ARTICLE

Global Impact of COVID-19 on Stroke Care and IV Thrombolysis

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Neurology® 2021;96:e2824-e2838. doi:10.1212/WNL.0000000000011885

Abstract

Objective

To measure the global impact of COVID-19 pandemic on volumes of IV thrombolysis (IVT), IVT transfers, and stroke hospitalizations over 4 months at the height of the pandemic (March 1 to June 30, 2020) compared with 2 control 4-month periods.

Methods

We conducted a cross-sectional, observational, retrospective study across 6 continents, 70 countries, and 457 stroke centers. Diagnoses were identified by their ICD-10 codes or classifications in stroke databases.

Results

There were 91,373 stroke admissions in the 4 months immediately before compared to 80,894 admissions during the pandemic months, representing an 11.5% (95% confidence interval [CI] −11.7 to −11.3, $p < 0.0001$) decline. There were 13,334 IVT therapies in the 4 months preceding compared to 11,570 procedures during the pandemic, representing a 13.2% (95% CI −13.8 to −12.7, $p < 0.0001$) drop. Interfacility IVT transfers decreased from 1,337 to 1,178, or an 11.9% decrease (95% CI −13.7 to −10.3, $p = 0.001$). Recovery of stroke hospitalization volume (9.5%, 95% CI 9.2–9.8, $p < 0.0001$) was noted over the 2 later (May, June) vs the 2 earlier (March, April) pandemic months. There was a 1.48% stroke rate across 119,967 COVID-19 hospitalizations. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was noted in 3.3% (1,722/52,026) of all stroke admissions.

Conclusions

The COVID-19 pandemic was associated with a global decline in the volume of stroke hospitalizations, IVT, and interfacility IVT transfers. Primary stroke centers and centers with higher COVID-19 inpatient volumes experienced steeper declines. Recovery of stroke hospitalization was noted in the later pandemic months.

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Glossary

CI = confidence interval; , **COVID-19** = coronavirus disease 2019; , **CSC** = comprehensive stroke center; , **ICD-10** = International Classification of Diseases–10; , **IQR** = interquartile range; , **IVT** = IV thrombolysis; , **PSC** = primary stroke center; , **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

The coronavirus disease 2019 (COVID-19) pandemic has restructured health care systems worldwide to care for critically ill patients with COVID-19.[1] The high virulence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and COVID-19–related morbidity and mortality have strained paradigms of health care worldwide. Several neurologic manifestations have been reported in association with SARS-CoV-2, including ischemic, hemorrhagic, and cerebral venous stroke. Whereas infection can trigger an inflammatory prothrombotic cascade and ischemic stroke, stroke can induce immune dysregulation and expose a patient's vulnerability to infection.[2] The heterogeneity of stroke subtypes that have emerged in association with SARS-CoV-2[3,4] suggests heterogeneous mechanisms of stroke including endothelial dysfunction, thrombotic diathesis, and nonspecific effects of inflammation.[5] Patients with COVID-19–associated stroke have been reported to have a higher risk for severe disability and mortality.[4,6,7]

Whereas there has been an increase in thromboembolic events reported with COVID-19,[8] a decline in acute stroke code activations, stroke hospitalizations, and mechanical thrombectomy volumes have been reported at local, regional, and national levels,[9-13] with most reports from comprehensive stroke centers (CSCs) in highly resourced countries. There is a relative paucity of information on the effect of the pandemic on acute stroke hospitalization volume and IV thrombolysis (IVT) acute treatment in low- or middle-income countries and in primary stroke centers (PSCs) without endovascular capability. There is also little information on the recovery of volumes in the later phases of the pandemic.

Objectives and Prespecified Hypothesis

In this context, the present study aims to broaden the scope of evaluating the effect of the COVID-19 pandemic on global stroke care to include developed and developing nations in the early and later phases of the COVID-19 pandemic. Our primary aim was to evaluate the effect of COVID-19 on stroke care as measured by the changes in volumes for (1) overall stroke hospitalizations and (2) IVT treatment (both direct presenting and patients transferred with IVT) for acute stroke across the prepandemic and pandemic periods in a multinational pool of PSCs and CSCs. In a secondary aim, the pandemic months were divided into an early (March 1, 2020, to April 30, 2020) and later phase (May 1, 2020, to June 30, 2020) to evaluate for stroke or IVT volume recovery in the later months.

We hypothesized that, in the face of the pandemic's strain on health care infrastructure, (1) a global reduction in all 3 aforementioned measurements of stroke care would occur over the pandemic in relation to both prepandemic periods, (2) hospitals with higher COVID-19 inpatient volumes would report greater decreases in stroke admissions and IVT volumes (direct and transfers) compared to hospitals with lower COVID-19 inpatient volumes, (3) the degree of decline in stroke hospitalizations and IVT volumes would be less profound in CSC compared to PSC, (4) a geographic variation would exist in the intensity of decline in stroke care, and (5) a recovery in stroke hospitalizations and IVT volumes would be observed in the 2 later pandemic months vs the early pandemic period.

Methods

Study Design

This was a cross-sectional, observational, retrospective study evaluating monthly volumes of consecutive patients hospitalized with a diagnosis of COVID-19, stroke, IVT treatment, and IVT transfers. The diagnoses were identified by their related ICD-10 codes (primary, secondary, or tertiary discharge codes) or classifications in clinical stroke databases maintained at participating centers. Case ascertainment was verified by a physician or stroke coordinator.

Setting and Participants

Data were collected from collaborators of the Society of Vascular and Interventional Neurology (SVIN) including the Latin America Stroke Group, Middle East North Africa Stroke and Interventional Neurotherapies Organization (MENA-SINO), the Japanese Society of Vascular & Interventional Neurology Society (JSVIN), and academic partners from 6 continents, 70 countries, and 457 centers. Centers were screened for potential external confounders that could explain any unexpected changes in volumes. Of the 457 centers, 54 centers were excluded due to incomplete data or confounders. One center in Africa (Zimbabwe) was excluded due to a health care worker strike from September to January. One center in Egypt was excluded due to the emergency department being closed most days in June 2020. One center in Arkansas was excluded from the stroke hospitalization volume analysis because this center became the designated center for all patients with stroke in its region during the pandemic, resulting in an abrupt increase in stroke volumes. One center in Malaysia was excluded as this was a new center in May 2020. Of the remaining 403 hospitals, 285 centers contributed to both stroke and thrombolysis volume data. For IVT transfers, centers with a mean of 4 or more transfers per month during the baseline control period were included.

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We compared the stroke, IVT, and IVT transfer diagnosis in the 4 initial months of the pandemic (March 1, 2020, to June 30, 2020) with (1) the immediately preceding 4 months (November 2019 to February 2020) as the primary analysis and (2) the equivalent 4 months in the previous year (March 1, 2019, to June 30, 2019) as the secondary analysis. The primary analysis provided a picture of stroke care utilization prior to COVID-19, whereas the secondary analysis allowed for the adjustment for seasonal variations in the risks for stroke.[14]

Study Variables and Outcomes Measures

Stroke hospitalization was defined as admission to a hospital with a TIA, ischemic stroke, or intracerebral hemorrhage. IVT was defined as acute ischemic stroke treatment with IVT. IVT transfer was defined as a patient who was treated with IVT and transferred to another stroke center. Centers were asked not to duplicate patients receiving IVT if both referral and recipient centers were included in this analysis; the patient was computed with the referring center, and as an IVT transfer for the recipient hospital. COVID-19 hospitalization was defined as any patient admitted with COVID-19 diagnosis to the hospital, which could encompass non-neurologic diagnosis.

Median monthly volumes for overall stroke hospitalizations and IVT treatments for direct presenting and transfer patients were computed and compared across the pandemic and prepandemic periods for the overall population and across the low, intermediate, and high volume strata based on mean monthly volume tertiles for COVID-19 hospitalizations (≤6.2 vs >6.2 to 61.9 vs >61.9 COVID-19 admissions/month), stroke admissions (≤39.0 vs >39.0 to 72.9 vs >72.9 stroke admissions/month), and IVT volume (≤4.0 vs >4.0 to 10.0 vs >10.0 IVT/month).

Standard Protocol Approvals, Registrations, and Patient Consents

This was an investigator-initiated project. The first and last authors wrote the first draft of the manuscript with subsequent input of all coauthors. There were no external funding sources. The institutional review boards from the coordinating sites (Emory University School of Medicine and Boston University School of Medicine) considered that the investigators did not have access to identifiable protected health information and thus no informed consent or institutional review board oversight was required since the study did not meet the federal description of human subject research.

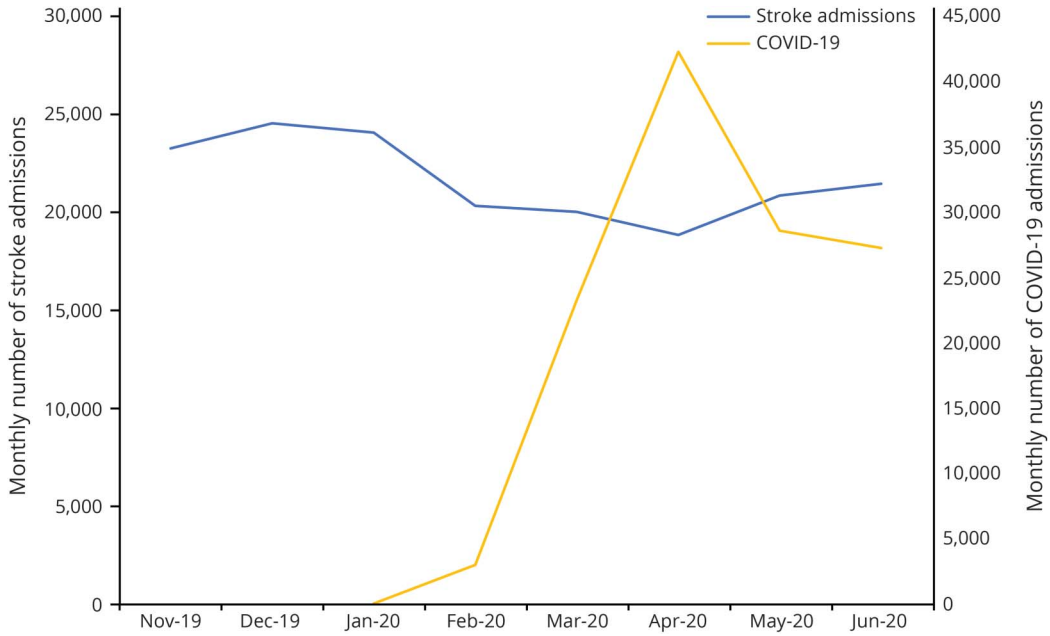
Data Availability

The authors declare that all supporting data are available within the article. Supplemental data are available from Dryad (tables e-1 to e-6, figure e-1, e-2, doi.org/10.5061/dryad.g1jwstqpw). Anonymized data are available upon reasonable request.

Statistics

The monthly volumes for IVT and stroke hospitalizations were compared for the period before (1 year and immediately before) and during the COVID-19 pandemic. The normality of the data was tested with the Shapiro-Wilk test. The nonparametric Wilcoxon signed-rank test was applied to compare differences in monthly volume between 2 time periods. The analyses were repeated in the setting of low, intermediate, and high COVID-19 and stroke volume hospitals.

Figure 1 Monthly Stroke vs Coronavirus Disease 2019 (COVID-19) Admissions



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We looked at the percentage change in the number of IV thrombolysis and stroke admissions before and during the COVID-19 pandemic. The 95% confidence intervals (CIs) for percentage change were calculated using the Wilson procedure without correction for continuity. The relative percentage decrease in volume between low, intermediate, and high-volume hospitals was tested using the z test of proportion. All data were analyzed using SAS version 9.4 (SAS Institute) and the significance level was set at a p value of < 0.05.

Results

There were 82,465, 91,373, and 80,894 stroke hospitalizations (overall n = 254,732) and 12,527, 13,334 and 11,570 IVT therapies (overall n = 37,431) included across the 4-month prior-year pandemic, 4-month immediately prepandemic, and 4-month pandemic periods, respectively. Country-specific data contributions and relative changes across the pandemic are summarized in table e-3 (doi.org/10.5061/dryad.g1jwstqpw).

Stroke Hospitalization

Monthly stroke hospitalization as compared with COVID-19 hospitalization volumes are represented in figure 1. In the primary analysis, there were 91,373 hospitalizations in the 4 months of the prepandemic period compared to 80,894 during the pandemic months, representing an 11.5% drop (95% CI −11.7 to −11.3, $p < 0.0001$; monthly median [interquartile range (IQR)] stroke hospitalization volume/center 54.0 [30.8–86.5] to 43.0 [24.3–71.3], $p < 0.0001$, n = 325 sites) (table 1). There was geographic variation of the decline in stroke hospitalization: Asia, −6.5% (95% CI −6.8 to −6.3, p<0.0001); North America, −18.8% (95% CI −19.3 to −18.3, $p < 0.0001$); Europe, −10.9% (95% CI −11.3 to −10.5,

Table 1 Stroke Volumes Immediately Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic

	Overall volume					Monthly volume, median (IQR)				
	N	n1	n2	Relative (%) change, % (95% CI)	*p* Value	N	Immediately before	During COVID-19	Difference[a] (95% CI)	*p* Value
Overall	325	91,373	80,894	−11.5 (−11.7 to −11.3)	<0.0001	325	54.0 (30.8–86.5)	43.0 (24.3–71.3)	−6.7 (−8.3 to −5.8)	<0.0001
Hospital COVID-19 volume[b]										
Low	85	29,835	28,890	−3.2 (−3.4 to −3.0)	<0.0001	85	51.5 (24.5–89.8)	46.3 (21.5–86.3)	−3.0 (−5.0 to 1.5)	0.002
Intermediate	102	24,849	21,879	−12.0 (−12.4 to −11.6)	<0.0001	102	50.2 (27.8–83.0)	38.8 (24.5–68.0)	−7.5 (−9.0 to −4.0)	<0.0001
High	91	26,575	21,913	−17.5 (−18.0 to −17.1)	<0.0001	91	61.3 (48.5–96.3)	49.0 (35.8–71.3)	−11.3 (−13.8 to −8.0)	<0.0001
Hospital stroke volume[c]										
Low	113	10,518	8,951	−14.9 (−15.6 to −14.2)	<0.0001	113	23.5 (16.5–31.0)	20.3 (12.0–25.8)	−3.2 (−4.3 to −2.0)	<0.0001
Intermediate	108	23,698	19,449	−17.9 (−18.4 to −17.5)	<0.0001	108	55.1 (48.0–61.3)	43.3 (37.6–52.4)	−9.6 (−11.0 to −7.7)	<0.0001
High	104	57,157	52,494	−8.2 (−8.4 to −7.9)	<0.0001	104	105.2 (87.9–146.3)	94.7 (72.4–145.3)	−11.8 (−16.0 to −8.5)	<0.0001
Primary vs comprehensive stroke center[d]										
Primary	89	14,782	12,222	−17.3 (−17.9 to −16.7)	<0.0001	89	31.5 (19.8–52.0)	26.0 (13.3–42.0)	−5.3 (−8.0 to 4.0)	<0.0001
Comprehensive	236	76,591	68,672	−10.3 (−10.6 to −10.1)	<0.0001	236	61.3 (39.1 to 95.9)	51.4 (30.4–85.7)	−7.5 (−9.2 to −6.0)	<0.0001

Abbreviations: CI = confidence interval; IQR = interquartile range; N = number of hospitals; n = number of admissions.
n1 and immediately before are based on 4 months before the pandemic (November 2019 to February 2020). n2 and during COVID-19 are based on March 2020 to June 2020. *p* Values are from Poisson means test (overall volume analysis) and Wilcoxon signed-rank test (monthly volume analysis).
[a] Difference denotes the median difference between the 2 time periods.
[b] *p*: Low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001.
[c] *p*: Low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001.
[d] *p*: Primary vs comprehensive <0.0001.

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p<0.0001); South America, −17.4% (95% CI −18.5 to −16.3, $p < 0.0001$); Africa, −30.2% (95% CI −32.2 to −28.3, $p < 0.0001$); whereas Oceania (−1.9%; 95% CI −2.5 to −1.5, $p = 0.3$) did not demonstrate significance (table e-1, doi.org/10.5061/dryad.g1jwstqpw). PSCs −17.3% (95% CI −17.9 to −16.7, n = 89) demonstrated greater declines compared to CSCs−10.3% (95% CI −10.6 to −10.1, n = 236) (table 1).

IV Thrombolysis

IV thrombolytic volumes declined with 13,334 interventions in the prepandemic period vs 11,570 during the pandemic, representing a 13.2% drop (95% CI −13.8 to −12.7, $p < 0.001$; median [IQR] monthly IVT volume/center 6.5 [2.8–12.0] to 5.3 [2.0–10.5], $p < 0.001$, n = 389 centers) (table 2, figure 2). IVT decline was seen in most continents: Asia, −9.9% (95% CI −11.0 to −8.9, p<0.0001); North America, −14.4% (95% CI −15.6 to −13.3, $p < 0.0001$); Europe, −13.5% (95% CI −14.4 to −12.6, $p < 0.0001$); South America, −24.2% (95% CI −27.6 to −21.0, $p < 0.0001$); Africa −23.5% (95% CI −29.8 to −18.2, $p < 0.01$). There was no appreciable difference in IVT in Oceania −1.9% (95% CI −3.9 to −0.92, $p = 0.7$) (table e-2, doi.org/10.5061/dryad.g1jwstqpw). IVT declines were greater in PSCs −15.5% (95% CI −16.9 to −14.2, n = 138 centers) vs CSCs −12.6% (95% CI −13.3 to −12.0, n = 251 centers, $p = 0.0001$) (table 2).

Recovery of Stroke and IVT Volume Analysis

In the recovery analysis, there were 38,616 stroke hospitalizations in the early 2 months of the pandemic compared to 42,278 stroke hospitalizations in the later 2 pandemic months, representing an increase of 9.5% (95% CI 9.2–9.8, $p < 0.0001$, n = 325 centers). The recovery in stroke hospitalization volume was seen in all strata of COVID-19 hospitalization burden, with a gradient of recovery more significant in low

Table 2 Tissue Plasminogen Activator (tPA) Procedure Volumes Immediately Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic

	Overall volume					Monthly volume, median (IQR)				
	N	n1	n2	Relative (%) change, % (95% CI)	*p* Value	N	Immediately Before	During COVID-19	Difference[a] (95% CI)	*p* Value
Overall	389	13,334	11,570	−13.2 (−13.8 to −12.7)	<0.0001	389	6.5 (2.8–12.0)	5.3 (2.0–10.5)	−0.75 (−1.0 to −0.50)	<0.0001
Hospital COVID-19 volume[b]										
Low	112	3,162	2,871	−9.2 (−10.3 to −8.2)	<0.0001	112	3.5 (1.5–8.5)	3.1 (1.3–8.1)	−0.25 (−0.50 to −0.19)	<0.0001
Intermediate	102	3,373	2,947	−12.6 (−13.8 to −11.6)	<0.0001	102	6.3 (3.3–13.0)	5.3 (2.5–10.8)	−0.75 (−1.0 to −0.25)	<0.0001
High	96	4,252	3,439	−19.1 (−20.3 to −18.0)	<0.0001	96	9.1 (5.6–15.3)	7.5 (4.0–12.5)	−1.9 (−2.5 to −1.0)	<0.0001
Hospital IV tPA volume[c]										
Low	133	1,052	929	−11.7 (−13.8 to −9.9)	0.003	133	1.8 (1.5–2.8)	1.3 (1.0–2.5)	−0.19 (−0.25 to −0.19)	0.007
Intermediate	133	3,553	3,049	−14.2 (−15.4 to −13.1)	<0.0001	133	6.8 (5.0–8.0)	5.3 (3.8–7.3)	−1.0 (−1.5 to −0.75)	<0.0001
High	123	8,729	7,592	−13.0 (−13.8 to −12.3)	<0.0001	123	15.3 (12.3–19.5)	13.8 (10.3–17.8)	−2.3 (−3.0 to −1.5)	<0.0001
Primary vs comprehensive stroke center[d]										
Primary	138	2,763	2,334	−15.5 (−16.9 to −14.2)	<0.0001	138	3.1 (1.5–6.5)	2.1 (1.3–5.5)	−0.25 (−0.75 to 0.19)	<0.0001
Comprehensive	251	10,571	9,236	−12.6 (−13.3 to −12.0)	<0.0001	251	8.8 (4.5–14.0)	7.3 (3.5–12.8)	−1.0 (−1.3 to −0.50)	<0.0001

Abbreviations: CI = confidence interval; IQR = interquartile range; N = number of hospitals; n = number of procedures.
n1 and immediately before are based on 4 months before the pandemic (November 2019 to February 2020). n2 and during COVID-19 are based on March 2020 to June 2020. *p* Values are from Poisson means test (overall volume analysis) and Wilcoxon signed-rank test (monthly volume analysis).
[a] Difference denotes the median difference between the 2 time periods.
[b] *p*: Low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001.
[c] *p*: Low vs intermediate 0.038; low vs high 0.234; intermediate vs high 0.076.
[d] *p*: Primary vs comprehensive 0.0001.

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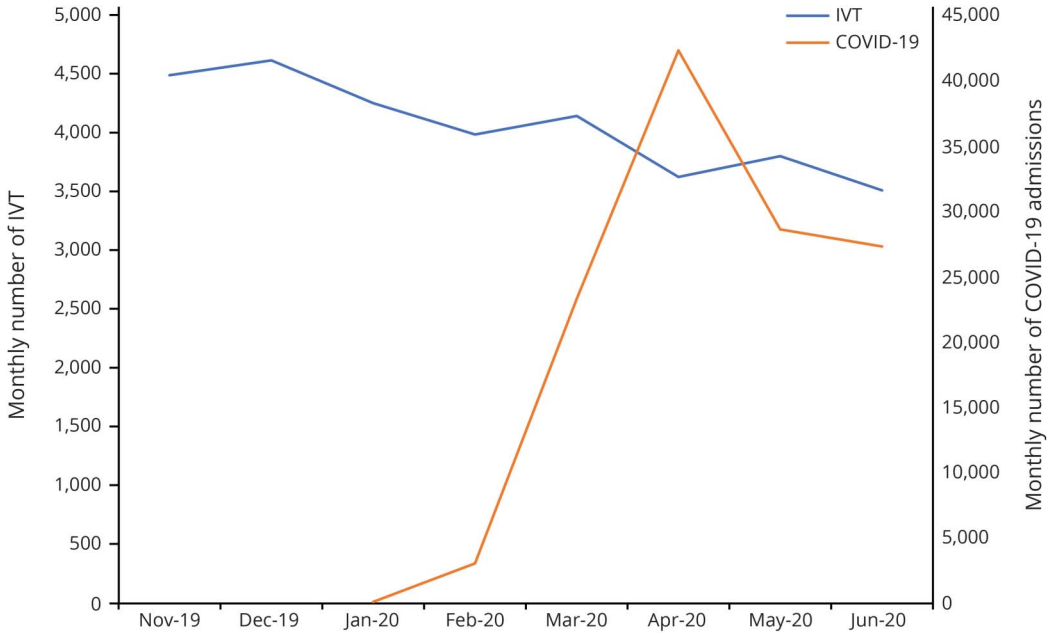
Figure 2 Monthly IV Thrombolysis (IVT) vs Coronavirus Disease 2019 (COVID-19) Admissions



(14.6%; 95% CI 14.0–15.2, $p < 0.0001$) vs intermediate (9.0%; 95% CI 8.4–9.5, $p < 0.0001$) vs high-volume (4.6%; 95% CI 4.2–5.0, $p < 0.0001$) COVID-19 hospitalization. There was a gradient in stroke hospitalization recovery by baseline hospital stroke volume, significant in high-volume (13.9%; 95% CI 13.5–14.3, $p < 0.0001$) stroke centers compared to intermediate or low volume centers, which in their strata did not demonstrate significance in recovery. Stroke hospitalization volume recovery was more significant in CSCs (10.9%; 95% CI 10.6–11.3, $p < 0.0001$) compared to PSCs (1.8%; 95% CI 1.5–2.1, $p = 0.3$) (table 3).

IV thrombolysis was administered to 5,714 patients in the early pandemic compared to 5,856 patients in the later pandemic months, representing a nonsignificant increase of 2.5% (95% CI 2.1–2.9, $p = 0.19$). Recovery in IVT volume was more significant in intermediate (6.1%, 95% CI 5.0–7.4) vs low (2.6%, 95% CI 1.9–3.6, $p < 0.0001$) COVID-19 hospitalization centers. A trend in IVT volume recovery was seen with CSCs (4.1%, 95% CI 3.6–4.7, $p = 0.053$).

IVT Transfer Analysis

There were 1,337 IVT transfers in the prepandemic compared to 1,178 in the pandemic months, representing an 11.9% drop (95% CI −13.7 to −10.3, $p = 0.001$). The IVT transfer declines were significant in the strata of hospitals with low (−18.3%, 95% CI −23.9 to −13.9, $p = 0.03$) and high (−14.9%, 95% CI −18.1 to −12.1, $p = 0.008$) COVID-19 volume (table 4).

Secondary Analysis

Table 5 reveals the volumes for stroke hospitalizations, IVT, and IVT transfers during the first 4 months of the pandemic vs the corresponding period in the prior year. There were significant declines in the overall and monthly volumes for all metrics.

Intersection of COVID-19, SARS-CoV-2 Infection, and Stroke Hospitalizations

A total of 269 centers provided data on SARS-CoV-2 infection and diagnosis of stroke in the same patient. A diagnosis of any stroke was present in 1.48% (1778/119,967) of COVID-19 hospitalizations, with continental variation: Africa 1.6% (47/2879), Asia 1.5% (317/20,858), Oceania 0.4% (1/257), Europe 1.4% (507/36,871), North America 1.2% (615/49,237), South America 3.0% (291/9,865) (table e-5, doi.org/10.5061/dryad.g1jwstqpw).

SARS-CoV-2 infection was present in 3.3% (1722/52,026) of stroke hospitalizations (table e-5, doi.org/10.5061/dryad.g1jwstqpw) with continental variation: Africa 3.1% (56/1828), Asia 2.7% (342/12,686), Oceania 0.1% (1/932), Europe 3.3% (502/15,220), North America 3.0% (527/17,855), South America 8.4% (294/3,505) (table e-6, doi.org/10.5061/dryad.g1jwstqpw).

Discussion

In this temporal analysis of more than 254,000 stroke hospitalizations worldwide, there was a global decrease in stroke admissions (−11.5%), IV thrombolysis (−13.2%), and IVT transfers (−11.9%) during the first 4 pandemic months, compared to the immediately preceding period, confirming our primary hypothesis. A decrease in volume was also seen in relation to the equivalent period in the prior year for all metrics. The declines in both stroke

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Table 3 Stroke and IV Tissue Plasminogen Activator (tPA) Overall Volumes During Early and Late Coronavirus Disease 2019 (COVID-19) Pandemic

	Stroke[a]					IV tPA[b]				
	N	Early COVID-19	Late COVID-19	Relative (%) change, % (95% CI)	*p* Value	N	Early COVID-19	Late COVID-19	Relative (%) change, % (95% CI)	*p* Value
Overall	325	38,616	42,278	9.5 (9.2 to 9.8)	<0.0001	389	5,714	5,856	2.5 (2.1 to −2.9)	0.187
Hospital COVID-19 volume										
Low	85	13,461	15,429	14.6 (14.0 to 15.2)	<0.0001	112	1,417	1,454	2.6 (1.9 to 3.6)	0.490
Intermediate	102	10,471	11,408	9.0 (8.4 to 9.5)	<0.0001	102	1,430	1,517	6.1 (5.0 to 7.4)	0.109
High	91	10,712	11,201	4.6 (4.2 to 5.0)	0.001	96	1,717	1,722	0.29 (0.12 to 0.68)	0.932
Hospital stroke/IV tPA volume										
Low	113	4,468	4,483	0.34 (0.21 to 0.56)	0.874	133	464	465	0.22 (0.04 to 0.12)	0.974
Intermediate	108	9,604	9,845	2.5 (2.2 to 2.8)	0.084	133	1,525	1,524	0.07 (0.01 to 0.38)	0.986
High	104	24,544	27,950	13.9 (13.5 to 14.3)	<0.0001	123	3,725	3,867	3.8 (3.2 to 4.5)	0.103
Primary vs comprehensive stroke center										
Primary	89	6,057	6,165	1.8 (1.5 to 2.1)	0.329	138	1,189	1,145	−3.7 (−2.8 to −4.9)	0.363
Comprehensive	236	32,559	36,113	10.9 (10.6 to 11.3)	<0.0001	251	4,525	4,711	4.1 (3.6 to 4.7)	0.053

Abbreviations: CI = confidence interval; N = number of hospitals.
The early and late COVID-19 periods are based on March 2020 to April 2020 and May 2020 to June 2020, respectively. *p* Value is from Poisson means test.
[a] Stroke volume analysis. Hospital COVID-19 volume: low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001. Hospital stroke volume: low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001. Primary vs comprehensive <0.0001.
[b] IV tPA volume analysis. Hospital COVID-19 volume: low vs intermediate <0.0001; low vs high <0.0001; intermediate vs high <0.0001. IV tPA volume: low vs intermediate 0.383; low vs high 0.0001; intermediate vs high <0.0001. Primary vs comprehensive = NA.

hospitalization and IVT were greater in PSCs compared to CSCs. Recovery of stroke hospitalization volume (+9.5%) was noted in the 2 subsequent months vs the 2 initial months of the pandemic, with greater recovery in hospitals with lower COVID-19 hospitalization volume, high-volume stroke centers, and CSCs.

Table 4 Tissue Plasminogen Activator (tPA) Transfer Volumes Immediately Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic

	Overall volume					Monthly volume, median (IQR)				
	N	n1	n2	Relative (%) change, % (95% CI)	*p* Value	N	Immediately before	During COVID-19	Difference[a] (95% CI)	*p* Value
Overall	39	1,337	1,178	−11.9 (−13.7 to −10.3)	0.001	39	7.5 (5.8 to 11.3)	7.3 (5.0 to 9.5)	−0.75 (−1.3 to 0.0)	0.027
Hospital COVID-19 volume[b]										
Low	7	229	187	−18.3 (−23.9 to −13.9)	0.032	7	6.5 (5.8 to 8.5)	6.8 (6.5 to 7.5)	−1.0 (−9.8 to 1.8)	0.688
Intermediate	14	428	404	−5.6 (−8.2 to −3.8)	0.341	14	7.5 (4.5 to 11.5)	7.5 (4.3 to 9.8)	−0.38 (−1.8 to 1.3)	0.352
High	14	538	458	−14.9 (−18.1 to −12.1)	0.008	14	8.0 (6.0 to 11.3)	6.8 (5.3 to 9.5)	−1.3 (−2.5 to 1.3)	0.107

Abbreviations: CI = confidence interval; IQR = interquartile range; N = number of hospitals; n = number of transfers.
n1 and immediately before are based on 4 months before the pandemic (November 2019 to February 2020). n2 and during COVID-19 are based on March 2020 to June 2020. *p* Values are from Poisson means test (overall volume analysis) and Wilcoxon signed-rank test (monthly volume analysis).
[a] Difference denotes the median difference between the 2 time periods.
[b] *p*: Low vs intermediate <0.0001; low vs high 0.239; intermediate vs high <0.0001.

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Table 5 Overall and Monthly Volumes 1 Year Before and During Coronavirus Disease 2019 (COVID-19) Pandemic

	Overall volume					Monthly volume, median (IQR)				
	N	n1	n2	Relative (%) change, % (95% CI)	*p* Value	N	1 year before	During COVID-19	Difference[a] (95% CI)	*p* Value
Stroke	297	82,465	72,554	−12.0 (−12.2 to −11.8)	<0.0001	297	50.3 (28.3 to 80.8)	42.0 (24.3 to 70.3)	−5.8 (−7.8 to −4.5)	<0.0001
IV tPA	377	12,527	11,198	−10.6 (−11.2 to −10.1)	<0.0001	377	6.0 (2.3 to 12.0)	5.3 (2.0 to 10.5)	−0.50 (−0.75 to −0.25)	<0.0001
IV tPA transfer	36	1,331	1,140	−14.4 (−16.3 to −12.6)	<0.0001	36	7.6 (5.3 to 12.0)	7.5 (5.5 to 9.5)	−1.1 (−2.0 to 0.25)	0.038

Abbreviations: CI = confidence interval; IQR = interquartile range; N = number of hospitals; n = number of admissions/procedures/transfers; tPA = tissue plasminogen activator.
n1 and 1 year before are based on 4-month data 1 year before the pandemic (March 2019 to June 2019). n2 and during COVID-19 are based on data from March 2020 to June 2020. *p* Values are from Poisson means test (overall volume analysis) and Wilcoxon signed-rank test (monthly volume analysis).
[a] Difference denotes the median difference between the 2 time periods.

The decreases in the volume of stroke care provided were noted across centers with high, intermediate, and low COVID-19 hospitalization burden, and also across high, intermediate, and low volume stroke and IVT centers. As hypothesized, the magnitude of decrease of stroke hospitalizations and IVT was greater in centers with higher COVID-19 inpatient volumes.

Our results concur with other recent reports on the collateral effects of the COVID-19 pandemic on stroke systems of care including studies from China,[11] Italy,[15] Spain,[10] France,[12,16] Germany,[17] Brazil,[18] Canada,[19] and the United States.[9,20-22] Although prior analyses have described temporal and regional changes in stroke hospitalizations and IVT, this is among the first descriptions of the change at a global level, including primary and CSCs. Hospital access related to high COVID-19 burden was unlikely a factor, as the decline was seen in centers with few or no patients with COVID-19.[23,24] Patient fear of contracting COVID-19 may have played a role, along with a decrease in presentation of TIA, mild, or moderate strokes, as reported by Diegoli et al.[18] Physical distancing measures may have prevented patients from the timely witnessing of a stroke. Similar to cardiovascular events, it is conceivable that there was a true population-level reduction in cerebrovascular events, possibly related to decreased consumption of high-sodium, fast foods, reduced exposure to ambient air pollution, or improvement in patient behaviors.[24] A reduction in exposure to other common viruses that may play a role in triggering vascular events may have also reduced stroke risk.

In the recovery analysis, there was a gradient of recovery in stroke hospitalization in hospitals with lower compared to higher COVID-19 burden. CSCs and high-volume stroke centers demonstrated greater recovery, suggesting patients with a higher acuity of care needs seeking care in these comprehensive centers.

Our subgroup of 264 centers including 119,967 COVID-19 hospitalizations expands on prior mechanical thrombectomy analysis that was limited to CSCs (Nogueira) and represents the largest sample reporting the concomitant diagnoses of stroke and SARS-CoV-2 infection to date. Our 1.48% stroke rate in COVID-19 hospitalizations is similar to the pooled incidence of 1.1%–1.2% (range, 0.9%–2.7%) of hospitalized patients with COVID-19.[4] The higher rate may be explained in part by the higher number of patients contracting SARS-CoV-2 over time and higher availability of testing. Some variation in the proportions are expected given the different definitions (all strokes vs ischemic only) and populations involved (all hospitalized vs severely infected only) across studies. We also provide another perspective on this relationship by reporting an incidence of 3.3% (1722/52,026) for SARS-CoV-2 infection across all stroke hospitalizations among centers with documented COVID-19 hospitalization.

Finally, 25 years after the landmark National Institute of Neurological Disorders and Stroke trials showing the benefit of tPA, we learned from this global analysis that as of 2020, the availability of IVT for acute stroke therapy continues to be lacking in multiple countries in Africa (i.e., Nigeria, Kenya, Zimbabwe, Ghana, Ethiopia, Sudan) owing to its high cost and relative implementation complexity, limiting our analysis of temporal IVT treatment trends for this continent. This void highlights a disparity of access to basic stroke therapy in multiple low-income countries across the world.

To our knowledge, this is the largest global study to date evaluating the intersection of the COVID-19 pandemic with stroke care. Our study included the participation of diverse geography of centers from 6 continents, 70 countries, and 457 CSCs and PSCs.

Our study has several limitations. The diagnosis of stroke/TIA in some centers was obtained using administrative coding of hospital ICD codes and hence there is a possibility of misclassification of diagnosis, potentially compounded by regional and national variations in stroke diagnosis and delivery of care. However, centers contributing to these data have systems to track stroke metrics of care, thus the relative

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changes in volume from this analysis are likely robust. Details on patient-level data including demographics, stroke subtypes, and clinical outcomes were not collected as these were outside the scope of the study. The definition of the pandemic period was arbitrary because the outbreak started and peaked at different times at different locations. This led to the computation of relative increases in volumes during the study period in the earlier affected regions, such as China, resulting in a potential underestimation of the global effect. Finally, the sampling varied with the availability of complete data in each subset of the analysis.

The COVID-19 pandemic was associated with an initial global decline in the volume of stroke hospitalizations, IVT, and interfacility IVT transfers. These reductions were observed regardless of COVID-19 hospitalization burden and prepandemic stroke and IVT volumes. PSCs and centers with higher COVID-19 inpatient volumes experienced steeper declines. Recovery of stroke hospitalization but not IVT volume was noted in the later phase of the pandemic months and associated with lower COVID-19 hospital burden, high volume, and CSCs. The findings of our study can inform future studies, preparedness,[25-27] and local policies in the event of a second COVID-19 surge or future pandemic.

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Study Funding

The authors report no targeted funding.

Disclosure

Dr. Nogueira reports consulting fees for advisory roles with Anaconda, Biogen, Cerenovus, Genentech, Imperative Care, Medtronic, Phenox, Prolong Pharmaceuticals, Stryker Neurovascular and stock options for advisory roles with Astrocyte, Brainomix, Cerebrotech, Ceretrieve, Corindus Vascular Robotics, Vesalio, Viz-AI, and Perfuze. Dr. Martins reports receiving lecture fees from Bayer, Medtronic, Penumbra and speaker / advisory board fees from Boehringer Ingelheim. Dr. Czlonkowska reports service as Expert Witness. Dr. Siegler served as a consultant for Ceribell and the institution of Dr. Siegler has received research support from the National Institutes of Health. The institution of Dr. Czap has received research support from the National Institutes of Health. Dr. Holmstedt served as a consultant for Astrazeneca and the institution of Dr. Holmstedt has received research support from the National Institutes of Health, the Patient-Centered Outcomes Research Institute, and CSPC Pharmaceuticals. Dr. Holmstedt served as a Study Adjudicator with Ischemia Care. Dr. Turan served on a scientific advisory or DSMB for Pfizer/Merck and Gore Inc. and has received publishing royalties from a publication relating to health care. Dr. Alexandrov served on a speakers bureau for Genentech and the institution of Dr. Alexandrov has received research support from the National Institutes of Health. Dr. Huang served on a scientific advisory or DSMB for ReNeuron and KMPHC. Dr. Raz served as an expert witness for law firms and has received publishing royalties from a publication relating to health care. Dr. Sheth served as a consultant for Penumbra and Cerenovus. The institution of Dr. Frankel has received research support from Nico Corporation, Inc. Dr. Rahman served as a consultant for the Ministry of Health and family Planning, Bangladesh, has received research support from the Ministry of Science and Technology, Bangladesh, and has received publishing royalties from a publication relating to health care. The institution of Dr. Sylaja has received research support from Sree Chitra Tirunal Institute for Medical Sciences and Technology. Dr. Farhoudi served as an officer or member of the board of directors for Kenes. Dr. Hokmabadi served on a speakers bureau for ArvandPharmed and Osve Pharmaceutical Company. The institution of Dr. Sakai has received research support from DaiichiSankyo and Terumo. Dr. Sakai has served as a lecture honoralium with Asahi Intec. Dr. Yagita served on a scientific advisory or DSMB for Shionogi, has served on a speakers bureau for Daiichi-Sankyo, Eisai, Bristol-

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Publication History

Received by *Neurology* October 30, 2020. Accepted in final form March 11, 2021.

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Global Impact of COVID-19 on Stroke Care and IV Thrombolysis
Raul G. Nogueira, Muhammad M. Qureshi, Mohamad Abdalkader, et al.
Neurology 2021;96;e2824-e2838 Published Online before print March 25, 2021
DOI 10.1212/WNL.0000000000011885

This information is current as of March 25, 2021

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