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Social Distancing, Stroke Admissions and Stroke Mortality During the COVID-19 Pandemic: A Multicenter, Longitudinal Study

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Objectives: We aimed to evaluate the relationship between social distancing, stroke admissions and stroke mortality during the COVID-19 pandemic, while accounting for the rate of COVID-19 admissions. *Methods:* We performed a longitudinal analysis of a multicenter, prospective, hospital-based registry of intensive care units from 19 hospitals from Brazil, comprising a 14-month period of the COVID-19 pandemic. We investigated whether the daily rate of admissions (DRA_{stroke}) and daily mortality rate for stroke were associated with the social distancing index (SDI), taking into account the daily rate of admissions for COVID-19 (DRA_{COVID}) in univariate and multivariate regression models. We also compared the clinical characteristics of patients with stroke admitted before and during the pandemic. *Results:* We found that DRA_{stroke} decreased significantly in association with a strong rise in the SDI during the early months of the pandemic. However, in the latter period of the pandemic, only minor changes were observed in the SDI, and still, DRA_{stroke} was inversely associated with the DRA_{COVID}. Throughout the pandemic, higher SDI and DRA_{COVID} were associated with higher in-hospital mortality for stroke. *Conclusions:* The severity of surges of the COVID-19 pandemic were independently and persistently associated with declines in stroke admissions, even during periods when social distancing policies were not intensified.

Key Words: Acute stroke—Epidemiology—Systems of care—COVID-19

Introduction

A relationship between COVID-19 and stroke has been speculated since the beginning of the pandemic, following initial case series of stroke as a presenting symptom of COVID-19, and given that COVID-19 is currently well known for its high risk of arterial and venous thromboembolic complications.[1,2] Many studies have addressed the rate of cerebrovascular events in patients admitted with COVID-19.[3–5] Stroke is the second most common neurological complication among COVID-19 patients, after encephalopathy, and the rate of stroke among hospitalized patients with COVID-19 has been reported as 1–3%.[6–9]

On the other hand, it has been hypothesized that social distancing, lockdown policies and the overwhelming burden of hospital admissions for COVID-19 could

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negatively influence the concern for stroke symptoms, the search for emergency care, and actual access to hospital care.[10–12] Indeed, it has been shown that in the first months of the pandemic and during periods of intense social distancing, hospital admissions for stroke, use of stroke imaging and of reperfusion therapies dropped significantly.[12–19] However, a long-term, longitudinal, quantitative assessment of a concurrent association between stroke admissions, stroke outcomes and social distancing has not been reported.

We therefore aimed to evaluate whether social distancing indexes had any association with the rate of stroke admissions and in-hospital mortality, taking into account the rate of intensive care unit (ICU) admissions for COVID-19, during a fourteen-month period of the ongoing pandemic in Brazil, using a large, prospective, hospital-based, ICU registry. We also aimed to compare the profile of stroke patients and their final hospital outcome between the pandemic and pre-pandemic periods.

Materials and methods

Study design, setting and ethical considerations

We performed a retrospective analysis of a prospective, multicenter, hospital-based registry oriented to clinical and administrative purposes.[20] This third party, cloud-based registry is used by ICUs pertaining to a network of 32 private hospitals in Brazil, nineteen of them located in 9 cities from the state of São Paulo. São Paulo is the most populated state of Brazil, with a population of over 44 million people, approximately 21% of the country's population.[21] COVID-19 in São Paulo has amounted to 3.8 million cases, ranking first in total number of cases in the country.[22] The first reported case of COVID-19 in Brazil was reported in São Paulo on February 26th, 2020. This study was approved by the local Institutional Review Board of the leading center with a waiver of informed consent.

Data collection, study population, variables and definitions

In this registry, consecutive patients are recruited once admitted to the ICU, and are followed up daily until hospital discharge. Registry data are extracted from local electronic medical records and are entered daily by trained nurses during working days. We selected patients from January 1st, 2019 to May 31st, 2021, and included patients with the following database codes for ICU admission: "Ischemic stroke", "Transient ischemic attack" "Intraparenchymal hemorrhage", "Intraparenchymal hemorrhage surgery", "Subarachnoid hemorrhage", "Cerebral venous thrombosis" and "COVID-19". We extracted admission variables, including demographics, comorbidities, cause of admission, and final hospital outcome (discharged alive or not).

We obtained social distancing indexes (SDI) during the pandemic period from the cities where the hospitals of the network are located from data made publicly available by the Health Secretariat of the State of São Paulo.[23] SDI is derived from cell phone data shared by the main phone companies in Brazil with the Health Secretariat. Adherence to social distancing was determined whenever the phone location during the day was maintained within 200 meters from its location between 10:00 PM and 02:00 AM. The SDI is updated daily and is represented as a percentage of identifiable cell phones adherent to the aforementioned criterion.[24] Mean SDI across the nine cities was used for statistical analysis.

Statistical analysis

Rate of admissions were reported as daily rate of admissions (DRA). Daily rates of in-hospital stroke mortality (DRM_{stroke}) were calculated as the ratio between the 14-day moving average of stroke-related deaths and the 14-day moving average of stroke admissions.

$$DRM_{stroke} = \frac{MA_{stroke(deaths)}}{MA_{stroke(admissions)}} \times 100$$

Other variables were reported as either a mean value ± standard deviation, a median value with an interquartile range (IQR), or as absolute frequencies and proportions. Pandemic and pre-pandemic characteristics of stroke patients were compared in univariate analysis using using Student's t-test or Wilcoxon two-sample rank sum test for quantitative variables and Fisher's exact test for binary variables, as appropriate. Independent predictors of mortality were assessed using multivariable logistic regression, with inclusion of variables associated with outcome in univariate analysis, and exclusion by stepwise, backward selection of variables.

To investigate the relationship between the daily rate of stroke admissions (DRA_{stroke}), DRM_{stroke}, SDI and the daily rate of COVID-19 admissions (DRA_{COVID}), we built univariate and multivariate generalized linear models having DRA_{stroke} or DRM_{stroke} as the dependent variable, using the Poisson method or linear regression, respectively. This analysis was performed for the whole pandemic period and also separately for each of the pandemic periods of acceleration and descent ("waves") of admissions. P-values below 0.01 were considered statistically significant. Statistical analysis were performed using R (version 21.04).

Results

The first ICU admission for COVID-19 occurred on March 2nd, 2020. Until May 31st, 2021, COVID-19 ICU admissions amounted to 7586 cases. Fig. 1 depicts the rate of admissions for COVID-19 and stroke, DRM_{stroke} and SDI during the study period. There were three periods of

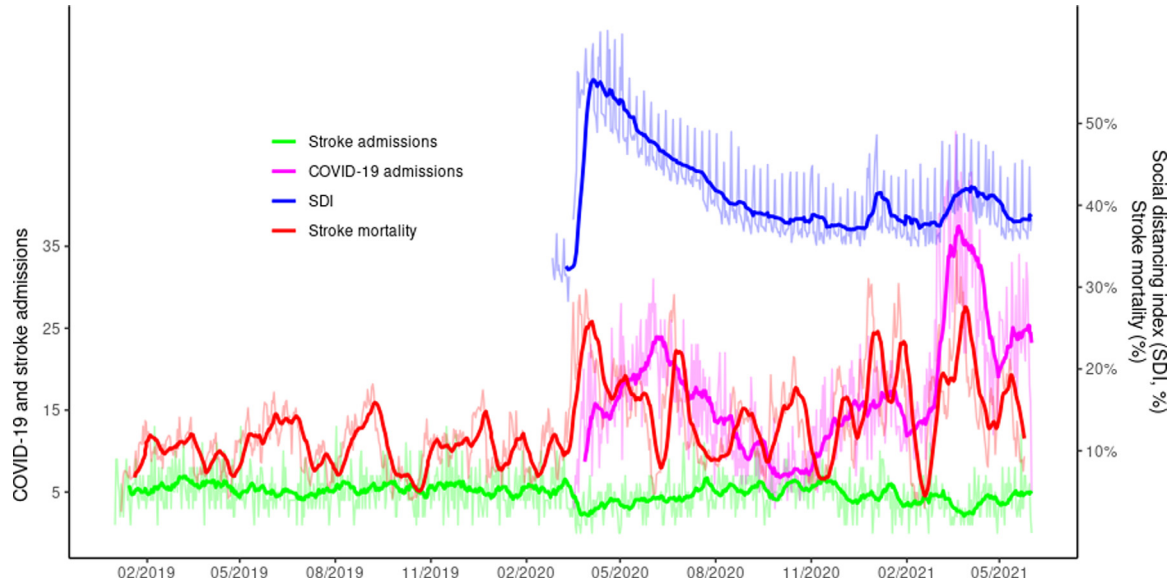

Fig. 1. *Title. Daily rate (light line) and 14-day moving average (bold line) of COVID-19 admissions, stroke admissions, stroke mortality rate, and social distancing index (SDI) from 2019 throughout the pandemic period.*

acceleration of COVID-19 admissions, starting on March 2020, November 2020, and February 2021. MA_{COVID} reached a nadir of 6.6 on September 23rd, between the first and second periods of acceleration.

During the study period, there were 4328 admissions for stroke. Admissions for stroke showed a fluctuating course during the pandemic, dropping early on at the beginning of March 2020. Patients admitted during the pandemic had higher mortality, and less often presented as transient ischemic attack or subarachnoid hemorrhage, with a larger proportion of ischemic strokes. Overall, the daily rate of admissions for stroke and for all stroke subtypes was lower during the pandemic period (Table 1). Stroke in-hospital mortality had higher peaks at the early beginning of the pandemic and during the two later surges of COVID-19 admissions (Fig. 1). In multivariable analysis, admission during the pandemic period was independently associated with hospital mortality (OR = 1.040; 95% confidence interval: 1.018−1.062), after adjusting for age (1.003; 1.002−1.004), stroke subtype

Table 1. *Comparative statistics of patients admitted for stroke.*

	Pre-pandemic period ($N = 2286$)	Pandemic period ($N = 2042$)
Age	65 ± 18	66 ± 17
Female sex	1277 (56)	1116 (55)
Hypertension	1441 (76)	1371 (77)
Diabetes	666 (35)	676 (38)
Atrial fibrillation	134 (7)	128 (7)
Chronic renal disease	123 (7)	122 (7)
Days in ICU	3 (2−5)	3 (2−5)
Stroke subtype*		
Ischemic stroke	1448 (63)	1398 (68)
Transient ischemic attack	353 (16)	235 (11)
Intraparenchymal hemorrhage	165 (7)	188 (9)
Subaracnoid hemorrhage	283 (12)	187 (9)
Cerebral venous thrombosis	37 (2)	34 (2)
In-hospital mortality*	236 (10)	295 (14)
Daily rate of admissions*	5.4 ± 2.4	4.5 ± 2.2
Ischemic stroke*	3.5 ± 1.8	3.0 ± 1.8
Transient ischemic attack*	1.5 ± 0.7	0.5 ± 0.7
Intraparenchymal hemorrhage*	1.2 ± 0.5	0.4 ± 0.6
Subaracnoid hemorrhage*	1.3 ± 0.6	0.4 ± 0.7
Cerebral venous thrombosis*	1.1 ± 0.3	0.1 ± 0.3

* $P < 0.001$. Data represented as mean ± standard deviation, n (%) or median (interquartile range).

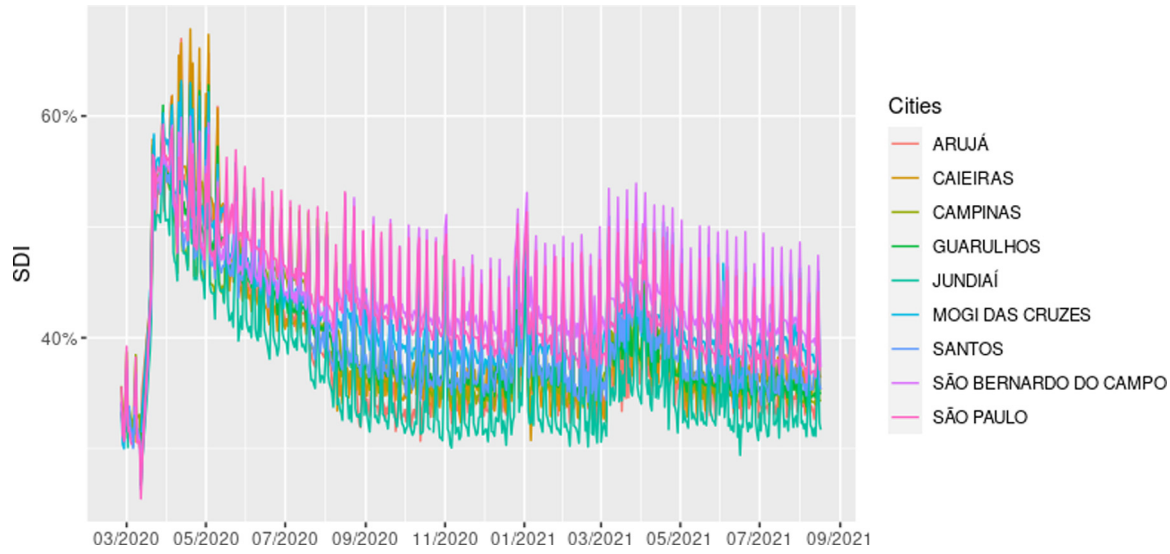

Fig. 2. *Social distancing indexes in the nine cities included in the registry.*

(ischemic stroke: 1.099, 1.064−1.134; intraparenchymal hemorrhage: 1.376, 1.313−1.443; subarachnoid hemorrhage: 1.269, 1.214−1.327; transient ischemic attack: reference), and atrial fibrillation (1.078, 1.035−1.124).

Using the nadir of MA_{COVID} as a divisor of the two periods of the pandemic, we found that social distancing showed distinct behaviors during the two main periods of COVID-19 acceleration (Fig. 1). In the first period, there was a sharp and early increase in the SDI and a gradual decrease during the following six months. This contrasted with the second period, when observed responses in the SDI due to the worsening of the pandemic were small. The pattern of SDI variation during the pandemic was similar across the cities (Fig. 2). When analyzing the whole pandemic period, both DRA_{COVID} and SDI were inversely associated with DRA_{stroke}. During the first period, DRA_{stroke} suffered a sharp decline inversely associated with SDI, while no association with DRA_{COVID} was observed. On the other hand, during the second period, DRA_{stroke} was inversely associated with DRA_{COVID}, when SDI showed minor variations that were unrelated to DRA_{stroke} (Table 2).

Discussion

In this study, the pandemic of COVID-19 was associated with reduced ICU admissions for stroke, with periods of acceleration of the pandemic timely correlated with

Table 2. *Social distancing and daily COVID-19 admissions as predictors of daily rate of stroke admissions.*

	B	95% CI	P
Univariate analysis			
SDI	-0.016	-0.024—(-0.008)	<0.001
DRA_{COVID}	-0.009	-0.014—(-0.004)	0.001
Multivariable analysis			
SDI	-0.015	-0.023—(-0.007)	<0.001
DRA_{COVID}	-0.008	-0.013—(-0.003)	0.002
Pandemic first period, univariate analysis			
SDI	-0.024	-0.033—(-0.015)	<0.001
DRA_{COVID}	0.004	-0.007—0.015	0.51
Pandemic first period, multivariable analysis			
SDI	-0.032	-0.045—(-0.020)	<0.001
DRA_{COVID}	0.012	-0.001—(-0.024)	0.035
Pandemic second period, univariate analysis			
SDI	-0.004	-0.022—0.013	0.62
DRA_{COVID}	-0.013	-0.020—(-0.007)	<0.001
Pandemic second period, multivariable analysis			
SDI	0.004	-0.014—0.021	0.68
DRA_{COVID}	-0.014	-0.020—(-0.007)	<0.001

CI: confidence interval. DRA_{COVID}: daily rate of admissions for COVID-19. SDI: social distancing index.

declining rates of stroke admissions, and an overall lower rate of stroke admissions when compared to 2019. While social distancing was also associated with reduced admissions for stroke, specially during the early phase of the pandemic, stroke admissions were still strongly affected by surges of COVID-19 even when social distancing responses to the pandemic were minor. All stroke subtypes were negatively affected by the rate of COVID-19 admissions, with approximately one less admission per day for every stroke subtype. Furthermore, patients admitted with stroke during the pandemic had higher mortality. These data provide an alarming picture that support the need for continuing public policies aiming at sustaining stroke awareness and stroke network preparedness during the pandemic.

These results corroborate other reports of declining stroke admissions during the pandemic period.[12,14,25] Nogueira et al reported a global picture of declining admissions for stroke and reduced use of mechanical thrombectomy from March to May, 2020.[15] While our study resonates with these findings, we also show that the effect of the pandemic on stroke care is still present over a year after the first cases. Moreover, we observed that more intense periods of intense social distancing were independently associated with declining admissions for stroke. However, stroke admissions also suffered intense descent when social distancing responses were weak, with a strong association with surges of COVID-19 admissions. We believe that two conclusions can be drawn from our data. First, the policies of stroke awareness and preparedness should be emphasized during periods when adoption of social distancing is necessary. Second, that access to stroke care does not necessarily entail relaxing of social distancing policies, and that the severity of the pandemic in this situation still acts as a strong drive for reducing stroke admissions.

In our study, stroke in-hospital mortality was not only higher during the pandemic, but was associated with periods of more intense social distancing and of higher admissions for COVID-19. We believe that this association may reflect two phenomena. First, that the increase in social distancing and the high demand for COVID-19 admissions promoted a selection of more severe patients with stroke for hospital admission. Second, that the burdensome pressure on systems of care imposed by COVID-19 surges might have impacted performance of stroke care. Indeed, some studies have shown that performance of stroke care declined during the pandemic, with increases in door-to-needle and door-to-groin times, and a reduction of intravenous thrombolysis and endovascular therapy procedures.[18,26–29] In one study, delays in stroke therapy were related to increased time from symptom detection to hospital arrival.[30] These findings underline the hypothesis that the drop in stroke admissions probably reflects increased barriers to stroke care. As our study suggests, however, these barriers cannot be solely attributed to social distancing policies, but rather derive from the severity of the pandemic itself, with the ensuing overwhelming of systems of care.

Global economic disparities could play an important role in the negative impact of the pandemic on stroke care. Shahjouei et al. reported that stroke patients with COVID-19 from countries with lower health expenditure had higher NIHSS scores at admission and lower rate of mechanical thrombectomy, which suggests that the negative impact of the COVID-19 pandemic on healthcare access is probably more severe in developing countries.[4] In our study setting, we have found stroke admissions to be still negatively impacted by the fluctuating course of the pandemic even 14 months after the first admission for COVID-19. Thus, the COVID-19 pandemic is still a developing scenario that could possibly increase the already significant global gap in stroke care.

This study has some important limitations. First, our database only includes patients admitted to ICU care. If disease severity of COVID-19 suffered a significant change during the pandemic, the rate to which ICU admissions reflected actual hospital admissions and disease incidence in the community might have changed over the 14-month period of the pandemic described in this study. However, the trends of ICU admissions for COVID-19 herein reported are very similar to the rate of new cases in São Paulo during the pandemic.[22] Second, some variables of interest such as metrics of performance of stroke care and stroke severity, such as the NIHSS, were not available. These unavailable data could have helped to better understand the underlying reasons for the higher mortality of stroke patients during the pandemic period, although, given the prior reports of the impact of COVID-19 on stroke severity and stroke care performance, we believe that both probably played a role.

The strength of our study is that it represents a large scale, longitudinal, multicenter study encompassing over a year of the COVID-19 pandemic. By evaluating the phenomenon of declining stroke admissions at a latter period of the pandemic, we were able to assess the effect of the pandemic during periods when social distancing responses to the pandemic were different, and to better evaluate the complex interplay between of social distancing, pandemic surges and stroke care. Moreover, we were able to show that the impact of the COVID-19 pandemic on stroke care is still present event after a year of its outbreak.

The COVID-19 pandemic is an ongoing global health crisis that has led to over 5 million deaths and is still far from closure globally.[31] Our findings corroborate that continuing efforts are needed by public policy makers, private health sector stakeholders and the stroke community to ensure that access to optimal stroke care is provided to the community during the pandemic.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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