18.2)	18 (6.5)	P=0.104
0 – 2	0	6	
3 – 4	0	5	
5 – 6	4	6	
In-hospital Mortality or mRS (6)	8 (36.4)	43 (13.9)	P=0.012
In-hospital Mortality or mRS (5 | 6)	11 (50.0)	77 (24.8)	P=0.020
Hospitalized	22 (100)	-	-
Died	9/22 (40.9)	-	-

[a] Unadjusted odds ratios and 95% confidence intervals for association between individual co-variates and susceptibility among those tested for SARS-CoV-2.

SD: Standard Deviation, IQR: Interquartile Range, NIHSS: National Institutes of Health Stroke Scale, tPA: Tissue Plasminogen Activator, MT: Mechanical Thrombectomy

TABLE 2: Stroke Assessment and Outcome Characteristics among Ischemic Stroke Patients from HOPES Treated with tPA / MT, Stratified by COVID-19 Status.

	COVID-19 Positive (n = 7)	COVID-19 Negative (n = 82)	P-value
Stroke Assessments and Outcomes – n (%)			
Treatment			
tPA only	2 (28.6)	33 (40.2)	P=0.839
MT only	1 (14.3)	31 (37.8)	P=0.404
tPA / MT	4 (57.1)	18 (22.0)	P=0.106
Bleed			
Yes	4 (57.1)	26 (31.7)	P=0.342
No	3 (42.9)	55 (67.1)	P=0.380
NA	0 (0)	1 (1.2)	-
Type of Bleed			
HT1	0 (0)	10/26 (38.5)	P=0.342
HT2	0 (0)	2/26 (7.7)	P=0.999
PH1	1/4 (25.0)	8/26 (30.8)	P=0.999
PH2	2/4 (50.0)	5/26 (19.2)	P=0.472
SAH	1/4 (25.0)	1/26 (3.8)	P=0.615
Symptomatic bleed			
Yes	2/4 (50.0)	5/26 (19.2)	P=0.472
No	2/4 (50.0)	17/26 (65.4)	P=0.970
NA	0 (0)	4/26 (15.4)	P=0.958
NIHSS Total, Median (IQR)	17 (14.5 – 19)	13 (5 – 19)	P=0.297
Pre-morbid mRS – Median (IQR)	0 (0 – 2.5)	0 (0 – 0)	P=0.128
90-day mRS – Median (IQR)	6 (3 – 6)	3 (1 – 5)	P=0.201
Change in mRS – Median (IQR)	3 (1.5 – 5.0)	2 (1 – 4)	P=0.213
Improvement	0 (0)	1/75 (1.3)	P=0.999
No Change	2 (28.6)	15/75 (20.0)	P=0.962
Worsening	5 (71.4)	59/75 (78.7)	P=0.999
1 – 2	0	24	-
1	0	10	-
2	0	14	-
3 – 4	3	21	-
3	2	7	-
4	1	14	-
5 – 6	2	14	-
5	0	6	-
6	2	8	-
NA	-	7 (8.5)	-
Death	5 (71.4)	14 (17.1)	P=0.004

tPA: Tissue Plasminogen Activator, MT: Mechanical Thrombectomy, IQR: Interquartile Range, mRS: Modified Rankin Scale

either intravenous alteplase or mechanical thrombectomy. Treatment with both intravenous alteplase and/or mechanical thrombectomy occurred in 25.0% (4/16) of patients with SARS-CoV-2 infection and 8.3% (18/218) of patients without SARS-CoV-2 infection. Irrespective of SARS-CoV-2 status, 88/332 stroke patients had a severe outcome (modified Rankin score, 5-6) and 221 had a non-severe outcome (modified Rankin score, 0–4) (Supplementary Table 1). At the time of this reporting, 23 patients could not be reached for their 90-day follow-up. When stratified by SARS-CoV-2 testing status, severe outcomes–90-day modified Rankin score 5–6 or in-hospital mortality–were observed in 50.0% (11/22) of patients with SARS-CoV-2 infection and 18.4% (57/310) of patients without SARS-CoV-2 infection, respectively.

Characteristics of Acute Stroke Patients With SARS-CoV-2 Infection

Of the 22 patients with SARS-CoV-2 infection, 11 had a severe outcome (Supplementary Table 2). Across all patients, the primary presenting symptoms were mostly neurologic, with respiratory symptoms accounting for the remaining cases. Large vessel occlusion was present in 54.5% (6/11) and 9.1% (1/11) of patients who had severe and non-severe outcomes, respectively (P=0.067). No differences were observed in the number of patients on antithrombotic therapy prior to admission, with 8 out of all 22 COVID-19 patients reported taking antithrombotic prior to presentation. Elevated blood pressure at admission was observed among the patients with SARS-CoV-2 infection who experienced a severe (vs non-severe) outcome: mean SBP–161.5 vs 137.3 mmHg, OR (95% CI), 1.08 (1.02–1.17) (P=0.026); mean DBP–82.6 vs 77.0 mmHg. Although statistical significance was not demonstrated, abnormal results for several laboratory components (lymphocytes, aspartate aminotransferase, C-reactive protein, D-dimer) were observed among the group who ultimately had severe (vs non-severe) outcomes. Of patients who had a severe outcome, 90.9 % (10/11) were admitted to the ICU, compared to 45.5% (5/11) of the patients who experience non-severe outcomes, OR (95% CI): 12.00 (1.12–128.84) (P=0.034). The cause of death amongst patients with SARS-CoV-2 infection was determined to be primarily respiratory in 5/9 patients, neurological in 3/9 patients and unknown in 1 patient.

Stroke Assessment and Outcome Characteristics of Ischemic Stroke Patients Treated with intravenous alteplase and/or mechanical thrombectomy

Thrombolysis with intravenous alteplase and/or mechanical thrombectomy was performed in 82 patients without SARS-CoV-2 infection and 7 patients with SARS-CoV-2 infection (Table 2). Bleeding was observed in 4 (57.1%) patients with SARS-CoV-2 infection (two of which were symptomatic parenchymal hematoma type 2), compared to 26 (31.7%) patients without SARS-CoV-2 infection. The median 90-day modified Rankin score was higher for patients with SARS-CoV-2 infection (median, IQR: 6, 3–6) than for patients without SARS-CoV-2 infection (median, IQR: 3, 1–5). The 90-day modified Rankin score outcomes for treated ischemic stroke patients are outlined in Table 1 and depicted in Figure 2. Worsening of modified Rankin score (pre-morbid to 90-day) was observed in 5 (83.3%) and 59 (78.7%) of patients with SARS-CoV-2 infection and patients without SARS-CoV-2 infection, respectively. Improvement of modified Rankin score was seen in 1 (1.8%) patient with SARS-CoV-2 infection whose pre-morbid modified Rankin score assessment included presentation with a fractured leg. Overall, 71.4% (5/7) of treated patients with SARS-CoV-2 infection had a fatal outcome, compared to 17.1% (14/82) of treated patients without SARS-CoV-2 infection (P=0.004).

DISCUSSION

To date, many case reports and case series have been published suggesting an association between SARS-CoV-2 infection and thrombotic vascular events.[2-4,6,7,15] We aimed to provide further evidence by reviewing stroke patients who presented to our comprehensive stroke center during the peak pandemic phase and compared outcomes in patients with and without COVID-19 infectivity. To the best of our knowledge, this is largest case series comparing outcomes in stroke patients with and without SARS-CoV-2 infection at a single academic medical center in US.

Our study supports prior reports of serious cerebrovascular events in patients with SARS-CoV-2 infection and multiple mechanisms have been proposed to explain these events, including hypercoagulable state, inflammatory response, hypoxia, endothelial dysfunction with endothelielitis and vasculitis.[2-4] Within our cohort of patients, demographic and clinical characteristics were similar between the two groups. Stroke subtypes were also similar between the two groups and included ~ 80% ischemic and ~20% hemorrhagic events. Our findings suggest that the mean age of stroke in patients with SARS-CoV-2 infection is similar to uninfected population which contradicts the previously published reports suggesting that cerebrovascular complications in COVID-19 patients has a predilection for younger patients.[15]

Our study supports the prior reports that patients with SARS-CoV-2 infection had higher rates of death or disability than patients without SARS-CoV-2 infection.[6] The major hypothesis for this disparity in outcomes is thought to be secondary to the disease process and multiorgan failure that results from SARS-CoV-2 infection.[2,3,7,8] Our findings also revealed that patients with SARS-CoV-2 infection who were treated with IV thrombolysis, mechanical thrombectomy or both had a higher rate of complications, including intracranial hemorrhage and death, when compared with patients without SARS-CoV-2 infection receiving thrombolysis, which is likely attributed to the underlying immune and coagulopathic state of the disease.

Stroke patients with SARS-CoV-2 infection presenting with higher presenting NIHSS score had higher rates of death or disability, particularly those with LVO. Elevated blood pressures on presentation was another marker of higher death or disability rates.[2] Surprisingly, for patients taking antithrombotic therapy prior to presentation, no difference in rates of death or disability was noted compared to those not taking antithrombotic medications. D-dimer has been used

clinically in multiple institutions to predict hypercoagulability and as a prognostic tool,[3,16,17] similarly, in our study, patients with death or disability appeared to have higher D-dimer level, but no statistical significance was found.

Our study is limited by its retrospective nature and small number of patients. Further larger registries and studies are needed to better understand the correlation between SARS-CoV-2 infection and cerebrovascular events and to develop practice guidelines on ideal management of these patients.

CONCLUSION

Our study provides the 90-day disability and mortality outcomes in patients with SARS-CoV-2 infection presenting with stroke. Although current standards of hyperacute stroke treatment continue to be utilized in SARS-CoV-2 infection associated stroke syndrome, patients with SARS-CoV-2 infection in our study tended to have worse outcomes with thrombolysis compared to patients without SARS-CoV-2 infection.

ACKNOWLEDGEMENTS

The authors would like to thank the HOPES Registry team members and the CURATOR Registry team members with the Houston Methodist Research Institute and Centers for Outcomes Research.

DISCLOSURE

Nothing to disclose from all authors.

REFERENCES

1. Román GC, Spencer PS, Reis J, et al. The neurology of COVID-19 revisited: A proposal from the Environmental Neurology Specialty Group of the World Federation of Neurology to implement international neurological registries. *J Neurol Sci* 2020;414:116884.
2. Li Y, Li M, Wang M, et al. Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study. *Stroke Vasc Neurol* 2020;5(3):279–84.
3. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135(23):2033–40.
4. Reddy ST, Garg T, Shah C, et al. Cerebrovascular Disease in Patients with COVID-19: A Review of the Literature and Case Series. *Case Rep Neurol* 2020;12(2):199–209.
5. Ahmed MU, Hanif M, Ali MJ, et al. Neurological Manifestations of COVID-19 (SARS-CoV-2): A Review. *Front Neurol* 2020;11:518.
6. Carneiro T, Dashkoff J, Leung LY, et al. Intravenous tPA for Acute Ischemic Stroke in Patients with COVID-19. *J Stroke Cerebrovasc Dis* 2020;29(11):105201.
7. Taylor BES, Khandelwal P, Rallo MS, et al. Outcomes and Spectrum of Major Neurovascular Events Among COVID-19 Patients: A 3-Center Experience. *Neurosurg Open* 2020;1(3):okaa008.
8. Sweid A, Hammoud B, Weinberg JH, et al. Letter: Thrombotic Neurovascular Disease in COVID-19 Patients. *Neurosurgery* 2020;87(3):E400–6.
9. Gadhia R, McCane D, Lee J, et al. The HOPES Registry - Houston Methodist Hospital Outcomes-based Prospective Endpoints in Stroke. *J Stroke Cerebrovasc Dis* 2018;27(11):2973–6.
10. Cooray C, Matusevicius M, Wahlgren N, et al. Mobile Phone-Based Questionnaire for Assessing 3 Months Modified Rankin Score After Acute Stroke: A Pilot Study. *Circ Cardiovasc Qual Outcomes* 2015;8(6 Suppl 3):S125-130.
11. Vahidy FS, Nicolas JC, Meeks JR, et al. Racial and ethnic disparities in SARS-CoV-2 pandemic: analysis of a COVID-19 observational registry for a diverse US metropolitan population. *BMJ Open* 2020;10(8):e039849.
12. von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: Classification of Bleeding Events After Ischemic Stroke and Reperfusion Therapy. *Stroke* 2015;46(10):2981–6.
13. Quinn TJ, Taylor-Rowan M, Coyte A, et al. Pre-Stroke Modified Rankin Scale: Evaluation of Validity, Prognostic Accuracy, and Association with Treatment. *Front Neurol* 2017;8:275.
14. Charlson M, Szatrowski TP, Peterson J, et al. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994;47(11):1245–51.
15. Fifi JT, Mocco J. COVID-19 related stroke in young individuals. *Lancet Neurol* 2020;19(9):713–5.
16. Rico-Mesa JS, Rosas D, Ahmadian-Tehrani A, et al. The Role of Anticoagulation in COVID-19-Induced Hypercoagulability. *Curr Cardiol Rep* 2020;22(7):53.
17. Kollias A, Kyriakoulis KG, Dimakakos E, et al. Thromboembolic risk and anticoagulant therapy in COVID-19 patients: emerging evidence and call for action. *Br J Haematol* 2020;189(5):846–7.

SUPPLEMENTARY TABLE 1: Socio-demographic, clinical, and outcome characteristics among acute stroke patients from HOPES tested for SARS-CoV-2 at Houston Methodist through October 8th, 2020, stratified by severity of outcome.

	Severe Disability or Death, mRS (5 | 6) (n = 88)	mRS (0 – 4) (n = 221)	OR (95% CI)[a] P-value
Demographic and Social Characteristics – n (%)			
Age – Mean (SD)	72.2 (14.6)	65.8 (14.9)	1.03 (1.01 – 1.05), P<0.001
Female (vs. Male)	45 (51.1)	105 (47.5)	1.20 (0.73 – 1.98), P=0.470
Race			
White	51 (58.0)	135 (61.1)	Reference
Black	23 (26.1)	73 (33.0)	0.83 (0.47 – 1.46), P=0.532
Asian	8 (9.1)	5 (2.3)	4.24 (1.35 – 14.58), P=0.015
Other / Mixed / Not Reported	6 (6.8)	8 (3.6)	1.99 (0.63 – 5.99), P=0.224
Hispanic (vs. Non-Hispanic)	15 (17.0)	33 (14.9)	1.23 (0.62 – 2.37), P=0.542
Insurance Type			
Commercial	10 (11.4)	58 (26.2)	Reference
Medicare	46 (52.3)	127 (57.5)	2.10 (1.03 – 4.67), P=0.053
Medicaid	6 (6.8)	8 (3.6)	4.35 (1.21 – 15.43), P=0.021
Self-Pay	8 (9.1)	24 (10.9)	1.93 (0.67 – 5.51), P=0.216
Other	18 (20.5)	4 (1.8)	26.10 (7.96 – 106.30), P<0.001
Area Deprivation Index			
State Rank, Median (IQR)			1.03 (0.94 – 1.12), P=0.513
1 – 2	27 (30.7)	72 (32.6)	-
3 – 5	23 (26.1)	64 (29.0)	-
6 – 8	22 (25.0)	59 (26.7)	-
9 – 10	15 (17.0)	25 (11.3)	-
National Rank, Median (IQR)			1.00 (0.99 – 1.01), P=0.516
1 – 25	22 (25.0)	51 (23.1)	-
26 – 50	16 (18.2)	53 (24.0)	-
51 – 75	25 (28.4)	60 (27.1)	-
76 – 100	24 (27.3)	56 (25.3)	-
Household Income, Median (IQR)	61,280 (48,345 – 87,054)	61,939 (46,825 – 79,524)	1.00 (1.00 – 1.00), P=0.586
Poverty %, Median (IQR)	13.3 (7.6 – 20.4)	13.6 (7.6 – 20.2)	1.00 (0.96 – 1.03), P=0.832
Population Density (pop/mi2), Median (IQR)	3,180 (1,504 – 4,609)	3,014 (1,504 – 4,996)	1.00 (1.00 – 1.00), P=0.927
Comorbidities – n (%)			
Charlson Comorbidity Index Score, Median (IQR)	8 (6 – 11)	7 (4 – 11)	1.04 (0.98 – 1.10), P=0.177
Myocardial Infarction	34 (38.6)	60 (27.1)	1.69 (1.00 – 2.84), P=0.049
Congestive Heart Failure	38 (43.2)	80 (36.2)	1.34 (0.81 – 2.21), P=0.255
Peripheral Vascular Disease	26 (29.5)	76 (34.4)	0.80 (0.46 – 1.36), P=0.414
Dementia	20 (22.7)	28 (12.7)	2.03 (1.06 – 3.82), P=0.030
Chronic Obstructive Pulmonary Disease	16 (18.2)	60 (27.1)	0.60 (0.31 – 1.08), P=0.101
Connective Tissue Disease	2 (2.3)	23 (10.4)	0.20 (0.03 – 0.70), P=0.032
Peptic Ulcer	7 (8.0)	13 (5.9)	1.38 (0.50 – 3.50), P=0.506
Liver Disease (Mild)	11 (12.5)	28 (12.7)	0.98 (0.45 – 2.03), P=0.968
Liver Disease (Moderate to Severe)	4 (4.5)	6 (2.7)	1.71 (0.43 – 6.12), P=0.417
Diabetes w/o Complications	37 (42.0)	109 (49.3)	0.75 (0.45 – 1.22), P=0.248
Diabetes with Complications	20 (22.7)	63 (28.5)	0.74 (0.41 – 1.30), P=0.302
Chronic Kidney Disease (Mild to Moderate)	7 (8.0)	27 (12.2)	0.62 (0.24 – 1.41), P=0.283
Solid Tumor (Localized)	15 (17.0)	31 (14.0)	1.26 (0.63 – 2.43), P=0.502
Solid Tumor (Metastatic)	12 (13.6)	30 (13.6)	1.01 (0.47 – 2.02), P=0.989
AIDS	1 (1.1)	2 (0.9)	1.26 (0.06 – 13.30), P=0.852

SUPPLEMENTARY TABLE 1: (continued)

	Severe Disability or Death, mRS (5 | 6) (n = 88)	mRS (0 – 4) (n = 221)	OR (95% CI)[a] P-value
Stroke Assessments and Outcomes – n (%)			
Stroke Type			
Acute Ischemic Stroke (AIS)	57 (64.8)	25 (11.3)	P<0.001
Intracerebral Hemorrhage (ICH)	25 (28.4)	160 (72.4)	P<0.001
Subarachnoid Hemorrhage (SAH)	6 (6.8)	23 (10.4)	P=0.447
Transient Ischemic Attack (TIA)	0 (0)	13 (5.9)	P=0.044
NIHSS Total, Median (IQR)	18 (9 – 25.3)	4 (1 – 9)	P<0.001
Ischemic Stroke Patients Treated with tPA / MT			
tPA only	1 (1.1)	30 (13.6)	P=0.002
MT only	14 (15.9)	18 (8.1)	P=0.070
tPA + MT	10 (11.4)	13 (5.9)	P=0.157

[a] Unadjusted odds ratios and 95% confidence intervals for association between individual co-variates and severe clinical outcomes among those tested for SARS-CoV-2.

SD: Standard Deviation, IQR: Interquartile Range, tPA: Tissue Plasminogen Activator, MT: Mechanical Thrombectomy

SUPPLEMENTARY TABLE 2: Clinical factors and hospital course parameters among acute stroke patients from HOPES testing positive for SARS-CoV-2 and hospitalized at Houston Methodist through October 8th, 2020, stratified by severity of outcome.

	Severe Outcome among COVID-19 Cases (n = 11)	mRS (0 – 4) among COVID-19 Cases (n = 11)	OR (95% CI)[a] P-value
Vital Signs at Hospital Admission – Mean (SD)			
SBP (mmHg)	161.5 (19.5)	137.3 (16.8)	1.08 (1.02 – 1.17), P=0.026
DBP (mmHg)	82.6 (10.5)	77.0 (11.0)	1.05 (0.97 – 1.17), P=0.245
Respiratory Rate (breath / min)	18.6 (1.8)	19.0 (2.1)	0.90 (0.54 – 1.44), P=0.672
Temperature (°F)	98.2 (0.8)	98.3 (0.9)	0.91 (0.29 – 2.72), P=0.857
Oxygen Saturation (%)	97.9 (2.2)	97.1 (1.3)	1.30 (0.79 – 2.30), P=0.313
In-hospital Therapeutics – n (%)			
Hydroxychloroquine	0 (0)	3 (27.3)	-
Ribavirin	0 (0)	0 (0)	-
Azithromycin	0 (0)	2 (18.2)	-
Lopinavir/Ritonavir	0 (0)	0 (0)	-
Remdesivir	1/10 (10.0)	0 (0)	-
Tocilizumab	0 (0)	1 (9.1)	-
Antiplatelets / Anticoagulants	6/10 (60.0)	10 (90.9)	
Antiplatelets	4/10 (40.0)	7 (63.6)	0.38 (0.07 – 2.22), P=0.323
Anticoagulants	6/10 (60.0)	8 (72.7)	0.56 (0.09 – 3.52), P=0.578
Dexamethasone	2/10 (20.0)	1 (9.1)	2.50 (0.19 – 32.80), P=0.553
Laboratory Parameters – n (%)			
WBC count <4000/μl	0 (0)	0 (0)	-
Lymphocytes < 20%	9/10 (90.0)	6/11 (54.5)	7.50 (0.69 – 81.25), P=0.102
Platelet count <150,000/μl	0 (0)	0 (0)	-
B-natriuretic peptide >100 pg/ml	3/6 (50.0)	3/8 (37.5)	1.67 (0.19 – 14.27), P=0.685
Procalcitonin >0.25 ng/ml	1/3 (33.3)	0 (0)	-
Troponin ≥ 0.06 ng/ml	3/7 (42.9)	4/5 (80.0)	0.19 (0.01 – 2.66), P=0.274
Aspartate aminotransferase > 40 U/l	6/10 (60.0)	3/11 (27.3)	4.00 (0.64 – 25.02), P=0.166
Alanine aminotransferase >40 U/l	3/10 (30.0)	3/11 (27.3)	1.14 (0.17 – 7.60), P=0.900
Total Bilirubin ≥ 1.2 mg/dl	0 (0)	0 (0)	-
C-reactive protein >8.2 ng/ml	7/7 (100)	7/9 (77.8)	-
Ferritin level > 3000 ng/ml	0 (0)	0 (0)	-
Creatinine > 1.5 mg/dl	1/10 (10.0)	2/11 (18.2)	0.50 (0.04 – 6.55), P=0.662
Venous lactate > 2.2 mmol/l	1/6 (16.7)	2/5 (40.0)	0.30 (0.02 – 4.91), P=0.485
D-dimer (μg/mL) – Mean (SD)	9.0 (7.9)	5.6 (7.5)	P=0.341
Hospital Acuity of Care Factors – n (%)			
ICU admission	10 (90.9)	5 (45.5)	12.00 (1.12 – 128.84), P=0.034
Invasive Mechanical Ventilation	7 (63.6)	2 (18.2)	7.88 (1.10 – 56.12), P=0.044
Stroke Assessments and Outcomes – n (%)			
Stroke Type			
Acute Ischemic Stroke (AIS)	9 (81.8)	7 (63.6)	P=0.632
Intracerebral Hemorrhage (ICH)	1 (9.1)	2 (18.2)	P=0.999
Subarachnoid Hemorrhage (SAH)	1 (9.1)	0 (0)	P=0.999
Transient Ischemic Attack (TIA)	0 (0)	2 (18.2)	P=0.458
NIHSS Total, Median (IQR)	17 (11 – 21.3)	1 (0 – 8.3)	P=0.065
Ischemic Stroke Patients Treated with tPA / MT	5/9 (55.6)	2/7 (28.6)	P=0.568
tPA only	0 (0)	2 (18.2)	P=0.458
MT only	1 (10.0)	0 (0)	P=0.999
tPA + MT	4 (30.0)	0 (0)	P=0.097

SUPPLEMENTARY TABLE 2: (continued)

	Severe Outcome among COVID-19 Cases (n = 11)	mRS (0 – 4) among COVID-19 Cases (n = 11)	OR (95% CI)[a] P-value
ECHO R/L shunt	0 (0)	1 (9.1)	P=0.999
LVO	6 (54.5)	1 (9.1)	P=0.067
Vessel Affected			
MCA	3 (27.3)	1 (9.1)	P=0.580
PCA	1 (9.1)	0 (0)	P=0.999
Basilar	1 (9.1)	0 (0)	P=0.999
ACA	1 (9.1)	0 (0)	P=0.999
NA	5 (45.5)	10 (90.9)	-
Cause of Death			
Respiratory	5/9 (55.6)	-	-
Neurologic	3/9 (33.3)	-	-
Unknown	1/9 (11.1)	-	-
Presenting Symptom			
Respiratory	3 (27.3)	2 (18.2)	P=0.999
Neurologic	8 (72.7)	9 (81.8)	P=0.999
Encephalopathy	4	2	-
Motor	4	3	-
Posterior circulation	0	1	-
Dysarthria	0	1	-
Seizure	0	1	-
Sensory	0	1	-
Pre-admission Antiplatelet / Anticoagulation Therapy	5 (45.5)	3 (27.3)	P=0.658

[a] Unadjusted odds ratios and 95% confidence intervals for association between individual co-variates and severe clinical outcomes among confirmed COVID-19 cases.

SD: Standard Deviation, tPA: Tissue Plasminogen Activator, MT: Mechanical Thrombectomy