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Original Article

Impact of the COVID-19 Pandemic on Stroke Subtype Presentation in Patients Without COVID-19 Infection

Katherine M. Sawicka[1], Luciana Catanese[2], Janice Williams[3], Lisa Crellin[3], Troy Francis[4], Aristeidis H. Katsanos[2], Ashkan Shoamanesh[2], Jennifer Chen[5], Aleksandra Pikula[3] and Joanna D. Schaafsma[3]

[1]University of Toronto, Medicine, Division of Neurology, Toronto, Canada, [2]Hamilton Health Sciences, McMaster University, Medicine (Neurology), Hamilton, Canada, [3]University Health Network, Toronto Western Hospital, University of Toronto, Division of Neurology, Toronto, Canada, [4]University of Toronto, Toronto, Canada and [5]McMaster University, Hamilton, Canada

ABSTRACT: ***Background & Aims:*** It is unknown if the COVID-19 pandemic and public health measures had an immediate impact on stroke subtypes and etiologies in patients not infected with COVID-19. We aimed to evaluate if the proportion of non-COVID-19-related stroke subtypes (ischemic vs. hemorrhagic) and etiologies (cardioembolic, atherosclerosis, small vessel disease, and others) during the pandemic's first wave were different from prepandemic. ***Methods:*** For this retrospective cohort study, we included patients without COVID-19 with ischemic or hemorrhagic stroke at two large Canadian stroke centers between March–May 2019 (prepandemic cohort) and March–May 2020 (pandemic cohort). Proportions of stroke subtypes and etiologies were compared between cohorts using chi-square tests. ***Results:*** The prepandemic cohort consisted of 234 stroke patients and the pandemic cohort of 207 stroke patients. There were no major differences in baseline characteristics. The proportions of ischemic versus hemorrhagic stroke were similar (ischemic stroke: 77% prepandemic vs. 75% pandemic; hemorrhagic stroke:12% prepandemic vs. 14% pandemic; $p > 0.05$). There were no differences in etiologies, except for a decreased proportion of ischemic stroke due to atherosclerosis in the pandemic cohort (26% prepandemic vs. 15% pandemic; difference: 10.6%, 95%CI: 1.4-19.7; $p = 0.03$). Notably, during the pandemic, the cause of ischemic stroke was more often unknown because of incomplete work-up (13.3% prepandemic vs. 28.2% pandemic, difference: 14.9%, 95%-CI: 5.7–24.2; $p = <0.01$). ***Conclusions:*** In this study, the pandemic had no clear effect on stroke subtypes and etiologies suggesting a limited impact of the pandemic on stroke triggers. However, the shift from atherosclerosis toward other causes warrants further exploration.

RÉSUMÉ : Incidence de la pandémie de COVID-19 sur les sous-types d'accident vasculaire cérébral chez les patients non infectés par la maladie. ***Contexte et but :*** On ne sait pas si la pandémie de COVID-19 et les mesures de santé publique ont eu une incidence immédiate sur les sous-types et les causes d'accident vasculaire cérébral [AVC] chez les patients non infectés par la COVID-19. L'étude visait donc à comparer la proportion des sous-types (ischémique ou hémorragique) et des causes (origine cardioembolique, athérosclérose, microangiopathie, etc.) d'AVC non liés à la COVID-19 survenus durant la première vague de pandémie avec celle d'avant la pandémie. ***Méthode :*** Il s'agit d'une étude de cohortes, rétrospective, composées de patients non infectés à la COVID-19 qui ont subi un AVC ischémique ou hémorragique et qui ont été traités dans deux grandes unités pour les accidents vasculaires cérébraux, entre mars et mai 2019 (cohorte d'avant la pandémie) et entre mars et mai 2020 (cohorte durant la pandémie). Les proportions des sous-types et des causes d'AVC ont été comparées, entre les deux cohortes, à l'aide de tests du khi carré. ***Résultats :*** La cohorte d'avant la pandémie comptait 234 patients ayant subi un AVC, et celle durant la pandémie, 207 patients. Il n'y avait pas de différence importante quant aux caractéristiques de base. La proportion d'AVC ischémiques par rapport à celle d'AVC hémorragiques était comparable (AVC ischémiques : 77 % avant la pandémie contre [c.] 75 % durant la pandémie; AVC hémorragiques : 12 % avant la pandémie c. 14 % durant la pandémie; $p > 0{,}05$). Il n'y avait pas non plus de différence quant aux causes, à l'exception d'une diminution de la proportion d'AVC ischémiques attribuables à l'athérosclérose dans la cohorte durant la pandémie (26 % avant la pandémie c. 15 % durant la pandémie; écart : 10,6 %; IC à 95 % : 1,4-19,7; $p = 0{,}03$). Point digne de mention : durant la pandémie, les causes des AVC ischémiques étaient plus souvent inconnues qu'auparavant en raison de bilans incomplets (13,3 % avant la pandémie c. 28,2 % durant la pandémie; écart; 14,9 %; IC à 95 % : 5,7-24,2; $p = < 0{,}01$). ***Conclusion :*** Il ressort de l'étude que la vague de COVID-19 n'a pas eu beaucoup d'influence sur les sous-types et les causes d'AVC, ce qui donne à penser que la pandémie a eu une faible incidence sur les déclencheurs des AVC. Toutefois, le glissement des causes, de l'athérosclérose vers d'autres origines, mériterait de faire l'objet d'études ultérieures.

Keywords: Acute stroke; COVID-19; Stroke etiology; Stroke admission

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Corresponding author: Katherine M. Sawicka, St. Michael's Hospital, Department of Neurology, 30 Bond Street, 3 Shuter, Office 3-040, Toronto, ON M5B 1W8, Canada. Email: k.sawicka@mail.utoronto.ca

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Introduction

In contrast to extensively explored risk factors that increase the risk of stroke over time, there are fewer reports on how acute stroke triggers impact stroke subtypes and etiologies. Stroke triggers include anger, heavy eating, alcohol overuse, drug use, emotional upset, and psychological distress.[1,2]

During the first wave of the COVID-19 pandemic, and associated lockdown, acute social changes included increased unemployment, mandated work from home, ceased childcare, closure of exercise facilities, and shift to virtual chronic care management among many others.[3–5] These social changes impacted known stroke triggers during the first wave of the pandemic (March 2020 – June 2020). For example, alcohol sales in Canada increased by 15.97% and one in five Canadians reported drinking more alcohol in the early months of the pandemic.[6,7] Furthermore, many studies showed evidence that anxiety, depression, and psychological distress increased in the early pandemic in Canada and internationally.[6]

Previous studies have demonstrated acute alcohol overuse increases the risk of ischemic stroke by two to threefold and is thought to be related to cardiac arrhythmia causing embolism.[2,8] Given the observed increase in alcohol use in the early pandemic, it is of interest whether more embolic strokes have been triggered.

Negative emotions and psychological distress lead to sympathetic activation with catecholamine secretion and vasoconstriction. These physiological processes can result in ischemic or hemorrhagic stroke by means of increased heart rate, hypertension, plaque rupture, or in rare cases Takotsubo cardiomyopathy.[1,2,9,10] The observed increase in psychological distress in the early pandemic brings it into concern as another potential cause for increased embolic stroke.

Inspired by these immediate influences of the pandemic, we aimed to study the impact of these potential triggers on stroke presentation in patients without COVID-19. We quantified non-COVID-19-related stroke subtypes and etiologies during the first wave of the pandemic to gain insight on the immediate impact of the pandemic, through stroke triggers, on stroke subtypes and etiologies.

Methods

Study Design & Setting

This is a retrospective cohort study of consecutive patients admitted to two large neurovascular units in Ontario, Canada (Toronto Western Hospital [TWH] and Hamilton Health Sciences Center [HHSC]) during the periods March 17 – May 11 2019 and March 17 – May 11 2020. Data for this study were collected from review of electronic medical records and were part of the National Cerebrovascular Coronavirus-19 (CVASC-COVID-19) study.

Consecutive patients with ischemic or hemorrhagic stroke admitted to the neurovascular unit between March 17th and May 11th 2019 or 2020 were included in this study. Consecutive patients were identified by hospital administration codes indicating admission to the neurovascular unit. The lists of patients identified with hospital codes were cross-referenced with daily census lists for the neurovascular units ensuring no admitted patients during the study period were missed.

Both centers follow the Canadian Stroke Best Practice Recommendations for stroke work-up and management.[11] These guidelines include a minimum of brain parenchymal and vascular imaging and ECG on admission, fasting lipids and hemoglobin A1C levels, followed by cardiac work-up including a transthoracic echocardiogram and Holter monitoring. Additional stroke work-up including digital subtraction angiography, transesophageal echocardiogram, lumbar puncture, vasculitis serology screen, and hypercoagulability work-up is done by indication. Work-up for hemorrhagic stroke patients does not require routine transthoracic echocardiogram and Holter monitoring. Admission, work-up, and management policies did not change during pandemic.

At a minimum, all patients received brain and vascular head and neck imaging with CT, CT angiography, or MRI while in hospital. Additional investigations as part of Canadian Stroke Best Practice guidelines (such as transthoracic echocardiogram, Holter monitoring) were performed during the admission or were planned to be completed as an outpatient based on the clinical presentation of the patient.

Exclusion criteria were positive COVID-19 PCR at any point during admission or diagnosis of transient ischemic attack without stroke on imaging.

Patients from 2020 were considered the index cohort and patients from 2019 the reference cohort.

Outcome Variables

Primary Outcome

The primary outcome of this study was differences in the proportion of stroke subtype between cohorts.

Stroke subtype was categorized into arterial ischemic stroke (AIS), intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), or cerebral venous thrombosis (CVT). Stroke subtype was ascertained by confirmation of primary type of stroke on radiography (CT or MRI) obtained during admission; for example, if a patient had an ischemic stroke and secondary hemorrhagic transformation only AIS was recorded.

Secondary Outcomes

The secondary outcomes for this study were differences in stroke etiologies between cohorts.

Stroke etiology was ascertained by final diagnosis at discharge or at death as recorded on a discharge summary.

For AIS, etiologies were categorized using an extension of the basic Trial of Org 10172 in Acute Stroke Treatment classification as used in clinical practice: cardioembolic, small vessel disease, atherosclerosis, vasculitis, dissection, reversible cerebral vasoconstriction syndrome, other arteriopathy, prothrombotic state, or other stroke etiology.[12] Atherosclerosis included ipsilateral extracranial and intracranial atherosclerotic disease. If at time of discharge or death there was no etiology determined by the most responsible physician, undetermined AIS etiology was categorized into unknown with negative work-up, unknown with incomplete work-up, or unknown with more than 1 cause, or unknown with no etiology recorded. Importantly, embolic stroke of unknown source was categorized in the unknown negative work-up category. Unknown or incomplete work-up meant a patient was discharged or died before completing investigation outlined in the Canadian Stroke Best Practice Recommendations referenced above.

ICH etiologies included primary hypertensive, primary cerebral amyloid angiopathy, secondary to a vascular abnormality, unknown, and other.

For SAH, etiology was recorded as aneurysmal or non-aneurysmal.

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Data Sources

Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at Toronto Western Hospital, University Health Network.[13,14] REDCap is a secure, web-based software platform designed to support data capture for research studies.

Data collectors were provided with a data variable dictionary outlining criteria for data fields. Discrepant observations were resolved by a second data collector.

Statistical Analysis

Data were analyzed using R statistical software version 4.0.2.[15]

Descriptive statistics were used to summarize baseline, clinical, and admission characteristics between cohorts. Descriptive analyses were done with use of measures of central tendency reporting mean and standard deviation or counts and percentages, as appropriate.

To examine for differences between cohorts, tests of unequal proportions and means were conducted using chi-square tests and Student's t-tests, respectively, with alpha set at 0.05. Differences are reported as a point estimate.

Logistic regression models were used to test whether exposure to the pandemic was associated with each stroke subtype (AIS, ICH, SAH, and CVST) adjusting for age, sex, baseline modified Rankin score (mRS), and location prior to hospital (home, skilled nursing facility, or other hospital). These factors may have influenced the threshold to be referred to our center and hence change the distribution of stroke causes.

Descriptive analysis and statistical tests were done by omitting observations with missing data and analyzing the remaining data (listwise deletion). Missing data are summarized using descriptive statistics.

Research Ethics

Research Ethics Board approval was obtained at all participating sites.

Results

207 patients were included in the pandemic index cohort, and 234 patients were included in prepandemic reference cohort for the final analysis.

Table 1 summarizes baseline patient characteristics in both cohorts. Mean age was 69.1 years (SD = 16.2) in the index pandemic cohort and 68.8 years (SD = 14.4) in the reference prepandemic cohort. There was an almost equal number of males and females admitted in both cohorts. There were no statistically significant differences in vascular risk factors. There were otherwise no statistically significant differences in BMI, most pre-admission medications (except warfarin), or baseline mRS between cohorts. The index pandemic cohort had a statistically significant increased proportion of patients presenting from home (72.3% vs. 62.3%, absolute difference 9.9, 95% CI 0.8–19.1; $p = 0.03$) and a statistically significant decreased proportion of patients presenting from other hospitals (21.8% vs. 35.0%, absolute difference 13.2%, %, 95% CI 4.4–22.0, $p = <0.01$) compared to the reference prepandemic cohort.

Table 2 summarizes admission characteristics in both cohorts. There were no statistically significant differences in National Institute of Health Stroke Scale (NIHSS) score, stroke onset type (witnessed, unwitnessed, or unknown), laboratory parameters, or need for ICU admission between cohorts. Among the triage vitals, there was a statistically significant increase in mean systolic blood pressure in the index pandemic cohort (149.0 prepandemic vs. 155.7 pandemic, absolute difference of 6.7, 95%CI 0.88–12.52; $p = 0.02$).

Table 3 summarizes stroke subtypes and etiologies between cohorts. There were no significant differences in AIS, ICH, SAH, and CVST between cohorts (demonstrated in Figure 1). In terms of AIS etiology, there was evidence of an approximately 10% decrease in proportion of patients diagnosed with atherosclerosis in the index pandemic cohort (26.0% prepandemic vs. 15.4% pandemic cohort, absolute difference 10.6%, 95% CI 1.4–19.7, $p = 0.03$). Test of unequal proportions showed no significant difference in proportions of other etiologies.

Additionally, among patients with AIS, there was an over 50% increase in patients discharged with incomplete work-up in the index pandemic cohort (13.3% prepandemic vs. 28.2% pandemic, absolute difference 14.9%, 95% CI 5.7–24.2, $p = <0.01$). Among those with incomplete work-up, it was investigations such as echocardiograms, Holter Monitoring, and bloodwork that were missing. All patients had vascular imaging of the head and neck with CT or MRI. Approximately half of AIS patients with incomplete work-up died in hospital in both cohorts. Notably, there was a statistically significant increase in death among all patients with AIS in the pandemic (prepandemic 8.8% vs. pandemic 17.3%, absolute difference 8.5%, 95% CI 0.6–16.3, $p = 0.03$). A statistically significant increase between no recorded etiology for ICH was observed in the pandemic cohort (3.6 prepandemic vs. 32.1% pandemic, absolute difference 28.6%, 95% CI 6.4–50.8, $p = 0.01$). Otherwise, there were no significant differences in etiologies among patients with AIS, ICH, SAH, or CVT between cohorts.

During the pandemic, all patients still received brain parenchymal imaging, vascular imaging, ECG, and bloodwork. However, fewer patients with AIS had cardiac work-up with an inpatient echocardiogram in the pandemic cohort: 26.3% ($n = 41$) compared to 54.1% ($n = 98$) in the prepandemic cohort. This difference was statistically significant (absolute difference 27.9%, 95% CI 17.2-38.5%, $p < 0.0001$).

48.6% ($n = 88$) of all patients with AIS had at least 24 hours of heart rhythm monitoring in the prepandemic cohort which was similar to 39.7% ($n = 62$) in the pandemic cohort (absolute difference 8.9%; 95% CI -2.30–20.1%, $p = 0.1273$).

Length of stay was 6.2 days shorter in the pandemic cohort than the prepandemic cohort (mean prepandemic length of stay = 14.5 days vs. mean pandemic length of stay = 8.3 days, 95% CI 1.7–107, $p = 0.007$).

Logistic regression exploring the association between exposure to the pandemic and each stroke subtype (AIS, ICH, SAH, and CVT) adjusting for age, sex, baseline mRS, and location prior to hospital revealed no statistically significant associations ($p > 0.05$).

Most variables had no missing values. Among those that had missing values, most had less than 3% missing values except race (17% missing), BMI (54% missing), smoking status (66% missing), alcohol use (18% missing), HbA1c (35% missing), LDL (35% missing), and NIHSS (38% missing).

Discussion

This study does not provide evidence that the first wave of the COVID-19 pandemic had an immediate impact on stroke subtypes in patients without COVID-19 infection. During the pandemic, there was a lower proportion of strokes due to atherosclerosis

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Table 1: Baseline characteristics

Characteristic	Prepandemic cohort $N = 234$	Pandemic cohort $N = 207$	Difference (95% CI)	p-value
Age, y mean (SD)	68.8 (14.4)	69.1 (16.2)	−0.24 (−3.21 – 2.65)	0.87
Sex, *n* (%)				
Male	117 (50.0)	104 (50.2)	−0.2% (−9.8 – 9.4)	1
Female	117 (50.0)	103 (49.8)	0.2% (−9.4 – 9.8)	1
Race and ethnicity, *n* (%)	**$N = 229$ (97.9)**	**$N = 139$ (67.1)**		
Unknown or prefer not to answer	157 (68.6)	72 (51.8)	16.8% (5.9 – 27.6)*	0.002*
White	40 (17.5)	49 (35.3)	−18% (−27.7 – −7.9)*	0.0002*
Asian	12 (5.2)	9 (6.5)	−1.2% (−6.8 – 4.4)	0.7924
West Asian/Middle Eastern	9 (3.9)	4 (2.9)	1.1% (−3.3 – 5.4)	0.8111
Latin American	6 (2.6)	0 (0.0)	2.6% (0.0 – 5.3)	0.1337
Black	2 (0.8)	3 (2.2)	−1.3% (−4.6 – 2.0)	0.5701
Pacific Islander	1 (0.4)	2 (1.4)	−1.0% (−3.7 – 1.7)	0.6609
Arab	1 (0.4)	1 (0.7)	−0.3% (−2.2 – 1.6)	1
Body mass index, mean (SD)	27.5 (5.9)	29.2 (7.8)	−1.7 (−3.70 – 0.36)	0.11
Location prior to admission, *n* (%)	**$N = 234$ (100)**	**$N = 206$ (99.5)**		
Home	146 (62.3)	149 (72.3)	−9.9% (−19.1 – −0.8)	0.03*
Other hospital	82 (35.0)	45 (21.8)	13.2% (4.4 – 22.0)	<0.01*
Nursing home or skilled nursing facility	6 (2.6)	12 (5.8)	−3.2% (−7.5 – 1.0)	0.14
Pre-admission vascular risk factors, *n* (%)				
Hypertension**	55 (59.1)	41 (44.1)	15.1% (−0.2 – 30.3)	0.06
Dyslipidemia**	42 (45.2)	25 (41.0)	4.2% (−13.1 – 21.5)	0.72
Diabetes	59 (25.2)	49 (23.7)	1.5% (−7.0 – 10.0)	0.79
Coronary artery disease	28 (12.0)	20 (10.1)	1.8% (−4.5 – 8.1)	0.65
Congestive heart failure	23 (9.8)	24 (11.6)	−1.8% (−8.0 – 4.5)	0.66
Previous stroke or transient ischemic attack	52 (22.2)	49 (23.7)	−1.4% (−9.8 – 6.9)	0.80
Smoking History	99 (42.3)	68 (32.8)	9.5% (0.002 – 1.8)	0.052
Pre-admission medications				
Antihypertensive drugs				
ACE inhibitor	57 (24.4)	52 (25.1)	−0.8% (−9.3 – 7.8)	0.94
Angiotensin II receptor blocker	47 (20.1)	35 (16.9)	3.2% (−4.5 – 10.9)	0.46
Beta-blocker	76 (32.5)	65 (31.4)	1.1% (−8.1 – 10.2)	0.89
Calcium channel blocker	59 (25.2)	57 (27.5)	−2.3% (−11.0 – 6.4)	0.66
Diuretic	2 (0.9)	4 (1.9)	−1.1% (−3.7 – 1.6)	0.57
Diabetes oral medication	52 (22.2)	37 (17.9)	4.3% (−3.6 – 12.3)	0.31
Insulin	22 (9.4)	13 (6.3)	3.1% (−2.3 – 8.6)	0.30
Antiplatelets				
Aspirin only	60 (25.6)	57 (27.5)	−1.9% (−10.6 – 6.9)	0.73
Clopidogrel only	16 (6.8)	11 (5.3)	1.5% (−3.4 – 6.4)	0.64
Ticagrelor only	2 (0.9)	3(1.4)	−0.6% (−3.1 – 1.9)	0.89
Dual antiplatelet therapy	11 (4.7)	8 (3.9)	0.8% (−3.4 – 5.1)	0.84
Anticoagulants				
Warfarin	14 (6.0)	3 (1.4)	4.5% (0.6 – 48.4)	0.03*
Direct oral anticoagulant	28 (12.0)	28 (13.5)	−1.6% (−8.3 – 5.3)	0.73

(*Continued*)

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Table 1: (*Continued*)

Characteristic	Prepandemic cohort $N = 234$	Pandemic cohort $N = 207$	Difference (95% CI)	p-value
Statin	99 (42.3)	83 (40.1)	2.2% (−7.4 – 11.9)	0.71
Pre-admission mRS, mean (SD)	1 (1.1)	1 (1.4)	0 (−0.45 – 0.03)	0.09

For proportions, the two-sample test (Chi-square) was used for equality of proportions with continuity correction and 95% confidence intervals, alpha set at 0.05. For means, the Welch two-sample *t*-test was used with 95% confidence intervals, alpha set at 0.05.
CI: confidence interval; ACE: angiotensin-converting enzyme; mRS: modified Rankin score.
*Statistically significant; **based on $N = 93$ and $N = 61$ for University Health Network patients only.

Table 2: Admission characteristics

Characteristic	Prepandemic cohort $N = 234$	Pandemic cohort $N = 207$	Difference (95% CI)	*p*-value
Triage vitals, mean (SD)				
Temperature**	36.7 (0.5)	36.5 (0.7)	0.14 (−0.07 – 0.35)	0.18
Systolic blood pressure	149.0 (29.5)	155.7 (31.5)	−6.7 (−12.52 – −0.88)	0.02*
Glasgow Coma Scale	13.7 (2.9)	13.4 (2.7)	0.30 (−0.24 – 0.83)	0.27
Stroke onset**, *n* (%)				
Witnessed	52 (55.9)	30 (49.2)	6.7% (−10.7 – 24.2)	0.51
Wake-up	15 (16.1)	15 (24.6)	−8.5% (−23.0 – 6.0)	0.28
Unknown	26 (28.0)	15 (24.6)	3.4% (−12.1– 18.9)	0.78
NIHSS, mean (SD)	8.5 (7.5)	9.7 (8.2)	−1.2 (−3.01 – 0.63)	0.20
Laboratory parameters, mean (SD)				
Platelets	225.0 (89.8)	220.5 (72.3)	4.5 (−11.7 – 20.7)	0.58
LDL	2.5 (0.9)	2.4 (1.0)	0.07 (−0.19 – 0.34)	0.58
HbA1c	6.3 (1.4)	6.1 (1.6)	0.07 (−0.33 – 0.47)	0.72
ICU admission, *n* (%)	50 (21.3)	34 (16.4)	4.9% (−2.8 – 12.7)	0.23

For proportions, the two-sample test (Chi-square) was used for equality of proportions with continuity correction and 95% confidence intervals, alpha set at 0.05. For means, the Welch two-sample *t*-test was used with 95% confidence intervals, alpha set at 0.05.
CI: Confidence interval.
*Statistically significant; **based in $N = 93$ and $N = 61$ for University Health Network patients only.

and a significantly higher proportion of incomplete work-up at discharge among patients with AIS in the setting of decreased length of stay and increased number of deaths among AIS patients in the pandemic. This study also suggests that systolic blood pressure at presentation was higher during the pandemic than prepandemic.

Prior studies focused on the change in volume of stroke presentation during the pandemic compared to prepandemic and found a decrease in ischemic and hemorrhagic strokes, transient ischemic attacks, and stroke mimics during the pandemic.[16–19] In contrast to previous studies, we focused on stroke subtype and etiologies as a new point of interest in a large Canadian sample.

The index pandemic cohort and reference cohorts in our study are overall similar in terms of baseline characteristics. The average age and distribution of sex in both cohorts are like previously reported baseline characteristics in Western Europe, North America, and Australia indicating results may be generalized to tertiary hospitals outside of Ontario and Canada.[20] Also, the participating centers are large referral centers for stroke following the Canadian Best Practice Recommendations for stroke and are in cities with a high ethnic diversity where the initial lockdowns were similar to other provinces in Canada, which further increases the generalizability of the study results.

Prevalence of vascular risk factors between cohorts was the same suggesting that differences in stroke subtypes could be attributable to the COVID-19 lockdown.

One of the hypotheses from previous studies was that certain patients may avoid presentation to hospital during the pandemic, such as those with milder strokes.[16] In effort to address this source of bias, our secondary exploratory analysis adjusted for confounders between presenting to a hospital during the pandemic and having a certain stroke subtype including adjustment for age, biological sex, baseline mRS, and pre-hospital setting. This analysis showed that even when adjusting for these potential confounders, the distribution of stroke subtypes remained the same.

Interestingly, the index pandemic cohort demonstrated a 6.7 mmHg higher mean systolic blood pressure at triage than the prepandemic cohort. Given similar proportions of pre-admission hypertension, use of antihypertensives, small vessel disease AIS, and hypertensive ICH between cohorts, the difference of 6.7 mmHg may be an indicator for an acute stress response during

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Table 3: Stroke subtypes and etiology

Stroke type, *n* (%)	Prepandemic cohort *N* = 234	Pandemic cohort (*N* = 207)	Difference (95%CI)	*p*-value
Ischemic	**181 (77.4)**	**156 (75.4)**	**2.0% (−6.4 – 10.4)**	**0.71**
Cardio embolic	55 (30.4)	50 (32.1)	−1.6% (−12.2 – 8.9)	0.83
Small vessel disease	23 (12.7)	15 (9.6)	3.1% (−4.2 – 10.4)	0.47
Large artery disease	47 (26.0)	24 (15.4)	10.6% (1.4 – 19.7)	0.03*
Vasculitis	2 (1.1)	1 (0.6)	0.5% (−2.0 – 2.9)	1
Dissection	3 (1.7)	5 (3.2)	−1.5% (−5.5 – 2.4)	0.57
RCVS or nonspecific arteriopathy	0 (0)	0	–	–
Prothrombotic	4 (2.2)	2 (1.3)	0.9% (−2.4 – 4.3)	0.82
Other	8 (4.4)	3 (1.9)	2.5% (−1.8 – 6.8)	0.32
Unknown (more than 1 cause)	9 (5.0)	14 (9.0)	−4.0% (−10.1 – 2.1)	0.21
Unknown (negative work-up)	18 (9.9)	10 (6.4)	3.5% (−2.9 – 10.0)	0.33
Unknown (incomplete work-up)	24 (13.3)	44 (28.2)	−14.9% (−24.2 – −5.7)	<0.01*
No recorded etiology	2 (1.1)	3 (1.9)	−0.8% (−4.0 – 2.4)	0.87
Intraparenchymal hemorrhage (ICH)	**28 (12.0)**	**28 (13.5)**	**−1.6% (−8.3 – 5.1)**	**0.63**
Hypertensive	13 (46.4)	12 (42.9)	3.6% (−26.0 – 33.2)	1
Cerebral amyloid angiopathy	4 (14.3)	3 (10.7)	3.6% (−17.3 – 24.4)	1
Coagulopathy induced	1 (3.6)	0 (0)	3.6% (−6.9 – 14.0)	1
Vascular malformation	2 (7.1)	4 (14.3)	−7.1% (−26.8 – 12.5)	0.67
Other	6 (21.4)	3 (10.7)	10.7% (−11.9 – 33.3)	0.47
Unknown	4 (14.3)	10 (35.7)	−21.4% (−47.0 – 4.5)	0.12
No recorded	1 (3.6)	9 (32.1)	−28.6% (−50.8 – −6.4)	0.01*
Subarachnoid hemorrhage SAH	**25 (10.7)**	**21 (10.1)**	**0.5% (−5.6 – 6.7)**	**0.98**
Aneurysmal	12 (48.0)	5 (23.8)	24.2% (−7.1 – 57.2)	0.17
Non-aneurysmal	12 (48.0)	15 (71.4)	−23.4% (−55.3 – 8.5)	0.19
Cerebral venous sinus thrombosis	**0 (0)**	**2 (1.0)**	**−1.0% (−2.6 – 0.8)**	**0.43**

For proportions, the two-sample test (chi-square) was used for equality of proportions with continuity correction and 95% confidence intervals, alpha set at 0.05.
CI: confidence interval; RCVS: reversible cerebral vasoconstriction syndrome.
*Statistically significant.

a pandemic. This difference may not be large enough to consider blood pressure rise a stroke trigger; hence we cannot confirm a causal relationship with the pandemic. It is unlikely that this early in the pandemic blood pressure was elevated due to decreased blood pressure monitoring during the pandemic related to virtual care.[21]

Previous randomized control trials for chronic blood pressure management have used 2 mmHg as a minimally important clinical change suggesting that if this increase in systolic blood pressure in the index pandemic cohort is sustained and extends beyond fear of hospitalization, it could ultimately have clinical repercussions in latter parts of the pandemic.[22] This observed difference in hypertension is in keeping with our hypothesis around pandemic social stressors potentially triggering acute elevations in blood pressure. We also consider that there was significant deterrence of patients from hospital during the early pandemic, and therefore, perhaps mild strokes with lower elevations in blood pressure were not captured.[23] This highlights the need for ongoing blood pressure monitoring during lockdown and subsequent investigations of blood pressure trends and stroke subtypes further into the pandemic. Important confounders to consider in the relationship between the pandemic and blood pressure include access to blood pressure monitoring, medication adherence, access to refills, diet, and other acute and subacute causes for increased blood pressure.

There was a decrease in ischemic stroke due to atherosclerosis in the index pandemic cohort. Despite a larger number of patients having incomplete work-up in the index pandemic cohort, all patients in this study had head and neck vascular imaging with CT or MRI to investigate extracranial and intracranial vasculopathies, and thus, the reduced proportion of atherosclerosis cannot be explained by missed cases during the pandemic. Also, small vessel disease, similarly prevalent in both cohorts, is unlikely to be missed as stroke etiology because all patients had parenchymal imaging while in hospital. The lower proportion of atherosclerosis with a stable proportion of small vessel disease and other arteriopathies indirectly suggests that undetected cardioembolic sources, hypercoagulability, and rare stroke causes were more prevalent during the pandemic. This hypothesis is further supported by the notion that fewer patients had cardiac work-up during admission.

One of the reasons why so many patients had an incomplete work-up and consequently unknown stroke cause was the pressure to discharge patients during the pandemic to maintain hospital

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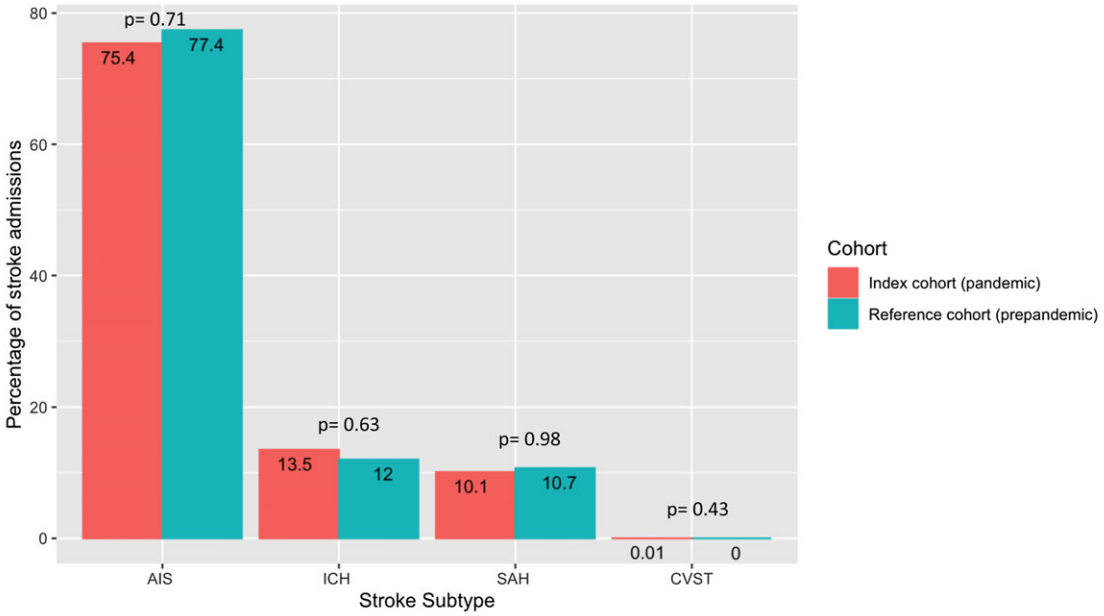

For proportions, the 2-sample test (Chi-square) was used for equality of proportions with continuity correction and 95% confidence intervals, alpha set at 0.05.
AIS: acute ischemic stroke, ICH: intracerebral hemorrhage, SAH: subarachnoid hemorrhage, CVST: cerebral venous sinus thrombosis , p: p-value for test of unequal proportions between cohorts

Fig. 1: Stroke subtypes in the prepandemic and pandemic cohorts.

capacity in the event of a surge for beds for patients infected with COVID-19. This was reflected by a decreased length of stay observed in this study. Incomplete work-up was dominated by a smaller number of echocardiograms.

The increased number of AIS deaths in hospital during the pandemic despite similar stroke severity, GCS, and ICU admissions is not well explained, and further investigation of the impact of pandemic-related measures on the delivery of care is warranted. This will be explored in a future study conducted by the CVASC-COVID-19 study group. The proportion of patients with unknown etiologies who died in hospital were equal in both cohorts, indicating that the increase in mortality during the pandemic is unlikely to be related to the primary and secondary outcomes of interest in this study.

As shown in Table 1, the proportion of patients coming from other hospitals significantly decreased in the pandemic cohort compared to the prepandemic cohort. This suggests that although there were no formal policy changes, some referral patterns from outside hospitals may have changed and the impact of this on stroke subtypes is unknown. A recent study showed that the stroke volume decrease during the pandemic was smaller at comprehensive stroke centers than primary stroke centers which may in part explain the decrease in referrals from other hospitals we observed in our cohort.[18]

Limitations

A limitation of this study is selection bias that arises from subsets of patients who were not captured in our data collection strategy. Patients who were seen in the emergency department by the neurovascular service for acute therapy assessment and repatriated back to a community hospital if they were ineligible for reperfusion treatment were not captured in this study. Repatriation policies did not change during the pandemic, and it is unlikely that this has significantly influenced a potential shift in stroke type or etiology.

This study also missed patients who never presented to the emergency department because either symptoms were mild, they refused assessment, or died before arrival. Mild symptoms or refusal to come to the hospital may have kept patients away from the hospital in higher proportions during the pandemic due to fear of contracting the virus in hospital. This is unknown and may have led to underestimating AIS in the index pandemic cohort. Death prior to arrival is rare, and missing these patients has likely not changed the results.

Another limitation of this study is that it was likely underpowered. Nonetheless, collaboration between two large tertiary hospitals made the results as robust as possible.

Measurement bias that may be present in this study applies to pandemic patients undergoing different investigations or urgency of investigations given competing elements related to the pandemic, for example, wanting to be discharged as soon as possible to minimize the risk of hospital-acquired COVID-19 infection.[23] This is likely reflected in the increased proportion of patients with incomplete work-up for AIS in the pandemic cohort and the increased number of patients with ICH being discharged without a recorded etiology. These observations highlight the need for communication with the neurovascular unit and outpatient services for comprehensive stroke management and secondary prevention as the pandemic progresses and pressure to discharge patients increases.

Another limitation of this study is missing values. No data were missing for the primary and secondary outcomes of this study limiting the potential for bias from missing data in the main analysis. Of note, there was a high proportion of missing data in certain demographics and stroke risk factors in this study. These values are largely thought to be missing at random. However, the high proportion of missing data on race and ethnicity data (17%) is suspected not to be random. Missing data on race and ethnicity data may be due to systemic biases around discussing and recording

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race and ethnicity in hospital settings. We suspect race and ethnicity other than white are underreported. This is important to consider given that this study shows differences in proportions of white and unknown categories between cohorts suggesting race and ethnicity may have played an important role on the relationship between the pandemic and stroke presentations. Inference from the observed differences in race and ethnicity is guarded given the high proportion of missing values in this category. Additional studies on race and ethnicity related to stroke presentation and subtypes during the pandemic are of further interest.

Classification of stroke etiology is subject to interpretation, so there is a risk of misclassification bias in this study. Because the overall stroke causes we found are consistent with what is reported in the literature and since at each institution, the same data extractors documented stroke etiology determined by the most responsible physician for the pandemic and prepandemic cohort, we believe that the impact of potential misclassification is limited. Unfortunately, data on stroke etiology at 90 days of follow-up were not available in this study. We can therefore only draw careful conclusions on a potential shift in stroke etiology during the pandemic.

Lastly, a major limitation of this study is the large number of secondary outcomes examined and therefore risk of statistical significance due to multiple comparison. Because of the large number of comparisons in this study, it is not surprising to have found at least a few significant differences purely by chance. Given this, we focus our conclusions on our predetermined primary and secondary outcomes of stroke subtype and etiologies and the need for future prospective studies.

Conclusion

Overall, our findings suggest that there was no major shift in stroke subtypes after the lockdown in the first wave of the COVID-19 pandemic in patients without COVID-19 infection. The decrease in AIS caused by atherosclerosis and increase of undetermined stroke etiology predominantly due to incomplete cardiac workup while the incidence of other stroke causes remained the same suggests that the pandemic-related measures may be related to a higher incidence of embolic strokes. This triggers interest in exploring stroke triggers in future studies.

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KMS led and contributed to data collection, statistical analysis, and manuscript writing.

LC[2] led grant application, design, and execution of the National Cerebrovascular Coronavirus-19 (CVASC-COVID-19) study and contributed to manuscript writing, and manuscript review.

JW contributed to data collection and manuscript review.

LC[1] contributed to data collection and manuscript review.

TF contributed to statistical analysis and manuscript review.

AHK contributed to design and execution of the CVASC-COVID-19 study at Hamilton Health Sciences Center and manuscript review.

JC data collection.

AP led grant application, design, and execution of the CVASC-COVID-19 study and contributed to manuscript writing and manuscript review.

JDS contributed to grant application, design, and execution of the CVASC-COVID-19 study at Toronto Western Hospital, data collection, manuscript writing, and manuscript review.

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