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Stroke in patients infected by the novel coronavirus and its causal mechanisms: A narrative review

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[Correction added on 19 January 2021, after first online publication: the article category and sub-category have been updated.]

Abstract

Objective: The current study aimed to evaluate the mechanisms of stroke development during the coronavirus disease 2019 (COVID-19) pandemic and analyze the related characteristics, such as etiology, age group, associated comorbidities, and prognosis.

Methods: A narrative was performed using the descriptors ["novel coronavirus"] AND ["stroke"] in the PubMed, Science Direct, Google Scholar, Lilacs, and Biblioteca Virtual em Saúde (BVS) databases, including studies published between December 1, 2019, and April 28, 2020.

Results: A total of 142 articles were identified, with 89 of them in the PubMed database, 46 in Science Direct, and 7 in Google Scholar. No articles were found using the defined keywords in the Lilacs and BVS databases. A total of 22 articles were included for final evaluation. We observed that infection by the novel coronavirus caused a greater risk of the occurrence of stroke, with several studies suggesting etiological mechanisms, such as the involvement of angiotensin-converting enzyme 2, viral invasion, and hypoxia as well as the increase in D-dimer and the reduction in platelets, which had been commonly observed in COVID-19 cases. The most common complication of stroke was found among the elderly with preexisting comorbidities, mainly cardiovascular disease. We detected reports of strokes among young people with no preexisting risk factors for thromboembolic events, in which the mechanism related to the viral infection was the most probable cause. In this review, we confirmed that stroke is part of the spectrum of clinical manifestations resulting from COVID-19 and is associated with a worse prognosis. Cerebrovascular lesions resulting from

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complications of the infection by the novel coronavirus occurred as a result of ischemic, hemorrhagic, and/or thromboembolic etiologies.

Conclusion: The occurrence of stroke during the pandemic as a result of the novel coronavirus has a multifactorial character, and emergency physicians should focus on systematic measures for its screening and accurate diagnosis as well as on appropriate interventions based on early decisionmaking that may have a favorable impact on reducing damage and saving lives.

KEYWORDS
adult health, COVID-19, novel coronavirus, stroke

1 | INTRODUCTION

In December 2019, the first cases of coronavirus disease 2019 (COVID-19) appeared in the city of Wuhan, China. This disease is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), one of the 5 betacoronaviruses that can infect human beings.[1] Over time, the virus spread worldwide, leading the World Health Organization to characterize the disease as a pandemic on March 11, 2020. By November 13, 2020, at least 52,487,476 cases and 1,290,653 deaths from COVID-19 have been confirmed worldwide, demonstrating its high power of dissemination and mortality, particularly in elderly men with preexisting comorbidities.[2,3] In Brazil, on the same date, there were 5,848,959 cases and 165,658 deaths from COVID-19.[2,3] COVID-19 presents a heterogeneous clinical picture, with fever, cough, anosmia, ageusia, fatigue, and dyspnea being common. Associated neurological symptoms may also occur as well as varying degrees of pulmonary involvement, which can culminate in severe respiratory failure and the crucial need for intensive care.[4] Regarding the neurological symptoms in patients with COVID-19, they usually manifest mildly and include headache, dizziness, and neuralgia. Other cases can be more severe, with neurological complications such as stroke.[5] Stroke has an ischemic etiology in 80% of cases, while the minority has a hemorrhagic cause.[6] Stroke is a medical emergency with an increasing incidence, and it is the second leading cause of death worldwide.[7] Recent studies have shown an association between COVID-19 and stroke. For example, Oxley et al[8] observed a higher occurrence of large-vessel stroke in patients aged younger than 50 years infected with the novel coronavirus in New York. Shahjouei et al,[9] after analyzing multinational data, also observed the occurrence of stroke in 0.9% of hospitalized patients infected with SARS-CoV-2, whereas the rate in the general population without COVID-19 is 0.5%. In addition to respiratory symptoms, the perception of neurological symptoms also should be considered as an indicator for the diagnosis of patients with COVID-19.[5] In most cases, stroke first occurs in the emergency sectors, in which the early identification of suspected cases is a priority as well as the appropriate decisionmaking, with significant impacts on the morbidity and mortality of these patients.[10]

Given the possibility of the association between COVID-19 and stroke, two lethal clinical conditions, it is important for health professionals, particularly those working in acute care settings, to understand and focus on the clinical picture and pathophysiology of these diseases to save as many lives as possible. Therefore, the objective of the present review was to summarize the literature to date on ischemic stroke and COVID-19, evaluating the mechanisms of stroke development during COVID-19.

2 | MATERIALS AND METHODS

We conducted a narrative review of studies on the novel coronavirus that contained information on associated stroke. The objectives were based on the population, intervention, comparisons, and outcomes strategy and choice of descriptors.[11] The PubMed, Science Direct, Lilacs, Biblioteca Virtual em Saúde (BVS), and Google Scholar databases were assessed as part of the bibliographical search strategy using the search terms ["novel coronavirus"] AND ["stroke"] and including published studies in the past year (from December 1, 2019 to April 28, 2020).[11] We did not account for gray literature/file box studies.

For this review, we developed a data extraction spreadsheet, adhering to a study eligibility form, describing the type of study, inclusion criteria, exclusion criteria, examiners' assessment, agreement for inclusion, number of participants, clinical outcomes, stroke and mortality prevalence, suggested assumptions, risk of bias, statistical methods used, and additional analyses.

A total of 6 reviewers performed the search strategy. As initial identification criteria, all of the articles were selected in accordance with the chosen descriptors. As inclusion criteria, we opted for studies in adult humans infected with the novel coronavirus in which there was an association of stroke as a neurological manifestation of COVID-19. In addition, we selected peer-reviewed articles or reviews of primary research, grey literature including policy papers, guides or guidelines, letters, editorials and comments. The chosen languages were English or Spanish. As exclusion criteria, we chose evaluation articles on animals, studies involving children and adolescents, abstracts of congresses or symposia, and book chapters as well as those articles in which although stroke was mentioned, it did not occur as a result of the novel coronavirus infection. We followed all the documentation steps of the identified, selected, included, and excluded articles. Because of the nature

of the review study, approval from the research ethics committee was not required.

3 | RESULTS

For the proposed review, 142 articles were identified: 89 articles in PubMed, 46 in ScienceDirect, and 7 in Google Scholar. The Lilacs and BVS did not present positive results for the descriptors. The analysis of the identified articles resulted in the exclusion of 26 duplications and another 2 articles that presented data published before the predefined time frame for the research. In the subsequent reading and analysis of the abstracts, several articles that were initially selected approached topics that differed from the review purpose, such as detailed data about the epidemiology of the virus and general clinical data from COVID-19 cases as well as tomographic results, used treatments (including surgical), and telemedicine data in general in the COVID-19 context. This selection resulted in 35 articles that were indicated for complete reading. Subsequently, 22 of these articles met the inclusion and exclusion criteria and were selected for the final review.

In the reference list of the included studies, the publications had the following origins: 8 were North American; 7 were Chinese; 2 were Italian; and 1 each was from France, the United Kingdom, Spain, Colombia, and Pakistan. The population comprised patients with COVID-19, and the sample size ranged from 1 (case report) to a final sample of 764 patients evaluated. Regarding the study design, 9 systematic reviews, 10 retrospective studies (5 cohort studies and 5 characterized as case series), and 3 correspondences were analyzed. Table 1 shows the characteristics of the studies included in the analysis.

A representative number of articles in the present review identified stroke and other thromboembolic complications among the manifestations of COVID-19.[12–19] Neurological symptoms, including stroke, have been observed in past epidemics by other betacoronaviruses, indicating the potential risk of neurological symptoms and acute cerebrovascular complications in infections with the novel coronavirus.[13,18] Baig et al[17] demonstrated this relationship with the nervous system in a study that found that 36.4% of the analyzed patients with COVID-19 had neurological symptoms. Thus, the importance of identifying the possibility of stroke in patients with COVID-19 has been confirmed by several studies, with a higher prevalence in the critically ill.[12,14–16] Conde Cardona et al[19] also correlated greater severity of the disease in those with neurological symptoms. When the presence of stroke was verified, this correlation was even more significant: 5.7% in severe cases compared with 0.8% in nonsevere cases ($P < 0.05$).[19] Venous or arterial thromboembolic disorders, defined as pulmonary embolism, ischemic stroke, deep venous thrombosis, or myocardial infarction, were also reported in 31% of patients confirmed with COVID-19.[20]

Elkind et al[21] stated that infection with the novel coronavirus increased the risk of cardiovascular events; whereas, Li et al[22] observed that patients with underlying cardiovascular disease had more severe clinical symptoms, higher severity scores on computed tomography images, and significantly higher mortality. These data were reinforced in recent studies in which the elderly and patients with cardiovascular disease showed a higher prevalence of acute stroke as a complication of COVID-19.[23–26] In addition to these lines of evidence, the disease severity was also associated with hypercoagulability, as indicated by the high concentration of D-dimers.[27] Giannis et al[28] concluded that the formation of intra-alveolar or systemic fibrin, caused by the dysregulation of the coagulation cascade, was also present in patients infected by other types of coronaviruses.

Thomas et al[29] evaluated patients in intensive care units, with an estimated cumulative incidence of venous thromboembolism of 27% (95% confidence interval [CI], 10%-47%) and that of arterial thrombosis of 4% (95% CI, 1%-12%). These values could justify the association of COVID-19 with stroke. Lodigiani et al[30] evaluated patients with COVID-19, and stroke was diagnosed in 2.48% of the hospitalized patients. The results of the study indicated that thromboembolic complications may represent an important part of the clinical picture of COVID-19 and could already be present at the time of hospital admission.

Fu et al[31] reported cases of pneumonia secondary to infection by the novel coronavirus with the occurrence of acute stroke in middle-aged patients without a history of arterial hypertension, diabetes, hyperlipidemia, or heart disease.

Vu et al[32] reported the clinical story of a young patient infected by the novel coronavirus with no preexisting comorbidities who developed hemorrhagic stroke. Thus, doctors and health professionals who work in acute care settings should track neurological symptoms in those infected and with preexisting comorbidities, usually elderly patients, as well as in those without preexisting comorbidities. The data showed that the stroke mechanism in these patients with different profiles does not appear to be similar. Figure 1 shows the probable pathophysiological mechanisms involving COVID-19 and the occurrence of neurological symptoms and stroke.

As a limitation of the study, no detailed description was provided for other neurological conditions that did not coincide with stroke as well as for post–COVID-19 neurological manifestations. Although we recognize their importance, it was not the priority objective of this review.

4 | DISCUSSION

The present narrative review highlighted the relevance of stroke as a clinical manifestation in patients with COVID-19, suggesting that it is a serious condition of clinical emergency that could lead to a worse prognosis and a longer hospitalization time for those infected by the virus as well as greater morbidity and mortality.

Recent clinical studies have suggested the possibility that the novel coronavirus could reach the central nervous system, but the exact route of access has not yet been demonstrated. However, probable pathophysiological mechanisms could explain this association. In previous studies with other coronaviruses and in an animal model of infection, central nervous system invasion had postulated to occur mainly by the transsynaptic transfer of virus particles, starting with infection in the peripheral nerve endings, such as the olfactory nerves.

TABLE 1 Characteristics of the studies included in the analysis

Publication date	Author and reference	Journal issue details	Location	Study type	Included population	Stroke prevalence, %
April 13, 2020	Troyer et al[12]	Brain Behav Immun 2020. https://doi.org/10.1016/j.bbi.2020.04.027	University of California San Diego, San Diego, CA, USA	Systematic review	217	20.2[a]
April 30, 2020	Wu et al[13]	Brain Behav Immun 2020. https://doi.org/10.1016/j.bbi.2020.03.031	Nanjing Medical University, Nanjing, China	Systematic review	214	36.7[b]
April 11, 2020	Asadi-Pooya et al[16]	J Neurol Sci 2020;413:116832. https://doi.org/10.1016/j.jns.2020.116832	Department of Neurology, Thomas Jefferson University; Pennsylvania, USA	Systematic review	–	–
April 1, 2020	Baig et al[17]	ACS Chem Neurosci 2020;11(7):995-998. https://doi.org/10.1021/acschemneuro.0c00122	Medical College, Aga Khan University, Karachi, Pakistan	Systematic review	–	–
April 6, 2020	Matías-Guiu et al[18]	Neurologia 2020;35(3):170-175. https://doi.org/10.1016/j.nrl.2020.03.001	Hospital Clínico San Carlos, San Carlos, Madrid, Spain	Systematic review	–	–
April 9, 2020	Giannis D et al[28]	J Clin Virol 2020;127:104362. https://doi.org/10.1016/j.jcv.2020.104362	The Feinstein Institutes for Medical Research; New York, USA	Systematic review	–	–
April 23, 2020	Wilson et al[14]	Clin Neurol Neurosurg 2020;193:105866. https://doi.org/10.1016/j.clineuro.2020.105866	University of Alberta; Alberta, Canada; and University of California; California, USA	Literature review	–	–
April 7, 2020	Gasmi et al[15]	Clin Immunol 2020;215:108409. https://doi.org/10.1016/j.clim.2020.108409	Société Francophone de Nutrithérapie, Villeurbanne, France	Literature review	–	2.30
April 27, 2020	Leung[1]	Mech Ageing Dev 2020;188:111255. https://doi.org/10.1016/j.mad.2020.111255	Department of Neurosurgery, Brigham and Women's Hospital, Boston, MA, USA	Literature review	154	5.7 and 21.8
April 23, 2020	Lodigiani et al[30]	Thromb Res 2020;191: 9-14. https://doi.org/10.1016/j.thromres.2020.04.024	Humanitas Clinical and Research Hospital, Rozzano, Milano, Italy	Cohort study	338	2.50[c]
April 20, 2020	Liu X et al[27]	Acta Pharm Sin B 2020. https://doi.org/10.1016/j.apsb.2020.04.008	Zhongnan Hospital of Wuhan University, Wuhan, China	Cohort study	–	–
April 25, 2020	Thomas W et al[29]	Thromb Res 2020. https://doi.org/10.1016/j.thromres.2020.04.028	Cambridge University Hospitals National Health Service Foundation Trust, Cambridge, UK	Cohort study	63	4
March 10, 2020	Gao et al[24]	BMJ Yale 2020;1-10. https://doi.org/10.1101/2020.03.07.20031393	The First People's Hospital of Jingmen, Jingmen, Hubei Province, China	Cohort study	213	–
April 10, 2020	Niu et al[23]	Arch Gerontol Geriatr 2020;89:104058. https://doi.org/10.1016/j.archger.2020.104058	Beijing Emergency Medical Center, Beijing, China	Cohort study	141	–
April 18, 2020	Li et al[22]	Nutr Metab Cardiovasc Dis 2020;30(7):1061-1067. https://doi.org/10.1016/j.numecd.2020.04.013	Huazhong University of Science and Technology, Wuhan, China	Series of cases	83	–
April 28, 2020	Avula et al[25]	Brain Behav Immun 2020;87:115-119. https://doi.org/10.1016/j.bbi.2020.04.077	Staten Island University Hospital, New York, NY, USA	Series of cases	4	100

(Continues)

TABLE 1 (Continued)

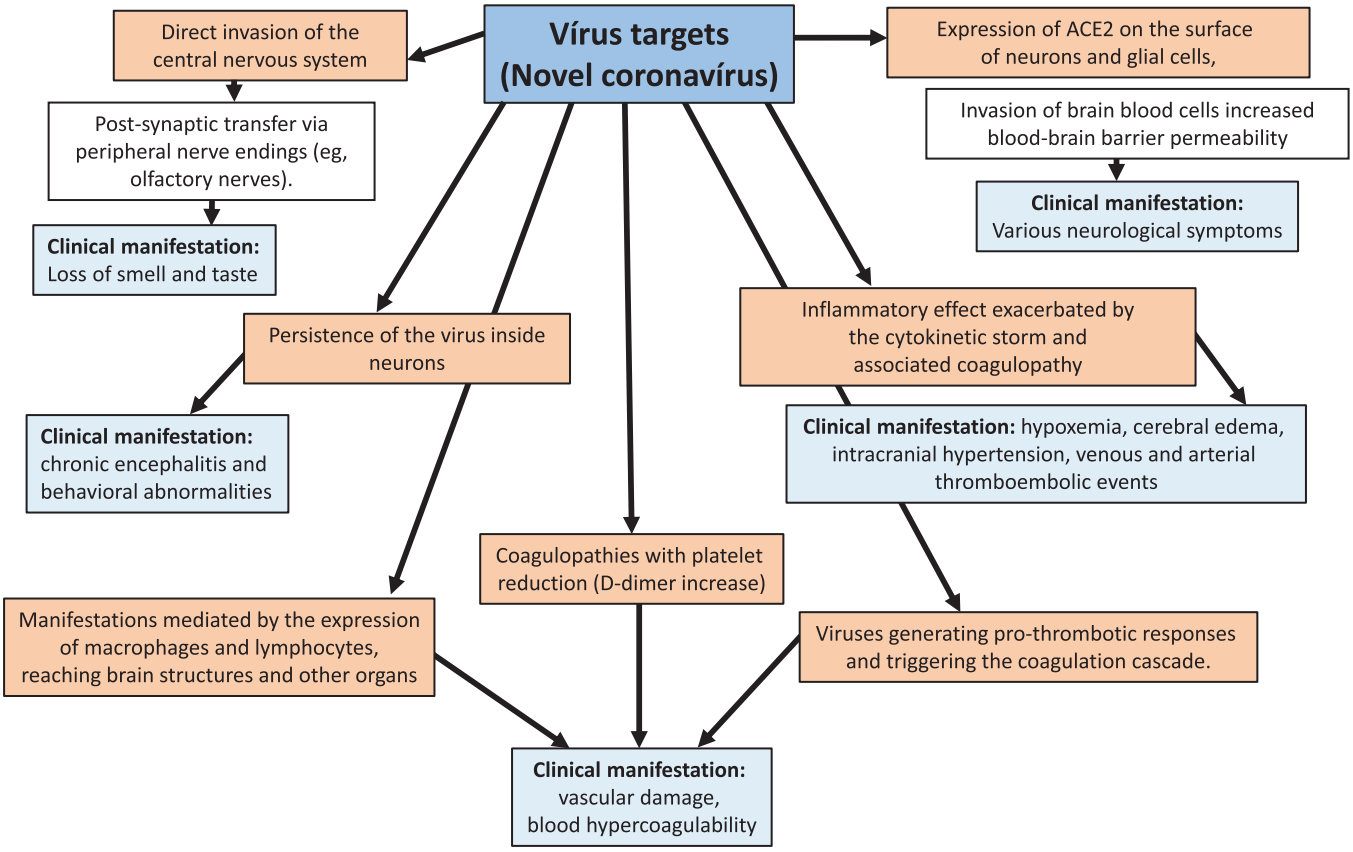
Publication date	Author and reference	Journal issue details	Location	Study type	Included population	Stroke prevalence, %
April 13, 2020	Vu et al[32]	Emerg Radiol 2020;27(3):229-232. https://doi.org/10.1007/s10140-020-01775-4	Maimonides Medical Center, Brooklyn, NY, USA	Case report	1	33.30
April 5, 2020	Fu et al[31]	BMC Neurology 2020;1-12. https://doi.org/10.21203/rs.3.rs-20943/v1	Hubei Provincial Hospital of integrated Chinese and Western Medicine; Wuhan, China	Case report	764	0.26
March 30, 2020	Zhai et al[26]	Research Square 2020;1-10. https://doi.org/10.21203/rs.3.rs-20393/v1	Hubei Provincial Hospital of Chinese Tradition Medicine, China	Case report	1	100
April 8, 2020	Conde Cardona et al[19]	J Neurol Sci 2020;412:116824. https://doi.org/10.1016/j.jns.2020.116824	Universidad Rafael Nuñez Cartagena, Colombia	Letter to the editor	–	–
April 14, 2020	Elkind et al[21]	Circulation 2020;141:e743-e745. https://doi.org/10.1161/CIRCULATIONAHA.120.046749	Columbia University, New York, NY, USA; and Stanford University, California, USA	Letter to the editor	–	–
April 22, 2020	Di Renzo et al[20]	Am J Obstet Gynecol 2020;223(1):135. https://doi.org/10.1016/j.ajog.2020.04.017	University of Perugia, Perugia, Italy	Correspondence	–	–

[a]Stroke prevalence was 20.2% among the 44.55% considered in severe condition in the sample.
[b]Stroke prevalence was 36.7% among the 36.44% considered in severe condition in the sample.
[c]Ischemic stroke prevalence.

This finding could explain peripheral neuronal manifestations, such as the loss of smell and taste, present in those infected by the novel coronavirus.[5] The virus could also explore a pathway mediated by both macrophages and the lymphatic pathways to reach the brain as well as other organs.[5] Another possible related mechanism is the persistence of the virus internally in neurons that could induce the death of neuronal cells (animal model), causing the development of chronic encephalitis and behavioral abnormalities.[15] angiotensin-converting enzyme 2 (ACE2) expressed on the surface of neurons, glial cells, and blood vessel endothelial cells is also a potential target of the virus. SARS-CoV-2 could infect cells in cerebral blood vessels, leading to increased permeability of the blood–brain barrier and invasion of pathogens in the brain. In addition, and indirectly, an inflammatory effect could be induced by cytokine storms, leading to cerebral edema and intracranial hypertension. Thus, infection by the novel coronavirus may lead to hypoxemia, enhanced by cytokine storms, part of the strong systemic inflammatory response with associated coagulopathy that could lead to venous and arterial thromboembolic events.[23,32] In cases of hemorrhagic events, the suggested cause was the theory of the involvement of SARS-CoV-2 and ACE2 expressed in the capillary endothelium. This interaction could result in arterial hypertension and, consequently, an increased risk of cerebral hemorrhage.[1,13,15,17,18]

The coagulation cascade could also be present due to the prothrombotic responses caused by the virus, resulting in the formation of blood clots.[31] Thus, in the infected population, there is unification of the inflammatory pathways and coagulation in the genesis of thromboembolic complications, possibly by activation of factors that compound the Virchow triad, including vascular damage, altered blood flow, and blood hypercoagulability.[33–37] Among stroke types, ischemic events are the most prevalent and directly associated with a worse prognosis for COVID-19.[12,22,24–26,28,32,38] Many studies have reinforced that age could be the main factor for this greater susceptibility of ischemic stroke among infected patients.[27,28] In addition to age, the presence of associated comorbidities, particularly cardiovascular disease, and the patient's hypercoagulability state have been shown to be aggravating factors for COVID-19.[21,23,27] Among hospitalized patients, the cumulative incidence of venous thromboembolism was higher than that of arterial thrombotic events (27% [95% CI, 10%-47%] vs 4% [95% CI, 1%-12%], respectively). Another relevant point was that most patients diagnosed with thrombotic conditions had at least one associated risk factor. The most significant were poorly controlled diabetes, obesity, and other comorbidities as well as a prolonged hospitalization time.[34,39,40]

Therefore, thromboembolic complications could represent a relevant part of the clinical picture of COVID-19 present from the initial hospitalization.[26,27] A recent study showed that the rate of Pulmonary Thromboembolism (PTE) detected in intensive care settings for patients without COVID-19 was <2%; however, in cases in which the novel coronavirus was detected, the rate was >20%.[41] The relevance of these complications has also been demonstrated in patients with acute respiratory discomfort syndrome not related to COVID-19, showing a lower rate of thromboembolic complications (2.1%) than in patients with acute respiratory discomfort syndrome caused by the novel coronavirus (11.7%).[42] Clinicians must be attentive when



Where: ACE-2 = Angiotensive 2 Conversion Enzyme. Figure developed by the authors.

FIGURE 1 Probable pathological mechanisms involving coronavirus disease 2019 and the occurrence of neurological symptoms and stroke. ACE2, angiotensin-converting enzyme 2

the initial symptoms coincide with neurological symptoms for appropriate interventions. Furthermore, the data suggested that patients with more severe systemic presentations would be more likely to have neurological symptoms, particularly acute cerebrovascular disease (5.7% vs 0.8%), impaired consciousness (14.8% vs 2.4%), and skeletal muscle injury (19.3% vs 4.8%) than those affected by a milder form of infection.[43] Recent studies have included headache, reduced consciousness, ataxia, acute cerebrovascular disease, seizures, hyposmia, hypogeusia, and neuralgia as neurological symptoms present in a cohort infected with the novel coronavirus, with a prevalence of these symptoms of ≈36.4%.[13]

Some authors also observed acute stroke after infection by the novel coronavirus in middle-aged patients with no previous comorbidities.[8,30] Despite having a low prevalence compared with ischemic stroke, the occurrence of hemorrhagic stroke was observed mainly in young patients without any previous risk factor.[33] Hypotheses for these events have been raised, such as virus invasion causing hemorrhages in the brain tissue by rupturing the brain capillaries.[13,17,18] Thus, the occurrence of cerebrovascular events in patients who would not be included in the risk range must be highlighted because, despite being quantitatively smaller, this complication has a strong social impact (based on disability-adjusted life years).[13,18,30,32,44] Another relevant point is the occurrence of bleeding events and their association with the use of anticoagulants. These drugs would be indicated for venous thromboembolism prophylaxis, making it possible to reduce mortality in patients with high levels of D-dimer.[45] However, Dogra et al[46] reported severe cases of massive bleeding with 100% mortality in which, in most cases, anticoagulation had been indicated as a result of high D-dimer levels. By contrast, other authors have stated that hemorrhagic stroke would occur regardless of cardiovascular risk factors, highlighting the importance of anticoagulation.[47] Carroll et al[48] observed that catastrophic brain hemorrhage could not be explained by the use of anticoagulants, claiming other mechanisms for the occurrence of these events. Thus, prophylaxis with anticoagulants would not be recommended for all patients infected by the novel coronavirus. Emergency physicians must assess the risk/benefit based on previous risk factors as well as perform the early diagnosis and treatment of neurological symptoms because the indiscriminate and noncritical use of anticoagulants could cause greater risks for the patients.[29,49]

Thus, 2 key points were highlighted for the assessment and decision making by professionals in the acute care settings regarding those infected with the novel coronavirus who also show stroke manifestations. The first is the attention to the manifestations of stroke in patients with risk factors or preexisting diseases in which stroke could occur as a result of a decompensation of underlying diseases. The

second is regarding previously healthy patients in whom the direct action of the virus would contribute both to the cytokine storm and a greater occurrence of thromboembolic events.[5,21]

The strengths of the present review include highlighting the strong emerging evidence for the importance of tracking neurological symptoms, as already performed for respiratory symptoms, in patients infected with the novel coronavirus. In the emergency department, where these patients usually have their first attendance, this screening should be performed early and systematically because once the diagnosis of neurological symptoms is confirmed in co-occurrence or as a complication of the viral disease, it will course with greater severity, with a higher prevalence of hospitalization in intensive care and higher mortality.

5 | CONCLUSION

In this review, we confirmed that stroke is part of the spectrum of clinical manifestations resulting from COVID-19 and is associated with a worse prognosis. Cerebrovascular lesions resulting from complications of the infection by the novel coronavirus occurred as a result of ischemic, hemorrhagic, and/or thromboembolic etiologies. Thus, the occurrence of stroke during the pandemic due to the novel coronavirus has a multifactorial character, and emergency physicians should focus on systematic measures for its screening and accurate diagnosis as well as the appropriate interventions based on early decisionmaking, which may have a favorable impact on reducing damage and saving lives.

CONFLICT OF INTEREST

All authors declare that they have no financial relationships with any organization that may have an interest in the work submitted in the previous 3 years and no other relationship or activity that may appear to have influenced the work submitted.

DATA-SHARING STATEMENT

All data used to prepare this article are available from the sources cited.

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