

CLINICAL AND POPULATION SCIENCES

Influence of the COVID-19 Pandemic on Treatment Times for Acute Ischemic Stroke

The Society of Vascular and Interventional Neurology Multicenter Collaboration

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BACKGROUND AND PURPOSE: The pandemic caused by the novel coronavirus disease 2019 (COVID-19) has led to an unprecedented paradigm shift in medical care. We sought to evaluate whether the COVID-19 pandemic may have contributed to delays in acute stroke management at comprehensive stroke centers.

METHODS: Pooled clinical data of consecutive adult stroke patients from 14 US comprehensive stroke centers (January 1, 2019, to July 31, 2020) were queried. The rate of thrombolysis for nontransferred patients within the Target: Stroke goal of 60 minutes was compared between patients admitted from March 1, 2019, and July 31, 2019 (pre-COVID-19), and March 1, 2020, to July 31, 2020 (COVID-19). The time from arrival to imaging and treatment with thrombolysis or thrombectomy, as continuous variables, were also assessed.

RESULTS: Of the 2955 patients who met inclusion criteria, 1491 were admitted during the pre-COVID-19 period and 1464 were admitted during COVID-19, 15% of whom underwent intravenous thrombolysis. Patients treated during COVID-19 were at lower odds of receiving thrombolysis within 60 minutes of arrival (odds ratio, 0.61 [95% CI, 0.38–0.98]; $P=0.04$), with a median delay in door-to-needle time of 4 minutes ($P=0.03$). The lower odds of achieving treatment in the Target: Stroke goal persisted after adjustment for all variables associated with earlier treatment (adjusted odds ratio, 0.55 [95% CI, 0.35–0.85]; $P<0.01$). The delay in thrombolysis appeared driven by the longer delay from imaging to bolus (median, 29 [interquartile range, 18–41] versus 22 [interquartile range, 13–37] minutes; $P=0.02$). There was no significant delay in door-to-groin puncture for patients who underwent thrombectomy (median, 83 [interquartile range, 63–133] versus 90 [interquartile range, 73–129] minutes; $P=0.30$). Delays in thrombolysis were observed in the months of June and July.

CONCLUSIONS: Evaluation for acute ischemic stroke during the COVID-19 period was associated with a small but significant delay in intravenous thrombolysis but no significant delay in thrombectomy time metrics. Taking steps to reduce delays from imaging to bolus time has the potential to attenuate this collateral effect of the pandemic.

GRAPHIC ABSTRACT: An online [graphic abstract](#) is available for this article.

Key Words: goals ■ groin ■ pandemics ■ punctures ■ thrombectomy

Since December 2019, the novel human coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to >29 million worldwide

infections and has claimed the lives of >900 000 people.¹ In an attempt to prevent health care-associated transmission of SARS-CoV-2, health care administrators and legislative

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Nonstandard Abbreviations and Acronyms

COVID-19	coronavirus disease 2019
CSC	comprehensive stroke center
CT	computed tomography
IQR	interquartile range
LVO	large vessel occlusion
MSU	mobile stroke unit
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

officials have mandated stringent contact precautions² leading to the consumption of personal protective equipment,³ implementation of decontamination procedures, and reduction in use of imaging-based diagnostic testing.^{4–6} Because of these and other responses, patients who present to the hospital with acute neurological symptoms may experience delays in their management as health care personnel make an effort to stem the spread of the virus.

In the present study, we evaluated the effect of the coronavirus disease 2019 (COVID-19) pandemic on systems of care in the management of acute stroke. We hypothesized that patients evaluated for acute stroke during this period would experience greater delays in time to imaging and treatment when compared with patients who were treated in identical months of the previous year.

METHODS

Study Design and Participants

Fully deidentified data will be made available upon reasonable request to the corresponding author. A retrospective observational registry involving prospectively maintained data from 14 comprehensive stroke centers (CSCs) across 9 US states was queried. As of September 16, 2020, these 9 states accounted for 47% of all COVID-19 cases in the United States and 37% of all COVID-19–associated deaths.¹ Participating centers were recruited based on affiliation with the Society of Vascular and Interventional Neurology. Sites contributed patient-level data that were prospectively collected as part of their local stroke registry. All consecutive adult patients ≥ 18 years of age who were admitted on dates between January 1, 2019, and July 31, 2020 were eligible for inclusion. Eligible patients must have experienced an acute ischemic stroke based on the diagnosis of the treating physician. The use of neuroimaging to confirm an ischemic stroke diagnosis was made at the discretion of the treating physician. This study was approved under waiver of informed consent by the local institutional review board at each participating center, and it is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Data Collection

Patient demographic information, including age, sex, race, and ethnicity, as well as pertinent medical history, stroke severity

according to baseline National Institutes of Health Stroke Scale score, timing of imaging and treatment (including treatment with intravenous thrombolysis or endovascular recanalization), duration of hospitalization, and discharge disposition, were captured. To ensure consistency of practice paradigms across sites, endovascular recanalization was only counted for patients with a proximal large vessel occlusion (LVO). A proximal LVO was defined as an occlusion of the intracranial internal carotid artery, proximal segment of the middle cerebral artery (M1), or basilar artery. Sites were classified as high volume if the annual number of thrombectomies exceeded 50, as has been previously associated with faster treatment times.⁷

Statistical Analysis

Descriptive statistics were used to summarize continuous and categorical variables. Normality of continuous data was assessed histographically and confirmed using the Shapiro-Wilk test. Continuous variables were reported as medians with interquartile range (IQR) or means with SD. Categorical variables were reported as proportions. Between-group comparisons for categorical data were made using χ^2 or Fisher exact test when contingency table cell counts were < 5 . Between-group comparisons for non-normally distributed continuous data were made using the Wilcoxon rank-sum test. To account for seasonal variations in treatment patterns and outcomes among patients with stroke,⁸ patients were categorized into the pre-COVID-19 period if they were evaluated between March 1, 2019, and July 31, 2019, while patients evaluated during the COVID-19 period were included if they were evaluated between March 1, 2020, and July 31, 2020. Time periods were also divided into weekly and monthly epochs between January 1, 2019, and July 31, 2020, as a separate analysis for illustrative purposes.

The primary outcome was selected as a ≤ 60 -minute delay from hospital arrival to intravenous thrombolysis (door-to-needle time) for patients treated in the emergency department (not in-hospital strokes or patients transferred from an outside hospital—for whom time of outside hospital arrival was not available), in accordance with recommendations by the Target: Stroke campaign.⁹ Secondary outcomes included the absolute time from hospital arrival to intravenous thrombolysis, hospital arrival to computed tomographic (CT) scan, hospital arrival to skin puncture (for patients who underwent endovascular recanalization), length of hospital stay, and discharge disposition. Because all patients treated in a mobile stroke unit (MSU) had < 0 -minute door-to-needle times and transferred patients were originally triaged outside of the participating CSC, analyses for time to thrombolysis treatment were restricted to non-MSU nontransferred patients, unless otherwise specified. The difference in the mean number of weekly and monthly event rates was evaluated using an independent samples *t* test. Logistic and linear regression models were generated to estimate the effect of the COVID-19 period on the primary and secondary outcomes of interest, with adjustment for all variables associated with earlier thrombolysis ($P < 0.1$) in univariate regression. Each regression model was clustered by site. All tests were 2 sided, with $P \leq 0.05$ considered statistically significant. As this was an exploratory analysis, *P* values are reported for convention and should be interpreted with caution. No adjustments were made for multiple comparisons. Missing data were not imputed.

RESULTS

Of the 12 187 patients with acute ischemic stroke presenting between January 1, 2019, and July 31, 2020, after excluding 4579 who were transferred from an outside hospital, 197 brought in by an MSU, 1061 with unreported arrival method, 77 in-hospital strokes, and 3318 patients admitted outside of the 2 study periods (pre-COVID-19 and COVID-19), 2955 were included in the formal analyses. Compared with patients admitted during identical months in 2019, those admitted during the COVID-19 period were younger but had some differences in vascular comorbidities and more severe baseline deficits (Table 1). While a similar proportion of patients arrived to the hospital by private vehicle or walk-in during the study periods, a smaller proportion of patients arrived to the hospital by emergency medical services with a larger proportion of patients transferred from an outside hospital during the COVID-19 period.

Three hundred ninety patients (15%) received intravenous thrombolysis, with 386 having available imaging and treatment times (99% of treated). There was a decrease in the odds of the primary outcome (door-to-needle time, ≤ 60 minutes) among patients treated during the COVID-19 period versus patients treated during the pre-COVID-19 period (odds ratio, 0.61 [95% CI, 0.38–0.98]; $P=0.04$; Table 2). After adjustment for variables associated with the primary outcome in univariate regression ($P<0.1$: arrival by Emergency Medical Services, White race, Hispanic ethnicity, history of dyslipidemia, higher National Institutes of Health Stroke Scale score, and treatment at a high-volume CSC) and clustering by site, there remained a significantly lower odds of achieving a door-to-needle time ≤ 60 minutes during the COVID-19 period (adjusted odds ratio, 0.55 [95% CI, 0.35–0.85]; $P<0.01$; Table I in the [Data Supplement](#)). After multivariable adjustment and clustering by site,

Table 1. Demographics by Seasonal Period

	All patients (n=2955)	Pre-COVID-19	COVID-19	P value
		March to July 2019 (n=1491)	March to July 2020 (n=1464)	
Age group, n (%)				0.03
<50	357/2942 (12%)	179/1491 (12%)	178/1451 (12%)	
50–69	1252/2942 (43%)	602/1491 (40%)	650/1451 (45%)	
≥ 70	1333/2942 (45%)	710/1491 (48%)	623/1451 (43%)	
Sex: female, n (%)	1398/2942 (48%)	723/1491 (48%)	675/1451 (43%)	0.28
Race, n (%)				<0.01
White	1501 (51%)	832 (56%)	669 (46%)	
Black	1000 (34%)	422 (28%)	578 (39%)	
Asian	56 (2%)	33 (2%)	23 (2%)	
Other/unknown	398 (13%)	204 (14%)	194 (13%)	
Hispanic, n (%)	688/2892 (24%)	381/1449 (26%)	307/1443 (21%)	<0.01
Arrival route, n (%)				<0.01
Emergency medical services	2006 (68%)	898 (60%)	1108 (76%)	
Private vehicle/walk-in	949 (32%)	593 (40%)	356 (24%)	
Medical history, n (%)				
Prior ischemic stroke	740 (25%)	321 (22%)	419 (29%)	<0.01
Hypertension	2272 (77%)	1173 (79%)	1099 (75%)	0.02
Diabetes	1152 (39%)	583 (39%)	569 (39%)	0.90
Dyslipidemia	1328 (45%)	709 (48%)	619 (42%)	<0.01
Atrial fibrillation/flutter	436 (15%)	243 (16%)	193 (13%)	0.02
Coronary artery disease	525 (18%)	286 (19%)	239 (16%)	0.04
Congestive heart failure	332 (11%)	143 (10%)	189 (13%)	<0.01
Active tobacco use	515 (17%)	243 (16%)	272 (19%)	0.10
NIHSS on admission, median (IQR)	4 (1–10)	3 (1–9)	4 (1–11)	<0.01
Treatment with intravenous thrombolysis, n (%)	391/2675 (15%)	205/1491 (14%)	186/1184 (16%)	0.15
Proximal LVO, n (%)	178/1513 (12%)	124/1118 (11%)	54/395 (14%)	0.17
Endovascular thrombectomy,* n (%)	114/178 (64%)	76/124 (61%)	38/54 (70%)	0.25

COVID-19 indicates coronavirus disease 2019; IQR, interquartile range; LVO, large vessel occlusion; and NIHSS, National Institutes of Health Stroke Scale.

*Analysis limited to patients with internal carotid, proximal middle cerebral (M1), or basilar artery occlusions.

Table 2. Outcomes by Seasonal Period

	All patients (n=2955)	Pre-COVID-19	COVID-19	P value
		March to July 2019 (n=1491)	March to July 2020 (n=1464)	
Door-to-needle \leq 60 min, n (%)	295/386 (77%)	164/203 (81%)	131/183 (72%)	0.03
Door-to-needle, min; median (IQR)	42 (27–59)	42 (27–55)	46 (31–64)	0.03
Door-to-CT time, min; median (IQR)	30 (13–90)	37 (15–101)	29 (14–77)	<0.01
CT-to-needle time, min; median (IQR)	23 (13–36)	22 (13–37)	29 (18–41)	0.02
Door-to-skin puncture,* min; median (IQR)	97 (77–134)	100 (80–151)	102 (87–127)	0.82
CT-to-skin puncture,* min; median (IQR)	87 (65–121)	90 (73–129)	83 (63–133)	0.30
Length of hospital stay, d; median (IQR)	4 (3–8)	4 (2–7)	4 (2–8)	0.46
Discharge disposition, n (%)				<0.01
Home/against medical advice	1707/2920 (58%)	872/1491 (58%)	835/1429 (58%)	
Acute rehabilitation facility	310/2920 (11%)	213/1491 (14%)	97/1429 (7%)	
Skilled nursing facility	185/2920 (6%)	150/1491 (10%)	35/1429 (2%)	
Long-term acute-care facility	11/2920 (<1%)	5/1491 (<1%)	6/1429 (<1%)	
Other/unspecified health care facility	401/2920 (14%)	95/1491 (6%)	306/1429 (21%)	
Hospice	117/2920 (4%)	59/1491 (4%)	58/1429 (4%)	
Expired	131/2920 (4%)	51/1491 (3%)	80/1429 (6%)	
Modified Rankin Scale at discharge, median (IQR)	3 (1–4)	3 (1–4)	4 (2–5)	<0.01

COVID-19 indicates coronavirus disease 2019; CT, computed tomography; and IQR interquartile range.

*Analysis limited to patients with internal carotid, proximal middle cerebral (M1), or basilar artery occlusions who were evaluated in the emergency department and not transferred from an outside hospital.

treatment at a high-volume site was not independently associated with the primary outcome (adjusted odds ratio, 1.07 [95% CI, 0.50–2.28]; $P=0.86$). When door-to-needle time was evaluated as a continuous variable, there was a small but statistically significant delay in door-to-needle time during the COVID-19 versus pre-COVID-19 period (median, 42 versus 46 minutes; $P=0.03$; $\beta=0.61$ [95% CI, 0.38–0.98]; $P=0.04$; Table 2). After adjustment for the aforementioned variables and clustering by site, the difference in door-to-needle was no longer significant (adjusted β , 20.8 [95% CI, –48.2 to 89.9]; $P=0.52$).

The delay in door-to-needle time was related to a delay in imaging to alteplase bolus (median, 29 versus 22 minutes; $P=0.02$), which occurred despite the shorter time from arrival to initial imaging during the COVID-19 period (median, 29 versus 37 minutes; $P<0.01$; Table 2). In multivariable regression, after adjusting for predictors of earlier CT ($P<0.1$: history of atrial fibrillation/flutter) and clustering by site, admission during COVID-19 was no longer an independent predictor of earlier CT (adjusted β , 184.5 [95% CI, –183.4 to 552.4]; $P=0.30$; adjusted $P_{\text{atrial fibrillation}}=0.23$).

When patients were grouped according to monthly epoch, the increase in door-to-needle times during the COVID-19 period appeared to begin in April of 2020 with persistent treatment delays during the months of June and July 2020 (Figure 1). These months coincided with the timeline in which new COVID-19 diagnoses peaked for several states during the later wave of the pandemic (eg, mid-July peaks were observed in California, Florida,

and Texas, which contributed 33% of the patients in this cohort). There remained a significantly shorter door-to-needle time among patients brought in by emergency medical services versus private vehicle/walk-in during either period (pre-COVID-19: median, 38 [IQR, 26–55] versus 46 [IQR, 35–60] minutes, $P=0.04$; COVID-19: median, 46 [IQR, 30–61] versus 65 [IQR, 47–73] minutes, $P<0.01$; Figure 2).

For patients who underwent thrombectomy for an occlusion of the ICA, M1, or basilar artery, patients admitted during the COVID-19 period had no significant delay from time from arrival to skin puncture when compared with patients admitted in the pre-COVID-19 period (Table 2).

DISCUSSION

The COVID-19 pandemic has created unprecedented challenges to our global and national health care systems, stressing our resources and shifting the paradigm for many clinical management strategies. One such consequence of the pandemic is delayed throughput and acute management of patients with acute ischemic stroke. In this observational study of 14 CSCs across 9 sites in the United States, we observed a small but persistent delay in time from patient arrival to treatment with standard-of-care intravenous thrombolysis. This delay appears, at least in part, due to delays from imaging to treatment initiation rather than arrival to imaging. Earlier imaging in patients with suspected acute stroke

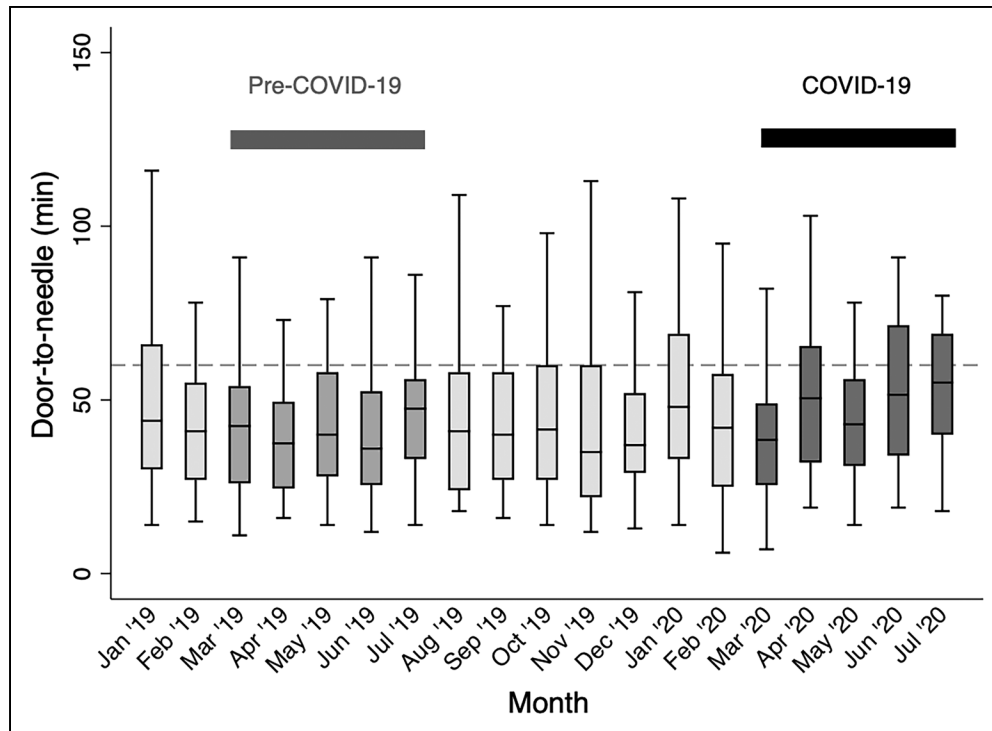


Figure 1. Door-to-needle times by month of arrival among nontransferred patients evaluated in the emergency department (not in-hospital strokes).

Boxes represent medians with interquartile range. Note that outliers have been excluded from the figure. Reference line (dashed) indicates Target: Stroke goal of 60-min door-to-needle time. COVID-19 indicates coronavirus disease 2019.

may have been influenced by the higher proportion of patients with comorbid vascular risk factors (specifically atrial fibrillation), which confounded the observation of earlier imaging in patients treated during the COVID-19 period. As anticipated, the donning and doffing of personal protective equipment and decontamination of critical health care resources (eg, CT and magnetic resonance imaging scanners)—among other workflow changes—likely contributed to delays in the care of critically ill patients with acute stroke. Due to the large scale of this study and its retrospective nature, we were unable to report which specific components of stroke workflow may have contributed to the delay from imaging to treatment. Unsurprisingly, patients who were brought in by emergency medical services were more rapidly treated during the COVID-19 period, and they were more rapidly treated during the seasonal control period, as demonstrated in prior studies.^{10,11}

While this study did not capture data on the presence of infection with the novel human coronavirus SARS-CoV-2, a small number of included patients evaluated during the COVID-19 period were infected with the virus. The treatment times, complications, and outcomes of these patients are being reported separately. Nevertheless, it is expected that health care providers would take additional precautions in caring for these patients whether the diagnosis of COVID-19 is known, unknown, or suspected. However, if such precautions contributed

to the delay in thrombolysis observed in this study, it was not a delay in imaging acquisition but rather a delay in thrombolysis initiation.

One site included in this analysis utilized an MSU, which has been shown to facilitate earlier CT imaging and thrombolysis initiation.¹² Because of the uniqueness of an MSU (notably its lack of universal availability and door-to-needle times of <0 minutes), we excluded imaging and treatment data for the 2% of the total cohort who were treated in the MSU. Data from the MSU site and other sites equipped with MSUs are being reported separately.

Our results are consistent with one retrospective analysis of patients treated at the Xuanwu Hospital in Beijing, in which the investigators observed a \approx 1-hour delay in door-to-skin puncture of the 55 patients with LVO when compared with patients treated in the 2 months prior (174 versus 126 minutes; $P=0.047$).¹³ At the onset of the pandemic in the United States, one New York Comprehensive Stroke Center reported longer arrival-to-CT times (16 versus 12 minutes; $P=0.05$) and longer door-to-puncture times (80 versus 71 minutes; $P=0.06$) but no difference in door-to-needle times (36 versus 35 minutes; $P=0.83$).¹⁴ In this larger, multicenter cohort, we found no delays in the treatment using endovascular thrombectomy for proximal LVO. The time from arrival to imaging in patients who underwent thrombectomy was no different between the two periods ($P=0.55$, data not

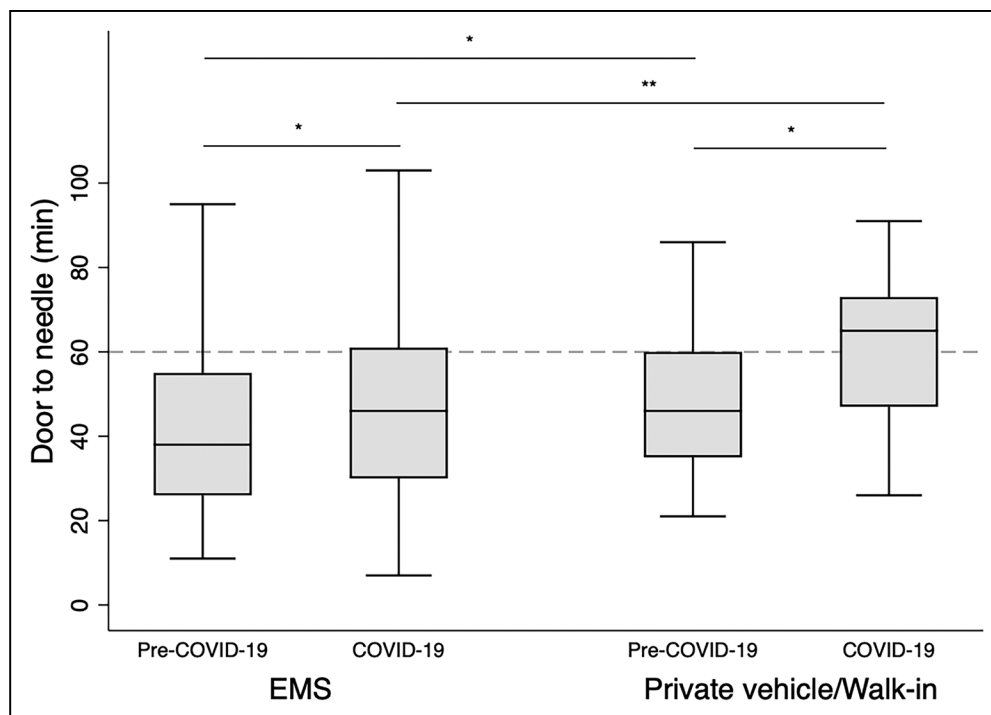


Figure 2. Door-to-needle time according to patient method of arrival.

Boxes represent medians with interquartile range. Note that outliers have been excluded from the figure. Patients were excluded from this analysis if they were transferred from an outside hospital, treated in a mobile stroke unit, or experienced an in-hospital stroke. Reference line (dashed) indicates Target: Stroke goal of 60-min door-to-needle time. COVID-19 indicates coronavirus disease 2019; and EMS, emergency medical services. * $P < 0.05$, ** $P < 0.01$.

shown) while the time from imaging to groin puncture was significantly shorter during the COVID-19 period ($P < 0.01$, data not shown). Based on rapidly published consensus recommendations,^{15,16} it is likely that neurointerventionalists in our network were able to quickly react to the pandemic without slowing throughput of patients with acute LVO.

Our findings are inconsistent with other observational data from 2 Egyptian centers, which reported no delay in thrombolysis.¹⁷ In that letter, Roushdy et al reported their experience with 242 patients (93 of whom were evaluated during the COVID-19 period) and found the door-to-needle times were similar among patients treated during or before COVID-19 (mean, 29.6 ± 10.5 versus 29.6 ± 4.9 minutes; $P = 0.22$). In a larger retrospective cohort of >1200 patients in Barcelona, the investigators also reported no significant delay in acute care, although rates of stroke presentation fell during the COVID-19 pandemic.¹⁸ It is likely that since such differences in treatment times are small (on the order of a median of 4 minutes, according to our experience), smaller cohorts are unlikely to detect significant differences between treatment periods. Our results also do not corroborate early indications of a rapid rise in the number of patients with acute stroke or LVO as a consequence of the pandemic. Early reports out of Wuhan, China,¹⁹ and other case series,^{20,21} suggested that the coronavirus may increase the number of patients with

embolic cerebral infarctions (as high as 5%). While we and others have certainly seen strokes in the setting of COVID-19, the early reports suggesting that there would be a dramatic spike in the number of LVOs may have been overstated. A comprehensive analysis of consecutive COVID-19 patients treated in the New York City was recently published, which estimated the risk of imaging-proven ischemic stroke in this population to be $<1\%$.²² We have observed a similar rate of radiography-proven cerebral infarctions in hospitalized patients with COVID-19.²³ While we⁶ and others^{24,25} have found that the rate of acute strokes may be falling during the COVID-19 pandemic, it is not likely to be the consequence of improved health care and primary prevention. On the contrary, it seems to be an unfortunate collateral effect of social distancing, the avoidance of health care institutions due to fear of contracting the virus,²⁶ and perhaps the downplay of milder neurological symptoms.^{6,25}

Limitations

While this study is the largest observational cohort to evaluate the collateral effect of the COVID-19 pandemic on acute stroke treatment, it has several limitations. Because of the retrospective nature of this investigation, not all data fields were captured with 100% completion. That said, the primary outcome of door-to-needle treatment time within 60 minutes was available for 99% of treated patients

during the 2 study periods. It is possible that the incompleteness of reported data (eg, missing cases from July 2020) could have contributed to a type II error. Missed cases from the end of the study period may have also contributed to the fall in reported stroke rates across included sites. However, several groups have already observed a smaller number of patients presenting to the hospital with stroke during the COVID-19 pandemic.^{6,24,25,27} Therefore, the incompleteness of data in later months is unlikely to explain the entire decrement of new stroke diagnoses. Furthermore, because the analyses in this investigation were limited by the available data from each center's prospectively maintained stroke registries, comparisons could only be made for variables with identical definitions. This limited any secondary analyses as to exclusions for intravenous thrombolysis or endovascular recanalization and prevented us from evaluating imaging modalities, imaging findings, and effects of treatment (eg, hemorrhagic complications). Because infection with the coronavirus was not captured as part of each center's prospective registry—and COVID-19 carries a high risk of in-hospital mortality—we did not explore in greater detail the functional outcomes of patients in this study. Outcomes in COVID-19-associated stroke have been reported separately as part of a larger, multinational study.²³ Whether delays in thrombolysis contribute meaningfully to patient outcomes should be explored in larger studies or by pooling the data published to date.

Conclusions

From our multicenter observational study of 14 CSCs in the United States, we observed a significant decrease in the number of patients presenting with acute ischemic stroke and a small but significant decrease in timing of acute thrombolysis. The delay in thrombolysis appeared to persist through the months of June and July, as the later wave of the pandemic spread beyond New York and east coast centers. Because the delay in care appears driven largely by the time from image acquisition to thrombolysis initiation, centers are encouraged to reevaluate their local paradigms to expedite stroke treatment once intracranial hemorrhage has been excluded.

ARTICLE INFORMATION

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Supplemental Materials

Table 1

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