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Global Impact of the COVID-19 Pandemic on Stroke Volumes and Cerebrovascular Events: One-Year Follow-up

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ABSTRACT

Background and Objectives: Declines in stroke admission, intravenous thrombolysis, and mechanical thrombectomy volumes were reported during the first wave of the COVID-19 pandemic. There is a paucity of data on the longer-term effect of the pandemic on stroke volumes over the course of a year and through the second wave of the pandemic. We sought to measure the impact of the COVID-19 pandemic on the volumes of stroke admissions, intracranial hemorrhage (ICH), intravenous thrombolysis (IVT), and mechanical thrombectomy over a one-year period at the onset of the pandemic (March 1, 2020, to February 28, 2021) compared with the immediately preceding year (March 1, 2019, to February 29, 2020).

Methods: We conducted a longitudinal retrospective study across 6 continents, 56 countries, and 275 stroke centers. We collected volume data for COVID-19 admissions and 4 stroke metrics: ischemic stroke admissions, ICH admissions, intravenous thrombolysis treatments, and mechanical thrombectomy procedures. Diagnoses were identified by their ICD-10 codes or classifications in stroke databases.

Results: There were 148,895 stroke admissions in the one-year immediately before compared to 138,453 admissions during the one-year pandemic, representing a 7% decline (95% confidence interval [95% CI 7.1, 6.9]; p<0.0001). ICH volumes declined from 29,585 to 28,156 (4.8%, [5.1, 4.6]; p<0.0001) and IVT volume from 24,584 to 23,077 (6.1%, [6.4, 5.8]; p<0.0001). Larger declines were observed at high volume compared to low volume centers (all p<0.0001). There was no significant change in mechanical thrombectomy volumes (0.7%, [0.6,0.9]; p=0.49).

Stroke was diagnosed in 1.3% [1.31,1.38] of 406,792 COVID-19 hospitalizations. SARS-CoV-2 infection was present in 2.9% ([2.82,2.97], 5,656/195,539) of all stroke hospitalizations.

Discussion: There was a global decline and shift to lower volume centers of stroke admission volumes, ICH volumes, and IVT volumes during the 1st year of the COVID-19 pandemic compared to the prior year. Mechanical thrombectomy volumes were preserved. These results suggest preservation in the stroke care of higher severity of disease through the first pandemic year.

Trial Registration Information: This study is registered under NCT04934020.

Keywords: COVID-19, acute stroke, ischemic stroke, intracranial hemorrhage, intravenous thrombolysis, mechanical thrombectomy

Classification of Evidence: not applicable as no intervention was conducted.

BACKGROUND:

More than two years after the COVID-19 pandemic was declared in early 2020, over 500 million confirmed cases and 6 million deaths have been reported worldwide. While pulmonary dysfunction is the most common symptom of COVID-19, infection also yields significant disruption of the coagulation system and is a potential trigger for ischemic stroke.[1–3]

Stroke represents an important complication in an estimated 1.1% to 1.5% of COVID-19 admitted patients.[4–8] As a result of the early surge in COVID-19 admissions, the allocation of healthcare resources and the delivery of stroke care have been impacted.[9–13] During the first wave of the COVID-19 pandemic in 2020, declines in stroke admission volumes, intravenous

thrombolysis (IVT), and mechanical thrombectomy have been reported across regional,[14–17] national[18–23] and global[6,24–29] studies. In our initial report covering the first 4 months of the COVID-19 pandemic, we observed a greater than 10% decrease in global stroke admissions, IVT treatments, and IVT transfers, followed by recovery of stroke volume in later months. This report demonstrated the substantial impact of the first wave of the COVID-19 pandemic on global stroke volumes. In the later part of 2020, a "second wave" of the pandemic caused surges in COVID-19 cases throughout the globe. The effects of changes in governmental responses to this second wave, including increased public education efforts and intermittent lockdowns during the 1st year, are scarce. Here, we report the impact of COVID-19 on global stroke volumes over the 1st year of the pandemic.

Study Objective and Hypothesis

The primary objective of this study was to evaluate the one-year volumes of the following stroke metrics: (1) ischemic stroke admissions, (2) intracranial hemorrhage (ICH) admissions, (3) intravenous thrombolysis, (4) mechanical thrombectomy (MT) during the pandemic (March 1, 2020, to February 28, 2021) and compare these metrics to the same one-year period immediately prior (March 1, 2019, to February 29, 2020).

Our primary prespecified hypotheses were that, in the setting of the pandemic's continued strain on healthcare resources, (1) there would be a reduction in all the aforementioned stroke metrics and (2) centers with more COVID-19 volumes would report greater decreases in stroke admissions.

METHODS:

Study design

This was a cross-sectional, observational, retrospective follow-up study evaluating monthly aggregate volumes of consecutive patients hospitalized with a diagnosis of ischemic stroke, intracranial hemorrhage, or COVID-19, and acute reperfusion therapies including intravenous thrombolysis and mechanical thrombectomy. The diagnosis was identified by stroke databases or related ICD-10 codes (primary, secondary, or tertiary discharge codes).

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (**eTable 1**). The study is registered NCT04934020 (clinicaltrials.gov).

Setting and participants

Data were collected from collaborators of a prior global study during the first wave of the pandemic, which consisted of 457 stroke centers across 70 countries.[7] These sites were selected by contact with stroke leaders of national and international stroke societies, who invited sites within their network to participate in this study. These societies included the Society of Vascular and Interventional Neurology, the European Stroke Organization, the Middle East North Africa Stroke and Interventional Neurotherapies Organization, the Japanese Society of Vascular and Interventional Neurology, and the Latin America Stroke Group. An additional 23 sites were invited by publicly available information via institution email addresses.

A comprehensive stroke center was defined as a center that offered mechanical thrombectomy; a primary stroke center (PSC) was defined as a center that did not. Centers with no thrombectomy service at the beginning of the study period that later became thrombectomy capable during the study period were classified as PSC; these centers were excluded from the mechanical thrombectomy analysis. Of the 480 centers invited to contribute to this follow-up one-year study, we received data from 275 stroke centers across 56 countries and 6 continents. Each center was verified for profound drops in volume (i.e. > 50%) that may have biased the analysis. Potential confounders including rerouting or diversion of cases to another hospital were inquired to centers where profound drops in volume were noted. Centers were excluded due to incomplete data during the study period for ischemic stroke (30 centers), intracranial hemorrhage (36 centers), intravenous thrombolysis (36 centers) and mechanical thrombectomy (76 centers).

We defined the beginning of the pandemic in each country based on the date of the first reported case.[30] (**eTable 2**) We defined the second wave with two definitions. Our primary definition was that the number of COVID-19 cases must decline by greater than 50% from the previous wave's peak and more than double at the next peak. The start date for this occurrence was chosen as the minimum closest to the second wave. Secondarily, we defined the second wave as the first definition, with the addition of two or more months apart between the peak of the first wave and the start of the second wave.[31] (**eTable 2**)

Data were collected between May 1, 2021, to September 15, 2021, via electronic medical record to capture completely coded data through the end of the study period, May 31, 2021. Data were submitted to the coordinating sites, Boston Medical Center and Emory University School of

Medicine, via excel sheet. Data verification was conducted with the receipt of data from each site by the lead author (TNN), with additional queries related to incomplete data entry returned to submitting authors, with deadline extension to October 30, 2021. The Principal Investigator (PI, TNN) and the lead statistician had access to all data. Investigators at the coordinating sites had access to site-level data for the purposes of data merging, data verification, and statistical analysis.

Study variables and outcome measures

Study variables were collected as monthly aggregate volumes. Ischemic stroke admission was defined as admission to a hospital with a transient ischemic attach (TIA) or ischemic stroke as the primary diagnosis. IVT was defined as acute ischemic stroke treatment with IVT. ICD-10 codes for ischemic stroke utilized were as follows: I63.0 (Cerebral Infarction), I63.1 (Cerebral infarction due to embolism of precerebral arteries), I63.2 (Cerebral infarction due to unspecified occlusion or stenosis of precerebral arteries), I63.3 (Cerebral infarction due to thrombosis of cerebral arteries), I63.4 (Cerebral infarction due to embolism of cerebral arteries), I63.5 (Cerebral infarction due to unspecified occlusion or stenosis of cerebral arteries), I63.8 (Other cerebral infarction), I63.9 (Cerebral infarction, unspecified). A physician, stroke or research coordinator verified case ascertainment by existing stroke databases, including the Get with the Guidelines Stroke Database, the Czech Republic National Stroke Database, and the Japan National Stroke Database.

Intracranial hemorrhage was defined as admission to a hospital with an intracranial or intracerebral hemorrhage as the primary diagnosis. ICD-10 codes for ICH utilized were as

follows: I61 (Nontraumatic ICH), I61.0 (Nontraumatic ICH in hemisphere, subcortical), I61.1 (Nontraumatic ICH in hemisphere, cortical), I61.2 (Nontraumatic ICH in hemisphere, unspecified), I61.3 (Non-traumatic ICH in the brain stem), I61.4 (Nontraumatic ICH in the cerebellum), I61.5 (Non-traumatic ICH, intraventricular), I61.6 (Nontraumatic ICH, multiple localized), I61.8 (Other non-traumatic ICH), I61.9 (Nontraumatic ICH, unspecified).

COVID-19 admission was defined as any patient admitted with a COVID-19 diagnosis to the hospital, encompassing a non-neurologic diagnosis. The ICD-10 code for COVID-19 diagnosis utilized was UO7.1.

Bias

Centers were screened for potential duplicate data. To avoid data reporting lag bias, we did not include centers with incomplete data for the variable of interest. Centers submitting data from a stroke network were asked not to duplicate IVT or large vessel occlusion patients transferred from a primary stroke center to a comprehensive stroke center. Primary stroke centers were excluded from the MT analysis. In certain nations, COVID-19 case volumes did not demonstrate distinct peaks, either due to consistently high volumes (e.g. Guatemala) or extremely low volumes (e.g. New Zealand), obscuring pandemic waves.

Statistical analysis

First, we compared percentage change in the absolute number of ischemic stroke, ICH, IVT, and MT admissions before and during the COVID-19 pandemic. The 95% confidence intervals for percentage change were calculated using the Wilson procedure without correction for

continuity.[32] The method is computationally simpler with good coverage properties. The differences in admissions across the two periods were assessed for significance using the Poisson Means test. The analysis was repeated by hospital volume (low, intermediate, or high), stroke center (primary or comprehensive), and hospital COVID-19 volume (low, intermediate, or high). The relative percentage decrease in volume between different categories (for example, low vs. intermediate hospital volume) was tested using the z test of proportion.

We then compared average monthly volumes (admissions/month) of ischemic stroke, ICH, IVT, and MT before and during the COVID-19 pandemic. The data were analyzed in a mixed design using a repeated-measures analysis of variance (PROC MIXED analysis in SAS) for accounting for the paired data structure and potential covariates. The auto-regressive, compound symmetrical, and unstructured variance-covariance matrix structures were analyzed for the best model determined by Akaike's Information Criterion. The unstructured matrix was the best fit and was used for the analyses. The monthly hospital volume analysis was adjusted for the date of the peak COVID-19 volume for each country, the start date of the second wave, and the continent. Estimated marginal means were calculated using the LSMEANS statement in PROC MIXED. Similar to the overall volume analysis, monthly volume analysis was stratified by hospital volume, stroke center, and COVID-19 volume.

Finally, we performed a supplementary analysis comparing percentage change in absolute volume and monthly volume between before and during COVID-19 periods across different continents of the world. All data were analyzed using SAS version 9.4 (SAS Institute), and the significance level was set at a P-value of <.05.

Standard Protocol Approvals, Registrations, and Patient Consents

This was an investigator-initiated study. As this was a continuation of our prior work, the institutional review boards from the coordinating sites (Emory University and Boston Medical Center) considered that the investigators did not have access to protected health information in this follow-up study, and thus no IRB oversight was required since the study did not meet the US federal description of human subject research. Site-specific IRB approval was obtained where required by local regulations or institutional policy. There was no protective health information data included in this study. The study was funded by the Society of Vascular and Interventional Neurology research pilot grant. This study was registered under NCT04934020.

Data Availability

Data are available upon reasonable request to the corresponding author.

RESULTS:

Overall, there were 345,089 ischemic stroke and intracranial hemorrhage admissions across the two epochs one-year pre-pandemic and the first year during the pandemic. There were 24,584, 23,077 IVT therapies (overall IVT, n= 47,661) and 18,375, 18,507 mechanical thrombectomy procedures (overall MT, n=36,882) included across the prior-year pandemic, and 1-year pandemic period, respectively **(Figure, A, B**). Data contributions by continent and their relative changes across the pandemic are presented in **eTables 3-6**.

Ischemic Stroke Admissions

There were 148,895 admissions for ischemic stroke in the 1-year pre-pandemic, and 138,453 admissions during the 1-year pandemic, representing a 7% absolute decrease ([95% CI -7.1,-6.9]; p<0.0001, n=245 sites) in ischemic stroke admissions; monthly mean (SE) volume decreased accordingly (43.8 (4.0) to 40.3 (3.9); p<0.0001, n=251 sites). The observed relative decrease in volumes was larger at higher volume stroke admission centers (low vs. intermediate vs. high; p<0.0001) and higher volume COVID-19 centers (low vs. intermediate vs. high; p<0.0001). In the tertile of high volume stroke centers, 32/71 (45%) of centers were high tertile COVID-19 centers. The observed decrease in volumes was smaller at comprehensive stroke centers than primary stroke centers (-6.8% vs. -8.2%; p<0.0001) (**Table 1**).

Geographic variation was noted in the change of ischemic stroke admissions over the 1-year period: Europe, -5.7% ([-5.9,-5.5]; p<0.0001); North America, -6.2% ([-6.5,-6.0]; p<0.0001); Asia, -10.6% ([-11.0,-10.3]; p<0.0001); South America, -13.3% ([-14.4,-12.2]; p<0.0001); Oceania, 4.7% ([4.0-5.4]; p=0.05); Africa, -15.3% ([-18.6,-12.5]; p=0.008) (**eTable 3**).

Intracranial Hemorrhage Admissions

There were 29,585 admissions for intracranial hemorrhage in the 1-year pre-pandemic, and 28,156 admissions during the 1-year pandemic, representing a 4.8% absolute decrease ([-5.1,-4.6]; p<0.0001, n=239 sites); monthly mean (SE) volume decreased (9.7 (1.1) to 9.2 (1.1); p=0.015, n=246 sites). The observed decrease in volumes was greater at high volume compared to intermediate volume (p<0.0001) centers and with a gradient of decrease in higher volume COVID-19 centers (low vs intermediate vs high; p<0.0001). At low volume ICH centers, there

was a 14.6% ([13.2,16.1]; p<0.0001) increase in ICH admissions. At low volume COVID-19 centers, there was no difference (-1.7%, [-2.0, -1.4]; p=0.27) in ICH admissions. In the tertile of high volume intracranial hemorrhage centers, 27/70 (39%) were high tertile COVID-19 centers. There was no observed decrease in ICH admissions at primary stroke centers (-3.2%, [-3.8, -2.7]; p=0.15) but a 5.1% ([-5.4, -4.8]; p<0.0001) decrease at comprehensive stroke centers (**Table 2**), with continental variation noted (**eTable 4**).

Intravenous Thrombolysis

There was a relative decline in intravenous thrombolysis, with 24,584 therapies in the pre-pandemic year compared to 23,077 during the pandemic year, representing a 6.1% absolute decrease ([-6.4,-5.8]; p<0.0001 n=239 sites); monthly mean (SE) volume decreased (7.5 (1.1) to 7.0 (1.1); p=0.006, n=244 sites). (**Figure, B**) There was a 7.1% ([6.8,8.2];p=0.02) increase in IVT at low volume IVT centers. For intermediate volume centers, there was no significant change (-3.1%, [-3.5,-2.7]; p=0.07), and for high volume centers, there was a 9.4% ([-9.8,-8.9];p<0.0001) relative decrease in IVT volume. The observed volume decrease was greater at higher volume COVID-19 centers (low vs. intermediate vs. high; p<0.0001). In the tertile of high volume IVT centers, 33/72 (46%) were high tertile COVID-19 centers. There was a larger relative decrease in IVT volumes at primary stroke centers than comprehensive stroke centers (-11.4% vs. -4.9%; p<0.0001) (**Table 3**) with continental variation (**eTable 5**).

Mechanical thrombectomy

There was no change in MT volume from the pre-pandemic to pandemic year (18,375 vs. 18,507, 0.7 ([0.6,0.9]; p=0.49, n=199 sites); monthly volume was also similar between the two epochs (6.2 (1.1) vs 6.3 (1.1); p=0.72, n=205 sites) (**Table 4, Figure, B**). Among all subgroups, the only difference was a 13.6% ([11.9,15.4]; p=0.001) relative increase at low MT volume centers (**Table 4**), with continental variation (**eTable 6**).

Rates of Concomitant Stroke with COVID-19 Admissions

Concomitant stroke diagnosis with COVID-19 admissions was reported by 218 centers. Overall, stroke diagnosis (any type) was present in 1.3% ([95%CI 1.31-1.38], 5,453/406,792) of COVID-19 admissions. There was continental variation: Africa 0.8% ([0.68-1.04], 87/10,321), Asia 1.6% ([1.52-1.75], 727/44,664), Oceania 0% ([0-1.11], 0/345), Europe 1.6% ([1.55-1.67], 2,689/166,692), North America 1.1% ([1.06-1.16], 1,688/152,654), and South America 0.8% (0.73-0.93], 262/32,116). (**Table 5**)

Concomitant SARS-CoV-2 infection with stroke admission was present in 2.9% ([95%CI, 2.82-2.97], 5,656/195,539) overall, with geographic variation: Africa 4.8% ([3.9-5.9], 87/1,802), Asia 1.5% ([1.37-1.58], 782/53,109), Oceania 0% ([0-0.08], 0/5,032), Europe 3.7% ([3.57-3.84], 2,811/75,993), North America 3.2% ([3.04-3.34], 1,714/53,730), South America 4.5% ([3.96-5.02], 262/5,873). (**Table 6**)

DISCUSSION:

In this cross-sectional study, after the onset of the COVID-19 pandemic, there were substantial decreases in ischemic stroke admissions (7.0%, [95%CI: 7.1,6,9]), ICH admissions (4.8%, [5.1,4.6]), and IVT use (6.1%, [6.4,5.8]) in the one-year of the pandemic compared to the year prior. However, there was no significant difference in the volume of MT between the pandemic and pre-pandemic year. As noted in our prior work with the first wave, among centers with high COVID-19 admission volumes, there was a greater decrease in stroke admission volumes compared to those with low COVID-19 admission volumes (6.6% vs. 11.0%; $p<0.0001$). These findings are consistent with recent national studies evaluating the impact of COVID-19 on stroke admissions during the second wave of the pandemic.[33]

We observed an overall relative decrease in ischemic stroke admission volume across 245 primary and comprehensive stroke centers worldwide. This trend was consistent across all prespecified subgroups. As hypothesized, centers with high COVID-19 volumes had greater decreases in stroke admission volume than those with low COVID-19 volumes. This may reflect a lack of capacity to accommodate stroke admissions at centers with high COVID-19 admissions or different stroke triage patterns during the COVID-19 pandemic. Comprehensive stroke centers experienced a smaller relative decrease in stroke admission volume than primary stroke centers (-6.8% vs. -8.2%).

Overall, ICH admission volumes decreased by 4.8% [5.1,4.6]. Of note, there was a 14.6% [13.2,16.1] increase in ICH volumes at low volume ICH centers. These results may indicate a partial shift in the volume of patients with ICH from intermediate and high-volume centers to

low volume centers, perhaps due to capacity limitations imposed by the high volume of COVID-19 patients at tertiary care centers.

The overall volume of IVT admissions decreased by 6.1% [6.4,5.8] during the pandemic year compared to the prior year, in line with our prior findings of decline in IVT volumes during the first wave of the pandemic.[7] This difference was driven by a large decrease in IVT at high volume centers (9.4%) while there was no significant difference at intermediate volume centers and a 7.1% [6.8,8.2%] increase in IVT at low volume centers.

No difference in overall mechanical thrombectomy volumes was observed in this study. The maintenance of mechanical thrombectomy volumes despite large decreases in overall stroke admission volumes suggests that the population of LVO patients was not significantly reduced through the pandemic year, concordant with early findings from the US Get With the Guidelines Stroke Registry.[21] Alternatively, any decline in mechanical thrombectomy volume related to the COVID-19 pandemic may have been offset by expanded indications for mechanical thrombectomy[34–41] or increased recruitment of cases by low volume centers.

Stroke represents an important complication in COVID-19 infection in an estimated 1.1% to 1.5% of COVID-19 admitted patients.[4,5,8] In our study, stroke was present in 1.3% of COVID-19 admitted patients, in alignment with previous studies. There were 2.9% of all hospitalized stroke patients with concomitant SARS-CoV-2 infection. While we cannot ascertain whether these cases were a direct complication of COVID-19 or an overlap of two conditions that are now

relatively common, we would favor the latter as it has become evident that stroke is a relatively rare complication of COVID-19.

Altogether, these results indicate a decrease in multiple measures of stroke volume and a shift of volumes towards previously lower volume centers but with the maintenance of mechanical thrombectomy volumes. The reduced volumes may suggest the reduced presentation of patients with mild stroke and TIA or changes in clinician decision-making, resulting in fewer admissions.[42,43] Alternatively, it is also possible that mild stroke patients were being triaged to the outpatient setting. Notably, mild strokes accounted for as many as 40% of all IVT cases and 10.7% of all EVT cases across 179 710 AIS patients in a US-based study.[44] This might explain the discrepancy in the relative declines amongst IVT and EVT observed in the current report. While the maintenance of mechanical thrombectomy volumes is reassuring as to the appropriate treatment of LVO patients, the shift seen in other volume measures toward lower volume centers is a trend to be noted. Previous studies have indicated that treatment at high volume centers is associated with better outcomes following stroke, ICH,[45] and mechanical thrombectomy.[46] In the Oceania region, where COVID-19 has been highly controlled, no differences were seen in stroke or intracranial hemorrhage admission volumes, and increases were seen in both IVT and thrombectomy volumes (e**Tables 5, 6**), further highlighting the effects of the pandemic. Additionally, COVID-19 was associated with 2.9% of stroke admissions in this study. Taken with recent studies suggesting that SARS-CoV-2 is likely to become endemic across the globe, this raises concern that SARS-CoV-2 may become an addition to other respiratory infections (influenza, mycoplasma pneumonia) known to trigger and present as a risk factor for stroke. Long term stroke metric and outcome data are important to evaluate whether these changes

persist beyond the pandemic. Some clinical practices for stroke diagnostic evaluation and management may be updated based on reorganization of stroke care during the pandemic.[47]

LIMITATIONS:

While we have robustly shown differences in population-level trends, our study is limited by the inability to characterize the reason for the changes in volumes over the subsequent waves of the pandemic. Inherent to our cross-sectional study design, we could not track changes on the patient level, and the observed population-level changes may be due to confounding factors. Future studies are important to understand patient-level factors influencing the observed trends in stroke volumes. Additionally, we had limited ability to study the effects of governmental policies (e.g., lockdowns) on stroke volumes since the COVID-19 pandemic has impacted every nation differently by timing and severity.

CONCLUSION:

During the first year of the COVID-19 pandemic, worldwide ischemic stroke admission, intracranial hemorrhage admission, and intravenous thrombolysis volumes were relatively decreased while there was no relative change in mechanical thrombectomy volumes. Further, shifts were seen in volumes toward lower-volume centers. A slight recovery in volumes was seen over the year compared to the initial months of the pandemic, but persistently low volumes raise concern that milder forms of a stroke may be untreated or are being redirected to the outpatient setting. Ongoing surveillance and additional future research is warranted to monitor stroke metrics[48–50] and long-term patient outcomes, ensure that public education measures are continued, and ensure patients continue to seek timely care for stroke.

WNL-2022-201299_etab ---http://links.lww.com/WNL/C442
WNL-2022-201299_coinvestigator_appendix1 --- http://links.lww.com/WNL/C443

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Table 1. Ischemic stroke admissions overall and monthly volumes before and during the COVID-19 pandemic.

		Overall volume				Monthly volume*			
	N	n1	n2	Change	*P*	N	Before COVID-19	During COVID-19	*P*
				% (95% CI)			Adjusted Mean (SE)		
Overall	245	148,895	138,453	-7.0 (-7.1 - -6.9)	<0.0001	251	43.8 (4.0)	40.3 (3.9)	<0.0001
Hospital Ischemic stroke volume†									
Low	83	19,437	18,440	-5.1 (-5.5 - -4.8)	<0.0001	84	18.5 (1.1)	17.6 (1.2)	0.081
Intermediate	82	41,789	39,145	-6.3 (-6.6 - -6.1)	<0.0001	84	40.6 (1.9)	38.2 (2.0)	0.0003
High	80	87,669	80,868	-7.8 (-7.9 - -7.6)	<0.0001	83	84.4 (6.3)	77.4 (6.4)	<0.0001
Primary vs. Comprehensive stroke center‡									
Primary	68	26,141	24,007	-8.2 (-8.5 - -7.8)	<0.0001	70	28.7 (4.9)	26.5 (5.0)	0.058
Comprehensive	177	122,754	114,446	-6.8 (-6.9 - -6.6)	<0.0001	181	49.3 (6.7)	45.4 (6.6)	<0.0001
Hospital COVID-19 volume§									
Low	70	37,281	34,811	-6.6 (-6.9 - -6.4)	<0.0001	71	35.5 (6.1)	32.7 (6.0)	0.011
Intermediate	70	42,660	40,391	-5.3 (-5.5 - -5.1)	<0.0001	71	50.8 (7.2)	47.9 (7.1)	0.004
High	70	47,129	41,931	-11.0 (-11.3 - -10.8)	<0.0001	72	45.1 (6.7)	39.3 (6.5)	<0.0001

Abbreviations: N=number of hospitals; n1=number of admissions during twelve months before COVID-19 pandemic; n2= number of admissions during twelve months of the COVID-19 pandemic; CI=confidence interval; SE=standard error

*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent

†*P*: Low vs Intermediate=<0.0001; Low vs High=<0.0001; Intermediate vs High=<0.0001

‡*P*: Primary vs. Comprehensive=<0.0001

§*P*: Low vs Intermediate=<0.0001; Low vs High=<0.0001; Intermediate vs High=<0.0001

Table 2. Intracerebral hemorrhage admissions overall and monthly volumes before and during the COVID-19 pandemic.

		Overall volume				Monthly volume*			
	N	n1	n2	Change	*P*	N	Before COVID-19	During COVID-19	*P*
				% (95% CI)			Adjusted Mean (SE)		
Overall	239	29,585	28,156	-4.8 (-5.1 - -4.6)	<0.0001	246	9.7 (1.1)	9.2 (1.1)	0.015
Hospital Intracerebral hemorrhage volume†									
Low	80	2,319	2,657	14.6 (13.2 - 16.1)	<0.0001	82	2.5 (0.27)	2.9 (0.30)	0.017
Intermediate	80	7,235	6,865	-5.1 (-5.6 - -4.6)	0.002	82	7.4 (0.51)	7.0 (0.52)	0.011
High	79	20,031	18,634	-7.0 (-7.3 - -6.6)	<0.0001	82	21.4 (2.9)	20.0 (2.7)	0.013
Primary vs. Comprehensive stroke center‡									
Primary	65	4,010	3,882	-3.2 (-3.8 - -2.7)	0.150	68	4.9 (0.99)	4.8 (0.98)	0.664
Comprehensive	174	25,575	24,274	-5.1 (-5.4 – 4.8)	<0.0001	178	11.0 (2.0)	10.3 (2.0)	0.014
Hospital COVID-19 volume§									
Low	68	8,434	8,292	-1.7 (-2.0 - -1.4)	0.272	69	8.5 (1.5)	8.3 (1.5)	0.478
Intermediate	70	7,229	6,939	-4.0 (-4.5 - -3.6)	0.015	71	7.4 (1.3)	7.1 (1.3)	0.184
High	69	10,772	9,727	-9.7 (-10.3 - -9.2)	<0.0001	71	12.1 (3.0)	10.8 (2.8)	0.044

Abbreviations: N=number of hospitals; n1=number of admissions during twelve months before COVID-19 pandemic; n2= number of admissions during twelve months of COVID-19 pandemic; CI=confidence interval; SE=standard error

*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent

†*P*: Low vs Intermediate=N/A; Low vs High=N/A; Intermediate vs High=<0.0001

‡*P*: Primary vs. Comprehensive=<0.0001

§*P*: Low vs Intermediate=<0.0001; Low vs High=<0.0001; Intermediate vs High=<0.0001

Table 3. Intravenous thrombolysis overall and monthly volumes before and during the COVID-19 pandemic.

		Overall volume				Monthly volume*			
	N	n1	n2	Change	*P*	N	Before COVID-19	During COVID-19	*P*
				% (95% CI)			Adjusted Mean (SE)		
Overall	239	24,584	23,077	-6.1 (-6.4 - -5.8)	<0.0001	244	7.5 (1.1)	7.0 (1.1)	0.006
Hospital Intravenous thrombolysis volume†									
Low	80	2,222	2,379	7.1 (6.8- 8.2)	0.021	81	1.9 (0.33)	2.1 (0.35)	0.157
Intermediate	80	6,804	6,596	-3.1 (-3.5 - -2.7)	0.072	82	7.0 (0.23)	6.8 (0.32)	0.425
High	79	15,558	14,102	-9.4 (-9.8 - -8.9)	<0.0001	81	16.3 (1.3)	14.9 (1.3)	0.001
Primary vs. Comprehensive stroke center‡									
Primary	62	4,621	4,092	-11.4 (-12.4 - -10.6)	<0.0001	64	7.0 (1.4)	6.4 (1.3)	0.092
Comprehensive	177	19,963	18,985	-4.9 (-5.2 - -4.6)	<0.0001	180	7.8 (1.2)	7.4 (1.1)	0.030
Hospital COVID-19 volume§									
Low	68	5,710	5,651	-1.0 (-1.3 - -0.80)	0.580	69	5.0 (1.2)	5.0 (1.2)	0.810
Intermediate	70	7,347	6,897	-6.1 (-6.7 - -5.6)	0.0002	71	7.6 (1.3)	7.2 (1.3)	0.122
High	67	8,470	7,426	-12.3 (-13.1 - -11.7)	<0.0001	69	9.6 (0.95)	8.5 (0.85)	0.003

Abbreviations: N=number of hospitals; n1=number of admissions during twelve months before COVID-19 pandemic; n2= number of admissions during twelve months of COVID-19 pandemic; CI=confidence interval; SE=standard error

*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent

†*P*: Low vs Intermediate=N/A; Low vs High=N/A; Intermediate vs High=<0.0001

‡*P*: Primary vs. Comprehensive=<0.0001

§*P*: Low vs Intermediate=<0.0001; Low vs High=<0.0001; Intermediate vs High=<0.0001

Table 4. Mechanical thrombectomy overall and monthly volumes before and during the COVID-19 pandemic.

		Overall volume				Monthly volume*			
	N	n1	n2	Change	*P*	N	Before COVID-19	During COVID-19	*P*
				% (95% CI)			Adjusted Mean (SE)		
Overall	199	18,375	18,507	0.7 (0.6 - 0.9)	0.492	205	6.2 (1.1)	6.3 (1.1)	0.715
Hospital Mechanical thrombectomy volume†									
Low	66	1,423	1,616	13.6 (11.9 - 15.4)	0.001	69	1.6 (0.24)	1.8 (0.28)	0.101
Intermediate	67	5,221	5,426	3.9 (3.4 - 4.5)	0.047	69	6.6 (0.27)	6.8 (0.32)	0.312
High	66	11,731	11,465	-2.3 (-2.6 - -2.0)	0.081	67	14.6 (1.2)	14.2 (1.2)	0.260
Primary vs. Comprehensive stroke center‡									
Primary	19	826	883	6.9 (5.4 - 8.8)	0.168	21	3.0 (1.0)	3.2 (1.1)	0.605
Comprehensive	180	17,549	17,624	0.4 (0.3 - 0.5)	0.689	184	6.5 (1.2)	6.6 (1.2)	0.844
Hospital COVID-19 volume§									
Low	56	4,076	4,043	-0.8 (-1.1 - -0.6)	0.714	57	5.3 (1.2)	5.2 (1.2)	0.830
Intermediate	51	4,705	4,817	2.4 (2.0 - 2.9)	0.251	54	6.9 (1.6)	7.1 (1.7)	0.601
High	63	6,771	6,720	-0.8 (-1.0 - -0.6)	0.661	64	5.6 (1.2)	5.6 (1.2)	0.770

Abbreviations: N=number of hospitals; n1=number of admissions during twelve months before COVID-19 pandemic; n2= number of admissions during twelve months of COVID-19 pandemic; CI=confidence interval; SE=standard error

*The monthly volume analysis is adjusted for the date of peak COVID-19 volume for each country, the start date of the second wave, and the continent

†*P*: Low vs Intermediate=<0.0001; Low vs High=<N/A; Intermediate vs High=N/A

‡*P*: Primary vs. Comprehensive=<0.0001

§*P*: Low vs Intermediate=N/A; Low vs High=1.0; Intermediate vs High=N/A

Table 5. Proportion of patients hospitalized with COVID-19 with concomitant diagnosis of stroke

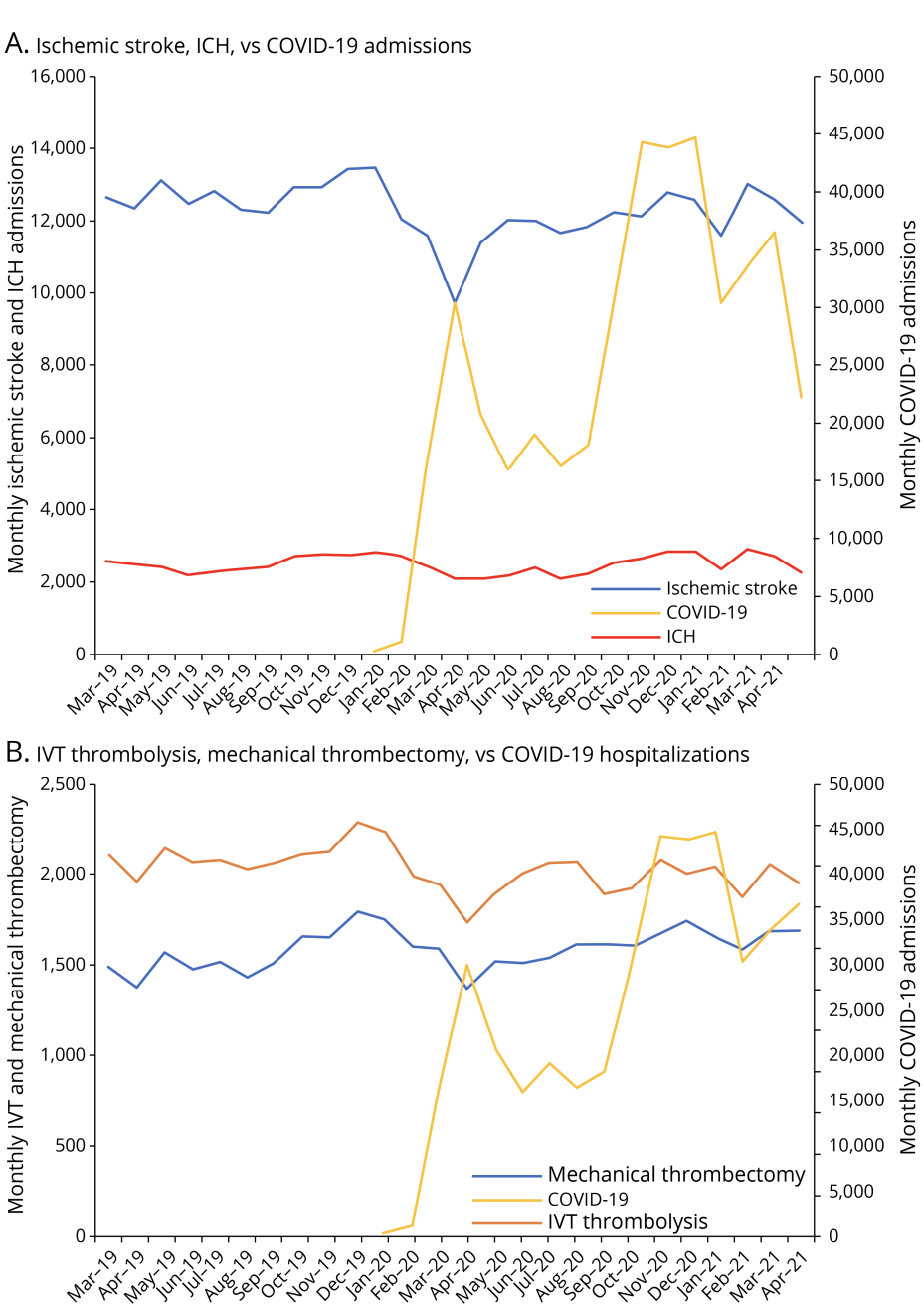
	Number of Centers	COVID-19 with any stroke	COVID-19 Hospitalization	%	95% CI	
Overall	218	5,453	406,792	1.34	1.31	1.38
Asia	51	727	44,664	1.63	1.52	1.75
North America	55	1,688	152,654	1.11	1.06	1.16
Europe	90	2,689	166,692	1.61	1.55	1.67
South America	11	262	32,116	0.82	0.73	0.93
Oceania	6	0	345	0	0	1.11
Africa	5	87	10,321	0.84	0.68	1.04

Table 6. Rates of Concomitant COVID-19 with Stroke Hospitalizations

	Number of Centers	COVID-19 with any stroke	Stroke Hospitalization	%	95% CI	
Overall	225	5,656	195,539	2.89	2.82	2.97
Asia	54	782	53,109	1.47	1.37	1.58
North America	57	1,714	53,730	3.19	3.04	3.34
Europe	93	2,811	75,993	3.7	3.57	3.84
South America	11	262	5,873	4.46	3.96	5.02
Oceania	5	0	5,032	0	0	0.08
Africa	5	87	1,802	4.8	3.93	5.92

Figure 1. Monthly volume for ischemic stroke admissions, intracranial hemorrhage admissions, intravenous thrombolysis, mechanical thrombectomy, and COVID-19 admissions

Figure 1a. Monthly admission volume for ischemic stroke (blue), intracranial hemorrhage (red) and COVID-19 (yellow)
Figure 1b. Monthly volume for intravenous thrombolysis (orange), mechanical thrombectomy (blue) and COVID-19 (yellow)



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