REVIEW ARTICLE

Study of Variables Related to Cerebrovascular Accident in Patients with COVID-19: A Literature Review

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Abstract

The objective of this article is to provide a bibliographic survey on the relationship between COVID-19 and stroke through a systematic review conducted in national and international journals without temporal delimitation, using articles indexed in multidisciplinary and health databases. The databases investigated were: BVS, PubMed, ERIC, SciELO, Web of Science, and Sociological Abstracts. Among the studies found, 43 articles were selected. Some of these were then used to produce the "literature review" section. Since stroke and COVID-19 can present similar symptoms, diagnosing stroke can be more challenging in some cases, highlighting the need for further research on the subject. The studies show a relationship between the severity of the condition and the occurrence of vascular events, with a higher incidence observed in patients hospitalized in intensive care units (ICUs). Additionally, it is important to mention the significance of d-dimer levels in the patient, as it is a factor with high predictive value for thrombotic events. The challenges in improving diagnosis and treatment are primarily due to the difficulty in understanding the pathophysiology, triggering events, and research on the topic.

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Abbreviations

CVA - Cerebrovascular Accident

IS - Ischemic Stroke

CT - Computed Tomography

1. Introduction

In December 2019, a group of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. This pneumonia was caused by a virus that would later be known as the new "coronavirus" (SARS-CoV-2). COVID-19 spread rapidly across China and was later exported to all continents. On January 30, 2020, the World Health Organization declared the disease a global public health emergency and listed it as a pandemic on March 11, 2020 [1].

According to the latest epidemiological bulletin issued by the Ministry of Health[2], as of June 30, 2023, over 660,000,000 cases of COVID-19 have been confirmed worldwide, with Brazil in 5th place {m/37,625,916/} among countries with the highest number of accumulated cases. In terms of total deaths, Brazil ranks 2nd globally, with 703,291 deaths.

Initially considered a respiratory disease, it is now clear that COVID-19 affects multiple organs, including the nervous system. The number of neurological manifestations of SARS-CoV-2 infection is increasing, which can impact both the central nervous system (CNS) and the peripheral nervous system (PNS). The second most common neurological manifestation of COVID-19 is stroke [3]. This diagnosis can be made through neuroimaging exams, such as computed tomography (CT) and magnetic resonance imaging (MRI), and/or through laboratory tests, such as biochemical markers evidenced in the literature [4].

Therefore, with the number of disease cases still high, there is a notable need for information that helps to characterize potential variables associated with stroke, which has had significant impacts on the prognosis of patients with COVID-19 [5]. This information could aid in preventing stroke with appropriate prophylaxis or initiating early treatment to reduce the damage caused.

This research proposal aims to use data analysis and information to correlate such risk or protective factors with the incidence of stroke in COVID-19. The knowledge gained from this study could guide physicians and healthcare professionals in managing this comorbidity more effectively.

1.1. Literature Review

The number of neurological manifestations of SARS-CoV-2 infection is increasing, affecting both the central nervous system (CNS) - including encephalopathies and strokes - and the peripheral nervous system, such as taste and smell dysfunctions, Guillain-Barré syndrome, and its variants [6]. Various mechanisms may explain the neurological manifestations of COVID-19, including systemic hyperinflammation and disseminated hypercoagulation, direct infection of the CNS (rare), and post-infectious immunological processes [3].

The second most common neurological manifestation of COVID-19 is stroke, occurring in 2% of patients[7], following only encephalopathy [8]. Initial cases of stroke were seen in older patients who had previously experienced ischemic stroke, had comorbidities, and elevated inflammatory markers. However, more recent reports describe ischemic events in younger patients. Interestingly, some of these patients did not have classic risk factors for stroke, and some had not even developed severe symptoms of COVID-19 before the stroke. Nevertheless, all patients exhibited a state of hypercoagulability and disseminated intravascular coagulation [9].

SARS-CoV-2 infection is associated with a pro-thrombotic state that can trigger venous and arterial thromboembolism and elevated levels of d-dimer [9]. Severe COVID-19 is associated with high release of pro-inflammatory cytokines that induce endothelial cell activation with tissue factor expression, leading to coagulation process activation and thrombin production. The circulation of free thrombin, uncontrolled by natural anticoagulants, can activate platelets and lead to thrombotic episodes [9]. SARS-CoV-2 has a spike protein unit that binds strongly to the human ACE-2 receptor. It can cause endothelial cell apoptosis and neuronal damage [10]. Viral infection may also promote endothelial cell dysfunction, leading to excessive thrombin production and inhibition of fibrinolysis [11]. Currently, various studies have reported the development of a COVID-19 hypercoagulable state, triggering a strong inflammatory response, leading to a hypercoagulable state and, consequently, thromboembolism [12][13][14]. Additionally, hypoxemia is related to increased blood viscosity and activation of hypoxia-related genes. Hypoxia-related genes mediate coagulation and fibrinolysis, favoring the occurrence of thrombotic events [15].

Although ischemic stroke has been recognized as a complication of COVID-19 (usually in severe cases), the mechanisms and phenotype are still not fully understood [10].

In a study [14] involving patients with neurological manifestations of COVID-19, stroke was present in 6 out of 214 (3%) hospitalized patients with COVID-19, with 5 of the 6 events occurring in patients with severe disease. Five of the six reported events were ischemic strokes, and one was hemorrhagic. Another retrospective study [16] in China, involving 219 hospitalized COVID-19 patients, found that 11 had strokes, with 10 being ischemic and 1 hemorrhagic. Patients with stroke were older, had more comorbidities including diabetes, hypertension, a history of stroke, and elevated inflammatory markers, including d-dimer and CRP. Another review [17] of six patients admitted to the National Hospital in Queen Square with COVID-19 who experienced stroke observed that the occlusions typically involved large vessels and frequently occurred in multiple vascular territories. In 5 of the 6 cases, strokes occurred between 8 and 24 days after the onset of COVID-19 symptoms. All patients had a highly pro-thrombotic state with very high levels of d-dimer, as well as elevated ferritin. Five of the six patients had detectable lupus anticoagulant, suggesting another potential pro-thrombotic mechanism for stroke in COVID-19 [18].

A systematic review published in the Journal of Neurology[7] analyzed the main comorbidities present in patients who experienced stroke during the course of the disease. The most prevalent comorbidities are hypertension, hyperlipidemia, and diabetes, with 66% (95% CI 51-81%; $p < 0.01$), 48% (95% CI 19-76%; $p < 0.01$), and 40% (95% CI 29-51%; $p < 0.01$), respectively.

To better understand the impact COVID-19 can have on a patient with stroke, a United Kingdom study[18] evaluated eleven other studies to compare patients with both conditions concurrently with patients who had stroke without the other disease. The analysis revealed that patients with COVID-19 and stroke were younger than those with stroke alone (combined median age difference = -6.0; 95% CI = -12.3; -1.4), and females were less frequently affected [150/395 vs. 773/1670; OR = 0.71 (95% CI: 0.51-0.99)]. Patients were less likely to have hypertension [257/385 vs. 835/1128; OR = 0.65 (95% CI: 0.45-0.96)] and a history of stroke [11/146 vs. 159/720; OR = 0.34 (95% CI: 0.18-0.63)]; there were no significant differences in other cardiovascular risk factors (diabetes mellitus, dyslipidemia, smoking, coronary artery disease, and atrial fibrillation). Acute ischemic stroke due to large vessel occlusion was more common in COVID-19 cases [127/251 vs. 613/1031; OR = 2.73 (95% CI: 1.63-4.57)]. The severity of stroke was greater in patients with both stroke and COVID-19 (combined median difference in NIHSS score 5; 95% CI = 3-9). Despite receiving treatment for acute stroke (intravenous thrombolysis and thrombectomy) in similar proportions, individuals with stroke and COVID-19 had higher hospital mortality (144/432 vs 191/1643; OR = 5.21, 95% CI: 3.43-7.90).

Regarding the prevention of ischemic stroke in COVID-19 patients, a study[19] developed a set of primary prevention methods, with patient risk classification detailed in Table 1.

Table 1.

Target Population	Current Recommendation	Possible Medications
General Population without COVID-19 Risk	Regular physical activity, adequate water/liquid intake, low-fat diet, low-salt diet	None
Asymptomatic COVID-19 Positive Patients	**No pharmacological prophylaxis, regular physical activity, adequate water/liquid intake, low-fat diet, low-salt diet**	DOACs, aspirin, clopidogrel
COVID-19 Outpatients	**Individual risk assessment for ischemic stroke (IS), regular physical activity, adequate water/liquid intake, low-fat diet, low-salt diet**	DOACs, aspirin, clopidogrel
COVID-19 Patients Hospitalized in General Wards	**Prophylactic low-molecular-weight heparin if not contraindicated, adequate water/liquid intake, low-fat diet, low-salt diet**	DOACs, aspirin, clopidogrel, tissue plasminogen activator (tPA), tocilizumab, dornase alfa, pirfenidone, tiotropium, colchicine, eculizumab
COVID-19 Patients Requiring ICU Admission	**Prophylactic low-molecular-weight heparin if not contraindicated**	**tPA, tocilizumab, dornase alfa, pirfenidone, tiotropium, colchicine, eculizumab**
Post-Discharge COVID-19 Patients	**Individual risk assessment for ischemic stroke (IS), prophylactic anticoagulation for 45 days if not contraindicated, regular physical activity, adequate water/liquid intake, low-fat diet, low-salt diet**	DOACs, aspirin, clopidogrel

2. Objectives

2.1. General objective

Identify possible risk and protective factors for the development of cerebrovascular accident (stroke) in patients with COVID-19 compared to patients not diagnosed with COVID-19 but who presented with stroke during their hospitalization, and provide information that enables the prevention or earlier diagnosis of such complications, thereby improving the management of this condition and assisting healthcare professionals in better managing their patients.

3. Methods and Materials

Literature Review: To conduct this literature review, searches were carried out in scientific databases, including PubMed, Virtual Health Library, SCIELO, and Google Scholar using combinations of keywords related to the topic, such as "COVID-19," "Stroke," "Cerebrovascular Accident," "Neurological Complications," "SARS-CoV-2," and "CVA." Studies published between 2011 and 2023 were considered to ensure the inclusion of updated research. After the search, studies used for this research were individually selected.

4. Results

The systematic review on the topic was conducted using the aforementioned method, and the following results were obtained:

SCIELO: 16 articles
PUBMED: 13 articles
Google Scholar: 8 articles
Virtual Health Library: 6 articles
TOTAL = 43 articles

In this way, the 43 articles found were read in full to evaluate which ones would be used in the final work. The most relevant information found in these articles was mentioned in the "Literature Review" section.

The results of this literature review showed several studies reporting the association between COVID-19 and the increased incidence of stroke in hospitalized patients. Among the main findings, the following variables are highlighted in relation to the occurrence of stroke in patients with COVID-19: • Advanced age: Elderly patients with COVID-19 are more likely to develop stroke and other cerebrovascular complications. • Pre-existing comorbidities: Individuals with underlying medical conditions, such as diabetes, hypertension, cardiovascular diseases, obesity, and lupus, are more susceptible to developing stroke during COVID-19 infection. • Severity of COVID-19: Patients with more severe cases of COVID-19, especially those requiring hospital care—particularly in intensive care units—and mechanical ventilation, are at higher risk

of stroke. • Systemic inflammation: COVID-19 triggers a systemic inflammatory response in the body, increasing the risk of vascular complications, including the formation of blood clots in the brain, consequently leading to an area of tissue ischemia, characterizing ischemic stroke. • Length of hospitalization: Patients hospitalized with COVID-19 for longer periods show a higher incidence of stroke. It is important to analyze whether this increased incidence is due to the more severe case, consequently longer hospitalization time, or prolonged stasis and higher propensity for contracting hospital-acquired infections and diseases.

5. Discussion

In this project, it was possible to conduct a literature review on the topics of COVID-19, stroke, and the relationship between these diseases. The literature review highlights the importance of considering stroke as a potential complication in patients with COVID-19, with greater emphasis on hospitalized patients. Variables such as advanced age, pre-existing comorbidities, severity of infection, and systemic inflammation are associated with an increased risk of developing stroke during SARS-CoV-2 infection. Many problems and complications related to stroke in hospitalized COVID-19 patients could be observed, in addition to protective factors and their pathophysiology [6]. This increase in thrombotic events is mainly due to the hypercoagulable state and endothelial injury. COVID-19, through its pathogenic mechanisms, promotes a strong inflammatory response in the body, with high release of cytokines, chemokines, and cellular activation. Additionally, the D-dimer has proven to be a good biomarker for the occurrence of stroke, but it does not negate the great importance already known for imaging exams [9]. The incidence of cerebrovascular events in COVID-19 patients varies widely according to the study. Risk assessment models can be used to support decisions about whether to use prophylaxis in the patient, but there is a broad consensus that severely ill patients admitted to hospitals should receive due prophylactic treatment. The most used treatment in these cases includes direct oral anticoagulants (DOACs), aspirin, clopidogrel, among other medications. However, attention should be paid to cases where the use of some medications as prophylaxis is contraindicated, so that their benefit does not outweigh the chances of risk.

6. Final Considerations

This study aimed to review the topic of COVID-19 and its cerebrovascular complications. Research has shown that COVID-19 infection can have variable and often unpredictable courses and outcomes, with strokes being significant complications of the disease. Its mechanisms and pathophysiology are still not fully understood, despite various studies on the topic, including its pathophysiology, prevention, and outcomes. In general, the study intended to provide data for a better understanding of these phenomena and, consequently, assist in the development of clinical and therapeutic interventions for the problem.

It is crucial for healthcare professionals to be attentive to neurological symptoms in patients with COVID-19, especially those in at-risk groups. Furthermore, additional research is necessary to deepen the understanding of pathological mechanisms and develop preventive and therapeutic strategies to reduce the impact of stroke in this population. Constant

vigilance and multidisciplinary collaboration are essential to adequately address this concerning public health issue.

Therefore, more high-quality studies and research on the subject should be conducted to further enhance the understanding of pathological mechanisms and develop prevention and treatment strategies to reduce the impact of stroke in this population. With a better understanding of the topic, a lower incidence of complications and mortality among COVID-19 patients is expected, making this final goal highly important in the post-pandemic era.

In conclusion, funding agencies, professional societies, patients, physicians, and researchers should work together to more effectively address the various knowledge gaps that remain unexplored.

6.1. Recommendations For Future Work

1. Studies that seek a better understanding of the pathophysiology of the disease, which still presents various unexplained gaps, so that there can be a clearer elucidation of triggering factors, prevention strategies, and therapeutic approaches.
2. Long-term studies to further understand the possible long-term consequences of both pharmacological treatments and potential sequelae of the disease, as it is still relatively new and not fully understood.
3. Studies that can effectively evaluate preventive and therapeutic interventions included in the research, potentially identifying new treatments and assessing the efficacy of existing medications, both for prevention and treatment of patients.
4. Multidisciplinary studies, involving professionals from various fields, to develop better prevention and treatment strategies for the disease in question, as patients are treated by interdisciplinary teams.

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