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Call to Action: SARS-CoV-2 and Cerebrovascular Disorders (CASCADE)

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Background and purpose: The novel severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), now named coronavirus disease 2019 (COVID-19), may change the risk of stroke through an enhanced systemic inflammatory response, hypercoagulable state, and endothelial damage in the cerebrovascular system. Moreover, due to the current pandemic, some countries have prioritized health resources towards COVID-19 management, making it more challenging to appropriately care for other potentially disabling and fatal diseases such as stroke. The aim of this study is to identify and describe changes in stroke epidemiological trends before, during, and after the COVID-19 pandemic. *Methods:* This is an international, multicenter, hospital-based study on stroke incidence and outcomes during the COVID-19 pandemic. We will describe patterns in stroke management, stroke hospitalization rate, and

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stroke severity, subtype (ischemic/hemorrhagic), and outcomes (including in-hospital mortality) in 2020 during COVID-19 pandemic, comparing them with the corresponding data from 2018 and 2019, and subsequently 2021. We will also use an interrupted time series (ITS) analysis to assess the change in stroke hospitalization rates before, during, and after COVID-19, in each participating center.

Conclusion: The proposed study will potentially enable us to better understand the changes in stroke care protocols, differential hospitalization rate, and severity of stroke, as it pertains to the COVID-19 pandemic. Ultimately, this will help guide clinical-based policies surrounding COVID-19 and other similar global pandemics to ensure that management of cerebrovascular comorbidity is appropriately prioritized during the global crisis. It will also guide public health guidelines for at-risk populations to reduce risks of complications from such comorbidities.

Key Words: SARS-CoV-2—COVID-19—Pandemic—Stroke—Incidence—Mortality—National crisis—Health policy

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Introduction

An emergence of pneumonia cases in Wuhan, Hubei Province, China, was first reported to the World Health Organization (WHO) on December 31, 2019.¹ A novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), which had not been previously identified in humans, was subsequently isolated from these patients, and was identified as the source of the acute respiratory illnesses, now named coronavirus disease 2019 (COVID-19). On March 11, 2020, COVID-19 was subsequently declared a global pandemic by the World Health Organization (WHO) and has spread to over 212 countries/territories worldwide so far.^{2,3} This has surpassed the spread of other viral respiratory tract diseases such as severe acute respiratory syndrome (SARS).^{4,5} Specifically, as of April 30th, 2020, there are 3,090,445 reported laboratory-confirmed cases worldwide³, and this number is expected to continue increasing. This has resulted in an unprecedented international public health crisis that has prompted numerous countries to implement nation-wide lockdowns to mitigate the spread of the virus and reduce the burden on healthcare systems.

The public health burden of COVID-19 has reached beyond that of any other infectious respiratory illness, as it may have associations with non-communicable diseases (NCDs), including cerebrovascular or cardiovascular disorders (CVDs). Patients with COVID-19 often have vascular risk factors and comorbidities,^{6,7} which may increase the need for hospitalization, and need for intensive care unit admissions and/or intubation. It may also induce vascular injury that would promote the risk of stroke.^{8–11}

While prevention and management of COVID-19 is a top global health priority, this should not come at the cost of compromising the treatment and management of other potentially life-threatening diseases.¹² The present multicenter, international study has been designed to assess changes in stroke rates, severity, subtypes (ischemic/hemorrhagic), and outcomes before, during, and after the

COVID-19 pandemic. The results of this initiative can be used as a monitoring model for public health authorities and policymakers regarding the system's capacity during a global crisis of this magnitude. Ultimately, enhanced simultaneous surveillance of NCD and COVID-19 comorbidity in populations would generate the empirical data needed to better understand the dual-disease burden and to target coordinated care.

Study design

The CASCADE Study (Call to Action: SARS-Cov-2 and Cerebrovascular DisordEr) is a retrospective and prospective international multicenter cohort study comparing the rate, severity and outcomes of stroke before, during, and following the COVID-19 outbreak.

The study aims to create a multicenter stroke registry to: (1) describe changes in stroke clinical care approach (including imaging, stroke-unit care admission, thrombolysis, thrombectomy, neurosurgery availability, and outpatient assistance in different countries during the COVID-19 outbreak); (2) evaluate the incidence of CVD in COVID-19 positive patients, as well as identifying clinical markers predictive of CVD occurrence in COVID-19 positive patients; (3) identify the clinical, neuroimaging and prognostic factors of CVD during the pandemic in comparison to the same period in 2018 and 2019, and subsequently, 2021.

Study population and data collection

CASCADE is a new initiative, and we foresee continuous collaboration across multiple participating centers worldwide (Fig. 1). Neurological and stroke centers, evaluating cerebrovascular disease patients (aged > 18) during the COVID-19 pandemic will be included in the project. For each participating center, the overall types of acute phase stroke therapy utilized, the crude and age-standardized stroke rate, vascular risk factors, stroke severity, and stroke outcomes such as in-hospital

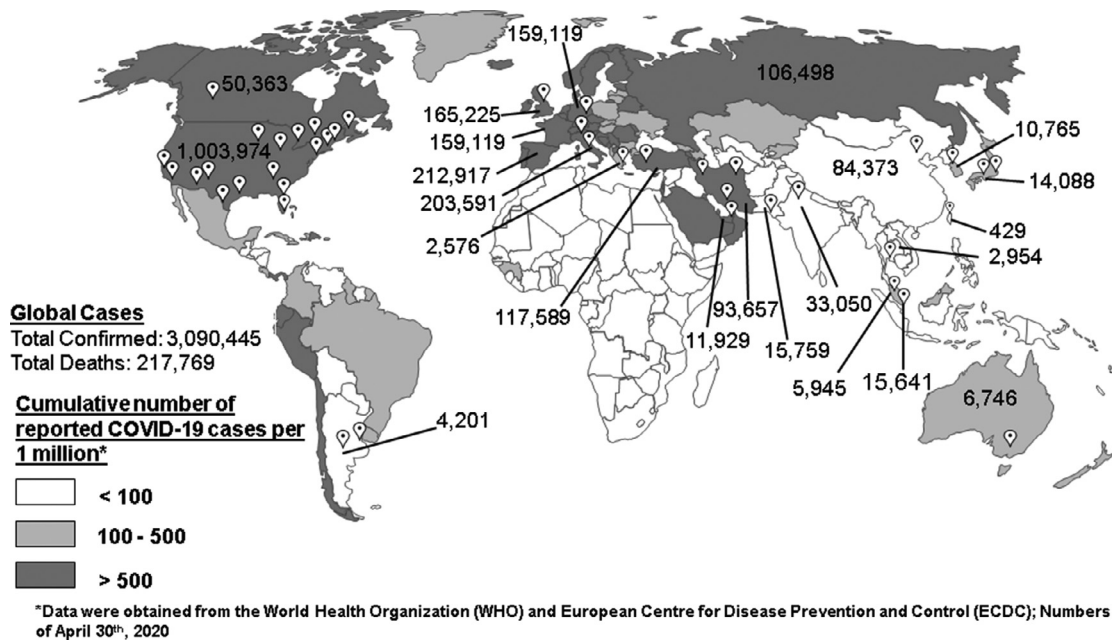


Fig. 1. World map depicting participating centers (white push pins) and their total COVID-19 cases, and total cases in the top 10 afflicted countries. Geographic distribution of the cumulative number of reported COVID-19 cases per 1 million population is illustrated in a color-gradient. Data on COVID-19 cases are updated as of April 30, 2020 (countries with more than 100 cases per one million of their population are highlighted).

mortality will be tracked and compared with the previous corresponding months in 2018 and 2019, and in 2021 or 2022 if the disease progresses through 2021.

Other important data include the date of the first report of COVID-19, the date of the latest quarantine, the date of the end of quarantine, the date and nature of phased social distancing and lock-down restrictions, and the date and nature of relaxation of social distancing and lock-down measures (if available) in each corresponding country/region, according to official local and governmental reports. We will also obtain data regarding COVID-19 from international databases; e.g. the European Centre for Disease Prevention and Control (ECDC),¹³ and the United Nations Educational, Scientific and Cultural Organization (UNESCO)-COVID-19 Educational Disruption and Response.¹⁴ Environmental data, specifically, national air quality, will be obtained through NASA's Giovanni OMI visualization tool.¹⁵ We have developed a set of common variables with their definitions to facilitate standardization of data-collection among participating centers (Supplement Table 1). The final database will include data regarding important variables, such as stroke incidence, stroke severity, vascular risk factors, medications, and outcome (e.g. in-hospital mortality and disability).

Stroke will be defined according to the Stroke Council of the American Heart Association/American Stroke Association census definition.¹⁶ The severity of stroke will be measured according to the National Institutes of Health Stroke Scale (NIHSS). Stroke disability will be assessed using the modified Rankin Scale (mRS) on admission, at discharge, and longitudinally (30 days and 3 months follow-ups), if available. Depending on the

participating centers' registry, we will include all stroke (first-ever-stroke and recurrence) cases, stroke subtypes such as acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), cerebral venous thrombosis, and subarachnoid hemorrhage (SAH). In addition, if available, we will monitor prospectively cases admitted with COVID-19 who develop strokes in hospital or within two weeks after their discharge. We will also identify stroke patients with a laboratory-confirmed COVID-19 diagnosis.¹⁷ Further, given the limited availability of COVID-19 laboratory testing in some centers, we will gather data regarding those clinically suspected of having COVID-19 following a stroke. With this approach, we can provide a broader understanding of the larger incidence of both the communicable and non-communicable related disease.

Ethical considerations

Local Ethics Committee approval will be obtained for each participating center. Data sharing will be according to the institutional Ethics Committee's policies and official agreements. We will use anonymized data, secured in protected servers. The confidential data will be saved in an encrypted and secured dataset (e.g., RedCap, <http://projectredcap.org/>, Vanderbilt University). Anonymized data obtained by each center will be pooled together to be analyzed by the designated data processing center. A subject ID coding will be designed to have a specific designation code for each participating center that is only shared with the data processing center and the corresponding site.

Statistical analysis plans

Crude and standardized hospitalization rates of stroke per month will be calculated using a direct method. We will use a Poisson regression model with a log link to compare the number of stroke hospitalizations during the COVID-19 pandemic, as compared to corresponding months in the previous and, possibly, upcoming years. We will calculate risk ratios [with 95% confidence intervals (CIs)] of the number of stroke hospitalizations within the pandemic period, as compared to the periods before and after COVID-19. We will use Kaplan-Meier survival method within the study period and Cox-regression model to estimate the hazard ratio (HR) with 95% CI of in-hospital mortality. An interrupted time series (ITS) analysis will be used to assess the change in stroke hospitalization rates after COVID-19 in each center. We will compare the proportion of different stroke care management (e.g. outpatient assistance, craniectomy utilization, discharge setting, supported discharge) between the COVID-19 pandemic and previous periods. These variables will be added as a time-varying confounder in the ITS regression model. Prevalence of stroke subtypes and important neuroimaging features (e.g. cortical vs. subcortical, anterior vs. posterior circulation, stroke size and location, etc.) will be estimated in proportion to total admitted strokes. These variables will also be analyzed in the ITS model as a time-varying confounder. Using an autoregressive integrated moving average (ARIMA) model (according to the Box-Jenkins-Tiao strategy), serial autocorrelations of the hospitalization rates will be assessed. The Q-statistic will test analytically whether the autocorrelation function is different from a white noise process. A lag plot will be created using the sample autocorrelation coefficients, plotted against the corresponding lags. We will calculate the Durbin-Watson (DW) statistic to test the autocorrelation of the errors in the segmented regression models.

Discussion

CASCADE is a new multicenter initiative to assess the impact of the COVID-19 pandemic on stroke occurrence, severity, care, and outcomes. The results of this initiative will have multiple clinical and public health implications. Similar to other major global crises (e.g. WWII), critical periods of time surrounding COVID-19 can be categorized as periods before, during, and after the pandemic. Since the 1918 flu pandemic,¹⁸ the world has not experienced a pandemic of this magnitude. Therefore, the pooling of epidemiological, clinical, and laboratory data on the COVID-19 pandemic is imperative to the success of national and global public health initiatives directed towards this novel virus, and future national and international health crises. In addition to the COVID-19 viral epidemiology, a successful model should also include other major diseases, including NCDs, identifying the risk for

vulnerable populations (i.e. those with prior comorbidities), and prioritizing preventive measures through strengthening public protections and improving access to health services. Combining these preventive measures for COVID-19 with measures surrounding life-threatening NCD, as well as focusing on screening and treatment programs during and after the pandemic is of major importance, and one of the priorities of the CASCADE study.

COVID-19 can affect stroke rate and outcomes through various direct and indirect pathways. Among 20,812 patients confirmed to have COVID-19 in China as of February 11, 2020, 2683 patients (12.8%) had hypertension, and 873 (4.2%) had cardiovascular disease.⁶ Similarly, in Italy, in a subset of 355 patients who died of COVID-19, 352 were found to have comorbidities, including diabetes in 35.5%, ischemic heart disease in 30%, atrial fibrillation in 24.5%, and stroke in 9.6% of patients.⁷ The systemic inflammatory response from SARS-Cov-2 may trigger the rupture or erosion of atherosclerotic plaque,^{8,11} destabilize previous stroke or coronary artery disease,⁹ and may be associated with acute cardiac injury such as myocarditis.^{8,10}

SARS-Cov-2 may also have a peripheral vascular detrimental effect due to its ability to act on Angiotensin-Converting Enzyme 2 (ACE2) receptors, which play a major role in regulating cardiovascular function.^{11,19} Furthermore, it also has a potential negative neurotropic effect due to the expression of ACE2 receptors on neurons and cerebral endothelial cells. This facilitates the rupture of the blood-brain barrier and cerebral arteries,²⁰ which suggests the development of more severe and devastating strokes²¹ in the presence of COVID-19. Finally, stroke-induced suppression of the innate and adaptive immune system is well described²² and may impact susceptibility to, and severity of, SARS-Cov-2 infection in the acute phase of stroke, ultimately impacting clinical outcomes.

Given that COVID-19 is closely related to SARS,²³ we anticipate similarities in cardiovascular presentations, such as arrhythmias. Specifically, in a cohort study ($n=121$), tachycardia (71.9%) and bradycardia (14.9%) were reported in patients with SARS.²⁴ In addition, hypoxemia resulting from severe respiratory illness in COVID-19, particularly in those with underlying CVDs such as stroke and heart failure, may also lead to atrial fibrillation⁷ and increased mortality rate.²⁵ Finally, COVID-19 has been associated with abnormalities in the coagulation cascade.²⁶

Similar to many other global health crises, COVID-19 may also indirectly affect the rate and severity of CVDs. Prioritization of medical resources towards COVID-19 precautions and assistance, as seen in many countries, may result in a reduction of resources for other potentially fatal diseases.²⁷ This is important as a healthcare system collapse under significant burden from COVID-19 may, directly and indirectly, affect all other major health conditions (e.g., stroke), resulting in higher mortality and

morbidity among both infected and non-infected patients. It is necessary to note that most countries heavily impacted by COVID-19 are those that are typically more impacted by the presence of concurrent NCD's, rather than communicable diseases in general (paper in preparation). As such, it is possible that the lack of prior exposure to a pandemic of this magnitude could have resulted in a lack of preparedness in terms of preventive and emergency management plans.

COVID-19 may also indirectly affect CVDs through heightened emotional responses, such as stress.²⁸ Specifically, within the 3 weeks following the 2011 Great East Japan Earthquake and Tsunami disaster, there was a significant increase in the number of cardiovascular events, including acute coronary syndrome or congestive heart failure, without any change in the rate of stroke.²⁹ A study observed a French population over 4 Football World Cup events, a time period that is considered stressful for the audience viewing the matches.³⁰ Interestingly, the study found a decrease in the rate of stroke, potentially due to a state of the euphoria associated with viewing the football game.³⁰ A similar study in Germany during the 2006 World Cup found that the incidence of cardiac emergencies increased significantly on days that the German team was playing.³¹ The difference in the incidence of CVDs during these national disasters and events may be explained by the heterogeneous nature of CVD occurrences.²⁹ Further, due to the implementation of mitigation strategies that have resulted in physical isolation of large subsets of the population, COVID-19 has indirectly, and beneficially, impacted air quality and pollution. Recent observational satellite images obtained from NASA depicted improvements in air quality over China during periods of quarantine in February 2020, a time which had seen nation-wide business closures and prohibited vehicular transportation. Specifically, up to 30% reductions in NO₂ emissions, and up to 40% reductions in CO₂ emissions have been observed.^{32,33} While similar reductions are normally seen during Chinese Lunar New Year due to business closures, the emissions typically increase once again in the following weeks.³⁴ However, due to the quarantine, the number of festivities and outdoor events have been reduced. Similar trends have been observed in states that have implemented "shelter-in-place" orders within the United States.³⁵ As of March 9, 2020, Italy, which had also implemented a nation-wide lockdown, has also seen improvements in air quality. Specifically, from March 14 until March 25, 2020, Rome had seen up to a 35% decrease in NO₂ as compared to the same period in 2019.³⁶ This is particularly important as air quality has been shown to have effects on stroke and other NCD's.³⁷ Conversely, it is possible that prolonged homestay due to the quarantine may lead to increased sedentary behaviors, physical inactivity, and unhealthy dietary intake habits, leading to increasing or worsening chronic health conditions.³⁸

The CASCADE study is feasible and can provide scientific answers for many of the aforementioned hypotheses. The data will be gathered in a challenging, resource-limited situation during the COVID-19 pandemic, which is having an enormous impact on healthcare and the economy in many countries. The proposed initiative can provide a wide range of information, from individual-based health related issues to changes in health policy in high, middle, and low-income countries. As well, the CASCADE registry can also be combined with other international stroke registries to expand the knowledge in this field. In addition, our data will reflect the real-world and systemic healthcare challenges currently facing many centers around the world. Data will be gathered based on available stroke information at each center. It is possible that those with transient ischemic attacks (TIAs) and minor strokes may not present to Emergency Rooms due to fear of contracting COVID-19 from the hospital, and/or social distancing measures. However, we would ultimately not expect to see a significant decrease in the rate of severe and fatal stroke presentations. Therefore, any changes in the rate, severity, and outcome of stroke within the study period will likely reflect the direct and indirect consequences of COVID-19.

Conclusion

The worldwide convergence of NCD and communicable infectious diseases has the potential to overstretch global health systems. The CASCADE initiative can potentially shed light on challenges related to stroke care as a major NCD within this context. Identifying and analyzing the current health-related data during the COVID-19 period will help to optimize resource allocation, conduct proper assessments to objectively identify the nature of the problem, implement strategies to address the issue in the most effective and efficient way, and better prepare for future viral outbreaks.

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Declaration of Competing Interest

Authors and investigators have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.jstrokecerebrovasdis.2020.104938](https://doi.org/10.1016/j.jstrokecerebrovasdis.2020.104938).

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