

NEUROLOGICAL BURDEN OF COVID-19: A STUDY OF Cerebrovascular EVENTS IN A BRAZILIAN TERTIARY HOSPITAL

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Abstract

Introduction: Neurological complications, particularly cerebrovascular diseases, have emerged as a significant concern in patients with coronavirus disease (COVID-19). Understanding these characteristics is essential for improving the clinical management and outcomes.

Materials and methods: This observational study analyzed data from patients hospitalized at Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo between 2020 and 2021. We included patients aged ≥ 18 years with a confirmed SARS-CoV-2 infection and a diagnosis of cerebrovascular disease within 60 days of symptom onset. Clinical, demographic, and outcome data were collected and analyzed.

Results: Among the 1998 patients with confirmed COVID-19, 550 (27.5%) presented with neurological symptoms. Fifty patients were diagnosed with cerebrovascular disease: 27 (54%) had ischemic stroke, 20 (40%) had hemorrhagic stroke, and three (6%) had cerebral venous thrombosis. Patients with neurological symptoms had significantly higher mortality rates and longer hospital stays than those without neurological symptoms.

Conclusion: This study highlights the severity and clinical impact of cerebrovascular events in COVID-19 patients. These findings reinforce the need for early neurological evaluation, and underscore the importance of accessible and cost-effective strategies for surveillance, prevention, and timely intervention in high-risk populations.

Key words: COVID-19, cerebrovascular disease, stroke, SARS-CoV-2, cerebral venous thrombosis, neurological complications

Resumen

Carga neurológica en COVID-19: estudio de eventos cerebrovasculares en un hospital terciario brasileño

Introducción: Las complicaciones neurológicas, en particular las enfermedades cerebrovasculares, han surgido como una preocupación importante en pacientes con enfermedad por coronavirus (COVID-19). Comprender estas características es esencial para mejorar el manejo clínico y los resultados.

Materiales y métodos: Este estudio observacional analizó datos de pacientes hospitalizados en el Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo entre 2020 y 2021. Incluimos pacientes ≥ 18 años con infección confirmada por SARS-CoV-2 y un diagnóstico de enfermedad cerebrovascular dentro de los 60 días posteriores al inicio de los síntomas. Se recopilaron y analizaron datos clínicos, demográficos y de resultados.

Resultados: Entre los 1998 pacientes con COVID-19 confirmada, 550 (27.5%) presentaron síntomas neurológicos. Cincuenta pacientes fueron diagnosticados con enfermedad cerebrovascular: 27 (54%) presentaron accidente cerebrovascular isquémico, 20 (40%) accidente cerebrovascular hemorrágico y tres (6%) trombosis venosa cerebral. Los pacientes con síntomas neurológicos tuvieron tasas de mortalidad significativamente más altas y estancias hospitalarias más prolongadas que aquellos sin síntomas neurológicos.

Conclusión: Este estudio destaca la gravedad y el impacto clínico de los eventos cerebrovasculares en pacientes con COVID-19. Estos hallazgos refuerzan la necesidad

de una evaluación neurológica temprana y subrayan la importancia de estrategias accesibles y rentables para la vigilancia, la prevención y la intervención oportuna en poblaciones de alto riesgo.

Palabras clave: COVID-19, enfermedad cerebrovascular, ACV, SARS-CoV-2, trombosis cerebral venosa, complicaciones neurológicas

KEY POINTS

Current knowledge

- The clinical impact of COVID-19 is still being observed. Regarding neurological aspects, evidence about the occurrence of cerebrovascular events is scarce.

Contribution of the article to current knowledge

- This research contributes by highlighting the clinical severity of these complications in Brazil, reinforcing the need for early diagnosis, prevention, and management strategies to reduce mortality and sequelae.

The relationship between infectious agents, particularly viral ones, and neurological manifestations with vascular involvement in the central nervous system has consistently been the subject of clinical and epidemiological studies and analyses¹.

Studies gained momentum mainly after December 2019, when in the city of Wuhan, China, the emergence of a new, highly pathogenic virus from the Coronaviridae family, called SARS-CoV-2, responsible for the COVID19 pandemic, was observed².

Neurotropism is a common feature of coronaviruses. Brain involvement may result from the dissemination of SARS-CoV-2 through systemic circulation or via the olfactory pathway through the cribriform plate during the early or late phase of infection. Given the epidemiological, health, morbidity, and mortality relevance of influenza-like syndromes with neurological complications, especially those caused by SARS-CoV-2, and the possible relationship with the occurrence of cerebrovascular disease, new studies are necessary to evaluate the presence of neurological signs and symptoms in patients

with COVID-19. The studies were conducted to prepare neurologists and non-neurologists for the rapid detection and treatment of potentially fatal and disabling conditions³⁻⁵.

Regarding cerebrovascular diseases associated with COVID-19, several studies initially attempted to establish, describe, or better study the relationship between the events and infectious agents. In May 2020, Ghannam et al. reported that cerebrovascular incidents accounted for 48.8% of all neurological events in patients with COVID-19; of these, 87.5% had ischemic strokes, 5% had cerebral venous thromboses, 5% had intraparenchymal hemorrhages, and 2.5% had subarachnoid hemorrhages⁶.

In this study, we will share the experience of a tertiary neurological reference center for cerebrovascular diseases that was part of the NeurocovBR study group during the first wave of COVID-19 cases, highlighting the study of neurological manifestations in patients with COVID19 and cerebrovascular diseases in the service.

Materials and methods

Local of the study

In March 2020, following the confirmation of the first case of COVID-19 in Brazil, the NeurocovBR study group was established^{7,8}.

The data presented in this work refer to cases evaluated only at the Hospital da Irmandade da Santa Casa de Misericórdia de São Paulo and aimed to study the cases of patients with COVID-19 and cerebrovascular diseases.

Inclusion criteria required patients to be 18 years of age or older, fulfill the World Health Organization criteria for COVID-19⁹, meet the provisional Ellul criteria for SARS-CoV-2 neurological-associated syndromes¹⁰, and exhibit novel neurological symptoms within 60 days of COVID-19 infection.

Data assessment

Demographic information was obtained from medical records, patient interviews, or, when necessary, interviews with a designated proxy if the patient was unable to provide details directly. The severity of COVID-19 was determined based on the symptoms and clinical signs observed on the day preceding the onset of initial neurological symptoms. To assess overall patient outcomes, we gathered in-hospital data, including the need for intensive care unit (ICU) admission and/or mechanical ven-

tilation (MV) support as well as the occurrence of complications. Additionally, we documented the duration of hospitalization, recorded mortality cases, and monitored the time to death. All patients underwent SARS-CoV-2 testing using one or both of the following methods: ELISA for IgA in serum samples and/or RT-PCR from oropharyngeal swabs. Vascular syndromes included confirmed cases of ischemic stroke, hemorrhagic stroke, and cerebral venous thrombosis.

Statistical analysis

Continuous data were expressed as the mean with standard deviation or as the median accompanied by the interquartile range (IQR). Categorical data are reported as frequencies and percentages.

Standard protocol approvals, registrations and patient consents

This study was approved by the ethics committee of the University of São Paulo (CAAE: 31378820.1.1001.0068) and ethics committees of the study sites. Written informed consent was obtained from all the patients or their next of kin, and their personal information was protected by ethical procedures. The study adhered to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments as well as relevant Brazilian regulations.

Results

Patient selection

Patients with positive test results for the Sars-CoV-2 virus (1998 patients) were included. Of these patients, 550 were admitted to the hospital because of neurological symptoms and 1448 without neurological symptoms. Neurological manifestations were monitored in the hospital environment through in-person evaluations by a neurology team. The inclusion of patients within the group with cerebrovascular

diseases (50 patients; 27 with ischemic stroke, 20 with hemorrhagic stroke and 3 with cerebral venous thrombosis) occurred through anamnesis, physical examination, and complementary tests that confirmed the presence of cerebrovascular disease.

Analysis of the length of hospital stay and the outcome of patients hospitalized with confirmed COVID-19 (hospital discharge versus death), in relation to the cases that presented neurological manifestations upon admission and those who were admitted to the hospital environment without neurological manifestations, showed that the length of hospital stay was longer among patients who died in relation to those who were discharged from hospital and that this difference was statistically significant among all patients classified with COVID-19 and in the subgroup of patients with neurological symptoms upon admission (Table 1).

Through these results, we can also observe the long hospitalization time of these patients from the first wave of covid19, observe the high mortality rate, and how admission with neurological symptoms was a determinant of greater severity (Fig. 1).

Analyzing the most frequent diagnoses during the syndromic approach upon hospital admission of patients, it can be seen that most patients were screened for neurological symptoms and respiratory symptoms, with most receiving a final diagnosis of neurological disease (cerebrovascular disease) and/or COVID-19. A more detailed analysis revealed that most patients with neurological symptoms were only diagnosed with COVID-19 through screening that was carried out during the pandemic, as these were not the predominant symptoms at admission (Table 2).

Table 1 | Analysis of length of hospital stay and outcome (hospital discharge versus death) in patients with COVID-19, in relation to cases that presented neurological manifestations, and those patients admitted to the hospital without neurological manifestations. São Paulo-SP, 2020-2021

Variable	Total n=1998	Discharge n=1231	Death n=767	p- value
Time in hospitalization (months)	11.3±14.3	25.8±6.3	61.2±24.1	≤0.001
Neurological (n=550)	10.6±21.9	9.3±18.6	14.8±30.1	≤0.001
Non- neurological (n=1448)	11.6±9.9	11.6±9.9	11.7±10.0	0.755

Figure 1 | Estimated survival time, according to clinical diagnosis of COVID19 and neurological or non-neurological symptoms during hospital admission. São Paulo-SP, 2020-2021. ($p \leq 0.001$ - Log Rank Test)

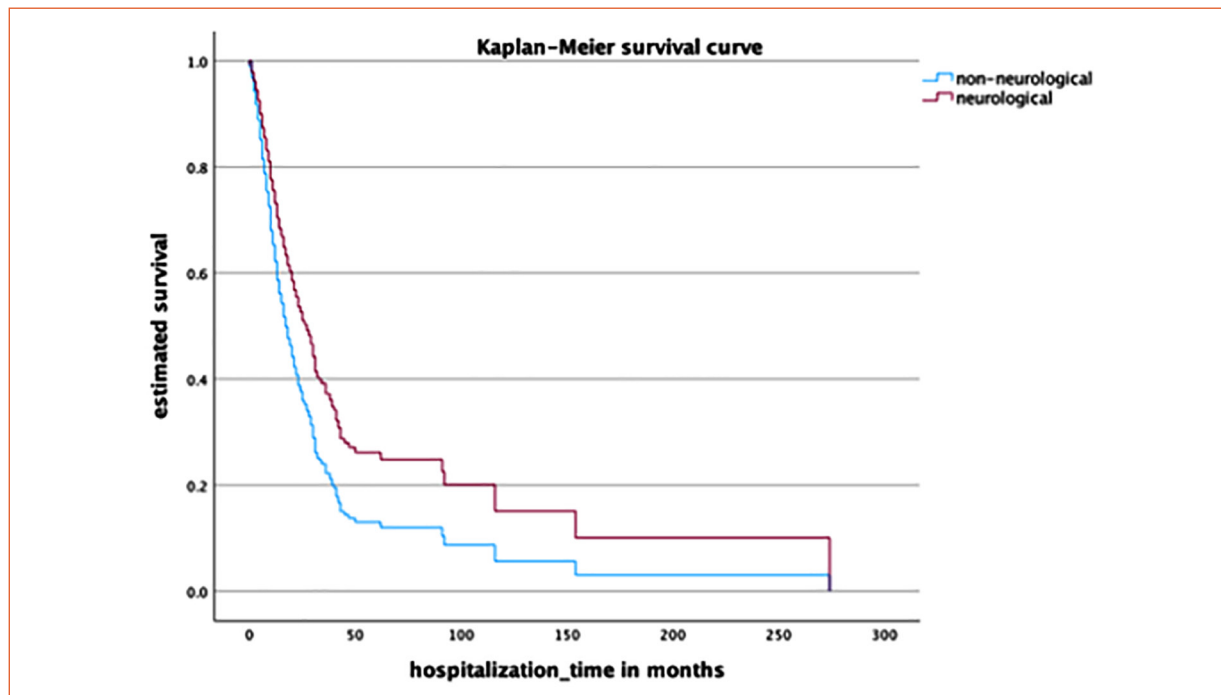


Table 2 | Prevalence of the most frequent syndromes according to the international coding of diseases, in patients with neurological symptoms and without neurological symptoms on admission, hospitalized, with confirmed diagnosis of COVID-19, São Paulo-SP, 2020-2021

Syndromic diagnoses in patients with COVID-19	Non-neurological n=1448 (%)	Neurological n=552 (%)
Vertebrobasilar syndrome	----	49 (8.9)
Carotid syndrome	1 (0.1)	20 (3.6)
Transient ischemic stroke	----	43 (7.8)
Subarachnoid hemorrhage	1 (0.1)	19 (3.4)
Cerebral infarction	----	34 (6.2)
Viral pneumonia	437 (30.2)	----
Adult respiratory distress syndrome	60 (4.1)	----
Acute respiratory failure	42 (2.9)	----

By assessing the prevalence of the main causes of death according to the international coding of the most frequent diseases in patients with and without neurological symptoms who were hospitalized and diagnosed with COVID-19, it can be seen that those who were admitted with neurological symptoms died due to neurological disease and not necessarily from the COVID-19 infection (Table 3).

Similarly, drawing a parallel, it is evident that patients with non-neurological symptoms and COVID-19 died mostly due to metabolic conditions, sepsis, and respiratory complications (i.e., not due to neurological causes) (Table 4).

Discussion

In this study, 1498 patients with COVID-19 were studied, of whom 552 presented with neu-

Table 3 | Prevalence of causes of death according to the international coding of most frequent diseases, in patients with neurological symptoms and without neurological symptoms, hospitalized and diagnosed with COVID-19, São Paulo-SP, 2020-2021

Most frequent deaths in patients with COVID-19	Non-neurological n=1448 (%)	Neurological n=552 (%)
Total deaths	809 (55.9)	425(77.0)
Septicemia	27 (1.9)	4 (0.7)
COVID-19	304 (21.0)	-----
Hyperkalemia	10 (0.7)	-----
Subarachnoid hemorrhage	1 (0.1)	19 (3.4)
Cerebrovascular disease	1 (0.1)	27 (4.9)
Respiratory failure	21 (1.5)	7 (1.3)
Circulatory shock	48 (3.3)	4 (0.7)
Severe acute respiratory syndrome	23 (1.6)	-----

Table 4 |Prevalence of comorbidities, initial symptoms and most frequent hospitalization indicators in patients with cerebrovascular disease hospitalized with COVID-19, comparison between patients with ischemic stroke and patients with hemorrhagic stroke. São Paulo-SP, 2020-2021

Variables Comorbidities Symptoms Hospitalization indicators	Total n=47 (%)	Stroke ischemic n=27 (57.4%)	Stroke hemorrhagic n=20 (42.6%)	p- value
SAH	26 (55.3)	18 (66.7)	8 (40.0)	0.069
DM	17 (36.2)	13 (48.1)	4 (20.0)	0.067
Alcoholism	2 (4.3)	1 (3.7)	1 (5.0)	0.828
Obesity	11 (23.4)	7 (25.9)	4 (20.0)	0.737
Active neoplasia	5 (10.6)	5 (18.5)	-----	0.063
Smoking	10 (21.3)	7 (25.9)	3 (15.0)	0.481
Previous stroke	5 (10.6)	5 (18.5)	-----	0.063
Fever	35 (74.5)	20 (74.1)	15 (75.0)	0.943
Cough	40 (85.0)	25 (92.6)	15 (75.0)	0.119
Myalgia	8 (17.0)	5 (18.5)	3 (15.0)	0.751
Headache	12 (25.5)	6 (22.2)	6 (30.0)	0.545
Diarrhea	3 (6.4)	2 (7.4)	1 (5.0)	0.739
Anosmia	1 (2.1)	1 (3.7)	-----	0.384
Hospitalization due to COVID	42 (89.4%)	26 (96.3%)	16 (80.0%)	0.148
COVID ICU	41 (87.2%)	25 (92.6%)	16 (80.0%)	0.379
VM by COVID	38 (80.9%)	22 (84.6%)	16 (80.0%)	0.898
Days of hospitalization (mean $\pm$ SD)	13.7 $\pm$ 9.7	13.5 $\pm$ 10.0	13.7 $\pm$ 6.9	0.510
COVID-19 classification				
Asymptomatic	1 (2.1%)	-----	1 (5.0%)	
Severe	9 (19.2%)	6 (22.2%)	3 (15.0%)	
Critical	30 (63.8%)	17 (63.0%)	13 (65.0%)	
Moderate	5 (10.6%)	3 (11.1%)	2 (10.0%)	
Mild	2 (4.3%)	1 (3.7%)	1 (5.0%)	

SAH: systemic arterial hypertension; DM: diabetes mellitus; ICU: intensive care unit; VM: mechanical ventilation

rological symptoms during hospitalization that were suspected to have neurological syndromes (sequelae of previous events, recrudescence of signs and/or symptoms, or acute conditions). The general objective of interconsultations is to distinguish between old conditions that have worsened due to the infectious condition or to identify new events that may require urgent, emergency, or specific outpatient procedures. We observed that approximately 2.3% of patients presented with neurological syndromes compatible with recent cerebrovascular disease (acute/subacute). Of the patients with confirmed cases of recent cerebrovascular disease, 27 were affected by ischemic stroke, 20 by hemorrhagic stroke (1 patient with both findings), and 3 by cerebral venous thrombosis. These data are like those of previous studies whose evaluation period is practically concomitant with that carried out by our group (first and second waves of COVID-19 cases before mass vaccination)^{11–14}.

When evaluating international records of cases of cerebrovascular disease in hospitalized patients with SARS-CoV-2 infection, we found that the overall risk of stroke varied considerably from places with a rate of 0.5%¹⁵, others with 0.9% of patients hospitalized with COVID-19¹⁶, and some with rates as high as 2%. This difference in incidence rates may be related to the profile of the hospital structures studied, given the difference in the severity of patients hospitalized with COVID-19 infection (higher in tertiary and quaternary services in the care lines) prevalence of cardiovascular risk factors in the population studied (higher in outpatient referral services for clinical specialties) ability to accurately determine and diagnose all strokes (at a time when medical services were overloaded) and differences in the availability of institutional complementary examinations during the pandemic period under study.

In the present study, 27.5% of patients hospitalized for COVID-19 presented neurological manifestations, notably 50 cases of acute cerebrovascular disease (54% ischemic, 40% hemorrhagic, and 6% cerebral venous thrombosis). Mao et al. (2020)¹¹, in their Wuhan cohort, identified neurological manifestations in 36.4% of patients, with cerebrovascular events being among the most serious findings, especially in patients

with severe disease and pre-existing risk factors. The comparison suggests a consistent pattern across different scenarios, reinforcing that the clinical severity and systemic inflammatory profile of COVID-19 are associated with significant neurological complications. However, the relatively high proportion of hemorrhagic stroke in our series may indicate regional differences related to comorbidities, anticoagulation use during hospitalization, and the severity of cases treated at a tertiary referral hospital.

When compared with data from Yaghi et al. (2020)¹⁶, who analyzed hospitalized patients in New York and found a stroke rate of 0.9% among those infected with SARS-CoV-2, our findings reveal a higher incidence (2.5%). These same authors highlighted that ischemic events were predominant and were associated with high levels of inflammatory and prothrombotic markers, suggesting a central role of the systemic inflammatory response in the pathophysiology. In contrast, in the present study, there was a more balanced distribution between ischemic and hemorrhagic events, which may reflect both differences in demographic profile and prevalence of hypertension and diabetes, as well as challenges in clinical management in the context of hospital overload. This comparison highlights that, although thrombotic mechanisms are consistent globally, clinical presentations and proportions of stroke subtypes may vary according to local and healthcare system characteristics.

The patients evaluated in the study at our center mostly presented with COVID-19 and cerebrovascular disease associated with severe inflammation and infection, and therefore, were in a hypercoagulable state. Significantly increased inflammation may be one of the reasons for abnormal coagulation function in the early phase and may also be one of the reasons for the onset and predisposition to cerebrovascular disease¹⁷. In general, the mechanism underlying cerebrovascular disease caused by COVID-19 remains unclear. Currently, most opinions still focus on the hypercoagulable state caused by systemic inflammation^{18,19}.

In recent years, evidence has shown that several acute and chronic cardiovascular conditions can occur after COVID-19 infection, including acute pulmonary embolism, deep vein

thrombosis, heart failure, arterial hypertension, atrial fibrillation and diabetes. All these conditions, especially if they remain undiagnosed and untreated, may represent concomitant risk factors for the onset of ischemic stroke. However, it is not yet possible to determine whether the onset of these new cardiovascular diseases represents a direct consequence of COVID-19, or whether the virus may merely act as a triggering factor in a clinical condition.

The data obtained are useful to alert the population of the risks and thus minimize the possibility of cerebrovascular disease events during hospitalization, in the convalescence and recovery phase of the infectious process, and after hospital discharge in COVID-19 survivors. Additional studies are needed to determine the potential benefits of anticoagulant therapy (as well as doses and duration of use) in reducing the risk of ischemic stroke²⁰.

Compared with reports of ischemic events, fewer cases of hemorrhagic stroke were observed in patients with COVID-19, as in our case series²¹. Based on a cohort of 755 COVID-19-positive patients (out of a total of 3824) in whom neuroimaging studies were performed during hospitalization, Dogra et al. estimated that the prevalence of intracranial hemorrhage (ICH) was 4.4% ($n = 37$), representing almost 11% of all cerebrovascular diseases in the investigated group. Almost 80% of ICH cases occur in male patients. The mean age of the COVID-19 patients with acute cerebrovascular disease was higher than that of individuals not affected by the infection. Fifteen percent of ICH cases were parenchymal hemorrhages with mass effects and brain herniation, with the mortality rate reaching 100%²².

Punctate hemorrhages accounted for 25% of intracranial hemorrhages, while small-to-moderate hemorrhages were observed in 60% of the patients. It is noteworthy that 67% of the investigated individuals received therapeutic anticoagulation and 9% received prophylactic anticoagulation before the onset of intracranial hemorrhage. Given these data, it seems that the use of anticoagulation, whether prophylactic or full, should always be associated with a good overall clinical evaluation so that the risks and benefits of this medical intervention can be weighed²².

In a systematic review, Maury et al. analyzed data on COVID-19-related intracranial hemorrhage from nine cohort studies from Belgium, China, France, Italy, the United Kingdom, and the United States. The estimated prevalence of ICH ranged from 0.2% in the French cohort, which included 46 centers, to 0.8% in a study of three centers in Italy^{23,24}. Data were closer to the values found in our case series.

Regarding cerebrovascular complications due to Sars-CoV-2 infection, the relationship between cerebral venous thrombosis (CVT) and COVID-19 is noteworthy because in infected individuals, the incidence of CVT is estimated at 42.8 per million²⁵.

The incidence was even higher among hospitalized COVID-19 patients (231 per million). For better understanding and comparison, the incidence of CVT in the pre-COVID era was estimated at 13.9–20.2 per million^{26–29}.

We had three cases in our case series, which within the context of more than a thousand patients infected by a virus with neurotropism and in serious conditions, we can conclude that it is within numbers close to pre-pandemic values.

For comparative analysis purposes, we can use the largest published series of cases of CVT associated with COVID-19 in 2024, Scutelnic et al.³⁰ published data collected in 21 hospitals in 13 countries, with 70 patients, showing that, although not significant, the mortality rate in patients with CVT and COVID-19 was higher than in controls (7% vs. 3%). These results may have clinical significance, indicating that COVID-19 contributes to the sequelae of CVT. In this study, most patients with CVT due to COVID-19 (87%) were asymptomatic, mild, or moderate. In addition, the initial characteristics were quite similar in the COVID-CVT and control groups, probably explaining the similar results in functional outcomes of surviving patients. The published data show important analyses regarding signs and symptoms, assessment of disability scales, and functional outcomes; however, few differences in relation to the results were observed in the pre-pandemic era³⁰.

Limitations include the fact that this is an observational study and is not multicenter, which limits external validity. Furthermore, data collection occurred during the first outbreak of the

pandemic, a period marked by overburdened health services and restricted access to additional testing, which may have led to underreporting or delayed diagnosis of cerebrovascular events. Another important aspect was the lack of post-discharge follow-up, making it impossible to assess the functional progress and possible late sequelae of patients.

In conclusion, the absolute number of cerebrovascular disease cases has considerably increased. The contribution of several risk factors has also changed in recent years, and we must remember the possibility of an association between cerebrovascular disease and infectious agents. In this study, we can observe the severity of cases associated with COVID-19 and thus provide information that may help in understanding the importance of effective, accessible, and economical measures to improve surveillance and prevention of cerebrovascular

diseases, especially in relation to the control of modifiable risk factors, such as systemic arterial hypertension (SAH), changes in lifestyle (smoking), and environmental factors (exposure to infectious agents). Thus, we must remember that access to intensive care and early rehabilitation can modify the outcomes and sequelae presented, as well as make clarifies how they are essential factors in the lines of care, especially in the public health environment, where they need to be implemented urgently to reduce the disabling sequelae resulting from stroke.

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Conflict of interest: None to declare

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