

Review Article

What is the real impact of severe acute respiratory syndrome coronavirus-2 on stroke: Do we more have to learn?

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ABSTRACT

Objectives: Coronaviruses are an infectious disease with a considerable spectrum of clinical presentation. Neurologic symptoms related to severe acute respiratory syndrome coronavirus (SARS-CoV-2) have been described recently in the literature. Among a wide variety of neurological symptoms, acute cerebrovascular disease is one of the most serious complications. This review aimed to reveal the current knowledge regarding stroke in new coronavirus infection as a way to improve its diagnosis and treatments.

Materials and Methods: A systematic literature review was carried out to identify the particularities of SARS-CoV-2 in patients with stroke. An electronic search of the literature was conducted in the PubMed database between December 1, 2019, and June 11, 2020. A total of 693 articles were extracted. We included articles in all languages and conference papers, reviews, published letters, and editorials were excluded from the study.

Results: Out of the 693 screened articles, 39 were selected for full-text review. Twenty-nine studies were excluded because they did not report stroke in COVID-19 patients. Thus, 10 papers were included in this review with a total of 22 patients.

Conclusion: A vascular (ischemic or hemorrhagic) neurological complication is a real event that may occur in patients with COVID-19. There is strong evidence that vascular complications may arise for the most part due to the well-recognized potentially fatal inflammatory storm, which reflects a hyperactivation of inflammatory factors and dysfunction of the coagulation system, especially D-dimer and platelet abnormalities.

Keywords: COVID-19, Neurological, Severe acute respiratory syndrome coronavirus-2, Stroke, Systematic review

INTRODUCTION

Coronaviruses (CoVs) cause enteric and respiratory diseases in humans. These viruses are enveloped non-segmented RNA.^[1] Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus are previous clinical entities outbreaks linked to CoVs and had already been well studied in the literature.^[2,3] However, another highly pathogenic coronavirus named SARS-CoV-2 emerged in December 2019 in China and spread worldwide.

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Symptoms ranged from asymptomatic infection to severe pneumonia that may lead to acute respiratory syndrome and other several clinical complications. The disease can manifest itself as a wide variety of signs and symptoms, which affect the most diverse systems of the body. Respiratory involvement is the most common symptom in patients with SARS-CoV-2; however, there are reports of neurological manifestations.^[1,2] Such clinical manifestations are seen, above all, in the moderate and severe forms of the disease. Neurological symptoms in COVID-19 include anosmia and hypogeusia, seizures, and stroke-related deficits.^[4] Among a wide variety of neurological complications, acute cerebrovascular disease is one of the most serious ones and affected 5.7% of patients in the study reported by Mao *et al.*^[5] This review aimed to reveal the current understanding regarding stroke in new coronavirus infection as a way to improve knowledge in the diagnosis, treatment, and prognosis factors.

MATERIALS AND METHODS

A systematic review of observational studies about COVID-19 in patients with stroke was carried out according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. An electronic search of the literature was conducted in the PubMed database between December 1, 2019, and June 11, 2020. Data extraction and the evaluation of literature quality were conducted independently by two investigators; any disagreement was resolved by another investigator. The keywords used were “COVID-19,” “Coronavirus,” “SARS-CoV-2,” “Novel coronavirus,” “2019 novel coronavirus infection,” “2019-nCoV infection,” “COVID-19 pandemic,” “Coronavirus disease-19,” “Coronavirus disease 2019,” “Stroke,” “Hemorrhagic stroke,” “Ischemic stroke,” “Acute hemorrhagic stroke,” and “Acute ischemic stroke.” The Boolean operator “AND” was used to filter and select documents that were at the intersection of keywords. Descriptors were crossed to maximize the number of publications [Figure 1] so that all the words in the first square crossed with all the words in the second square.

A total of 693 articles were extracted. We included articles in all languages. We excluded conference papers, reviews, letters, and editorials. Our work is summarized in the diagram [Figure 2].

RESULTS

An initial search included 693 articles. Out of these 693 screened articles, 39 were selected. After a full-text review, 29 studies were excluded because they did not report stroke in COVID-19 patients. Thus, 10 papers were included in this review, with a total of 22 patients.^[6-15]

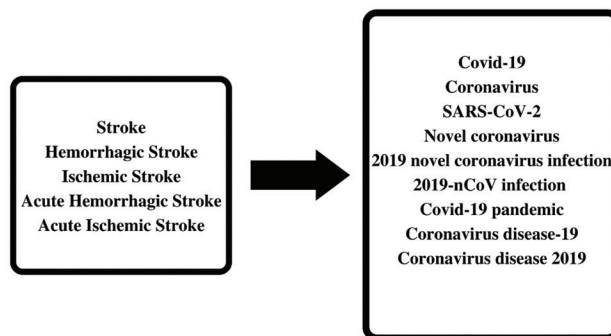


Figure 1: Schematic representation of the crossover of keywords.

Within the group of 22 patients who, concurrently, had a stroke and COVID-19 event, 21 (95.5%) patients had an ischemic stroke, and one patient had cerebral venous sinus thrombosis. The average age was 62.5 years, but 40% of patients were younger than 60 years, meaning it is not a uniform population. There was a tendency for ischemic brain events of large vessels to be in younger patients. Male was the most prevalent sex (68.2%).^[6-15]

In 20/22 (90.9%) patients, there were risk factors related to stroke. Arterial hypertension was the most prevalent risk factor (14/22, 63.6%), followed by diabetes (6/22, 27.3%), dyslipidemia (6/22, 22.7%), and cardiac disease (3/, 13.6%). Smoking and previous history of stroke were also reported, 9.1% in each group. In addition, there were only two elderly patients, and this was an isolated risk factor for stroke. In this sense, we realized that it is a group with a high prevalence of risk factors and the SARS-CoV-2 infection would be acting as a precipitating factor inducing physiological disturbances which would precipitate stroke in these patients.^[6-15]

Regarding the onset of stroke symptoms in the patients analyzed in relation to the onset of COVID-19 symptoms, it was possible in 14 patients. Three out of 14 (21.4%) patients had a stroke episode before the symptoms of COVID-19 were noticed. Twelve of 14 patients (one of them had stroke before and after the symptoms of COVID-19 appeared) had an episode of stroke after the appearance of COVID-19. Of these 12 patients, 7 (58.3%) had a sudden episode in the 1st week and 5 (41.7%) after the 1st week.^[6-15]

Regarding the characteristic of stroke in these patients and their laboratory tests, in 20 patients (90.2%), the stroke involved large intracranial vessels. A significant thrombogenic alteration was observed as well, and this may have influenced the eventual progression to a stroke, particularly when other atherogenic or cardiac factors were associated. Regarding D-dimer protein, it was checked in 19 patients, and 16 of them (84.2%) had high concentrations. This high prevalence of high rates of D-dimer increases the chance of cerebral ischemic events and may be seen as a risk factor of stroke. The prothrombin time (PT) test was

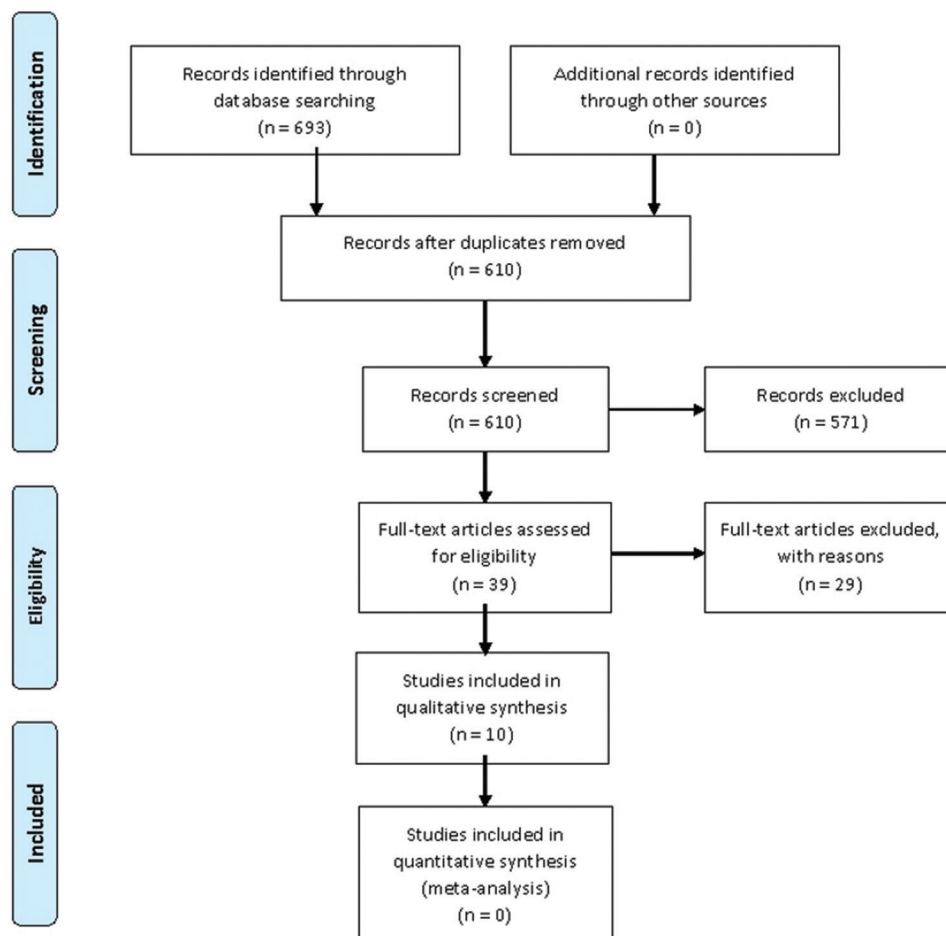


Figure 2: Preferred reporting items for systematic reviews and meta-analyses flow diagram.

reported in 16 patients, being normal in 1 patients (62.5%) and elevated in 6 patients (37.5%) [Table 1].^[6-15]

DISCUSSION

Physiopathology

COVID-19 involvement with thrombotic events

Significantly high levels of D-dimer protein and other fibrin degradation products have been increasingly correlated with poor prognosis in patients infected with SARS-CoV-2.^[16] Guan *et al.*^[17] analyzed the epidemic in the first 2 months in China. They identified that 260 (46.4%) of the 560 patients diagnosed with COVID-19 had elevated levels of D-dimer (≥ 0.5 mg/L), this elevation being more prominent in severe cases. Thus, high levels of fibrin degradation products have been increasingly correlated with poor outcomes in patients infected with SARS-CoV-2. This laboratory profile leads to a state of hypercoagulability, which can be associated with a worsening in the functioning of several organs. COVID-19 patients in a state of hypercoagulability due to hyperfibrinogenemia, a

higher formation of fibrin and polymerization, are predisposed to the appearance of thrombi.^[18]

Inflammatory responses by COVID-19

The cytokine storm consists of one of the leading causes of acute respiratory distress syndrome and multiple organ failure,^[19] which is an immunological phenomenon frequently seen in serious patients infected with SARS-CoV-2. In a study evaluating the outcome of patients with persistent and high levels of inflammatory cytokines,^[20] it was concluded that the overproduction of pro-inflammatory cytokines such as tumor necrosis factor, interleukin (IL)-6, and IL-1B could cause up to death if high concentrations persist unabated overtime.

In one of the first studies that addressed the topic, Huang *et al.*^[21] investigated the clinical findings and the cytokine profile of critically ill patients in Wuhan, suggesting that the cytokine storm may be associated with the severity of the disease. Another study that corroborates this reasoning argues that high levels of cytokines, specifically IL-2R and

Table 1: Acute vascular neurological manifestation in patients with SARV-CoV-2 infection.

Study	Patients	Age	Gender	UD Hypertension: 100%	D-dimer	Type of stroke	Treatment	Outcome
Avula <i>et al.</i> , 2020 ^[6]	4	81*	75%, F 25%, M	Dyslipidemia: 75% Diabetes: 25%	Elevated: 50%	IS	Aspirin	75% died
Saiegh <i>et al.</i> , 2020 ^[7]	2	46.5*	50%, F 50%, M	None: 50% ns: 50%	ns	IS ICH	External ventricular drain and specific surgery	Survive
Beyrouti <i>et al.</i> , 2020 ^[8]	6	69.8*	33.3%, F 66.6%, M	Hypertension: 66.6%	Elevated: 100%	IS	Anticoagulation: 66.6% Intravenous thrombolysis: 16.6%	16.6% died
González-Pinto <i>et al.</i> 2020 ^[9]	1	36	F	ns	Elevated	IS	Supportive measures	Survive
Oxley <i>et al.</i> , 2020 ^[10]	5	40.4*	20%, F 80%, M	Hypertension: 20% Dyslipidemia: 20% Diabetes: 40%	Elevated: 60%	IS	Aspirin: 60% Clot retrieval: 80% Intravenous thrombolysis: 20% Anticoagulation: 40%	Survive
Moshayei <i>et al.</i> , 2020 ^[11]	1	80	M	Heart failure, cardiovascular shock, and ischemic bilateral lower limbs	ns	IS	Supportive measures	Survive
Hughes <i>et al.</i> , 2020 ^[12]	1	59	F	ns	ns	CVST	LMWH	Survive
Viguiet <i>et al.</i> , 2020 ^[13]	1	73	M	ns	Elevated	IS	LMWH	Survive
Tunç <i>et al.</i> , 2020 ^[14]	4	65.3*	50% M 50% F	Diabetes: 25% Hypertension: 75%	Elevated: 75%	IS	Antithrombotic therapy	Survive
Goldberg <i>et al.</i> , 2020 ^[15]	1	64	M	Hypertension, aplastic anemia, and splenectomy	Elevated	IS	ns	ns

*Median, F: Female, M: Male, y: Years, UD: Underlying disorders, IS: Ischemic stroke, ICH: Intracerebral hemorrhage, CVST: Cerebral venous sinus thrombosis, ns: Not specified, LMWH: Low-molecular-weight heparin, D-dimer elevated levels: >250 ng/ml

IL-6, in serum, can predict the severity of the disease and the prognosis of patients.^[22]

Renin cerebral angiotensin system in stroke pathophysiology

Another widely discussed issue is the affinity that the virus has for angiotensin-converting enzyme 2 (ACE2) receptors, which is a mechanism used by the virus to enter human cells. ACE2 receptor is determinate to viral tropism in host humans.^[23] ACE2 is expressed in several tissues as such as airway epithelia, kidney cells, small intestine, lung parenchyma, vascular endothelial tissue, and widely throughout the central nervous system.^[23,24] The brain expresses ACE2 receptors at different sites, such as glial cells, neurons, astrocytes, and oligodendrocytes. This expression can cause these cells to become potential targets for SARS-CoV-2.^[23,24] However, ACE2 demonstrated beneficial cardioprotective and neuroprotective actions.^[23,24]

The SARS-CoV-2 binds to the ACE2 through its spike protein, and the transmembrane protein serine protease 2 (TMPRSS2) is also required for viral entry into cells.^[24] TMPRSS2 active spike protein through proteolytic breakdown is a possible way that SARS-CoV-2 can enter in the host cell.^[24] The renin, secreted from juxtaglomerular cells in the kidney, cleaves angiotensinogen produced by the liver to angiotensin I, after that, angiotensin I is cleaved to angiotensin II. Angiotensin II promotes vasoconstriction, aldosterone secretion, pro-inflammatory status, and procoagulation action. In addition, angiotensin II can worsen heart and pulmonary failure. ACE2 eventually directly cleaves angiotensin I and angiotensin II to angiotensin (1-7) at the least stage.^[24] Angiotensin (1-7) produces vasodilatation and has anti-inflammatory effects. Thus, the overexpression of ACE2 in neuronal cells or endothelial progenitor cells promotes protective effect from inflammatory complication as ischemic stroke.^[24] SARS-CoV-2 depletes ACE2 stock and, thus, predisposing the host to develop stroke [Figure 3].^[23,24]

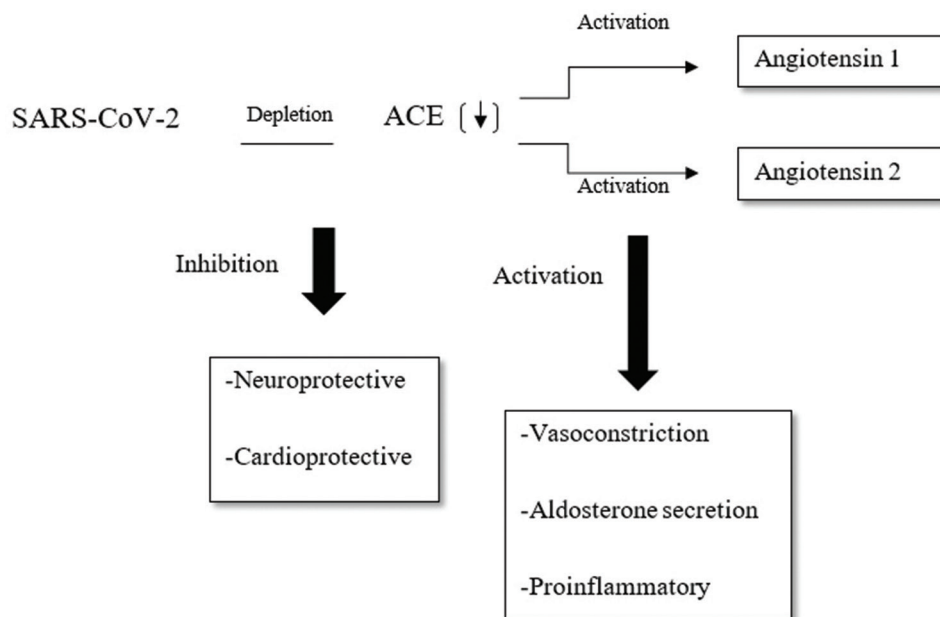


Figure 3: Pathophysiology of stroke predisposition in COVID-19. Severe acute respiratory syndrome coronavirus-2 depletes ACE2 receptor and promotes pro-inflammatory effect. ACE2: Angiotensin-converting enzyme 2.

SARS-CoV-2 depletes ACE2 and worses endothelial function in organs as brain and heart.^[23,24] This fact also explains the theory that SARS-CoV-2 action on ACE2 predisposes mainly elder and male patients to develop stroke because this receptor is naturally decreased in this population.^[23,24] Another point is that the COVID-19 promotes greater metabolic expenditure and this also predisposes to stroke.^[23,24]

Treatment

At present, patients with ischemic stroke symptoms should be treated as suspected or possible to have SARS-CoV-2 infection. Reverse transcription polymerase chain reaction test and CT chest can be necessary for all stroke patients to discard COVID-19 in pandemic era.^[25,26] Stroke members team should wear appropriate personal protective equipment, including use a combination of surgical mask gloves, goggles or face shield, and gowns. Image investigation and blood investigation are crucial to understand the clinical status of the patient and should be performed as soon as available. Routine thromboprophylaxis is not recommended in ambulatory patients with respiratory symptoms or acute medical illness.^[25,26] In the emergency room, patients diagnosed with ischemic stroke should receive the standard of stroke care and specific treatment with intravenous (IV) thrombolysis or mechanical thrombectomy is reserve to selected patients.^[25,26] Our proposed management is summarized in [Figure 4].

SARS-CoV-2-infected patients have a high hypercoagulability state due to elevated concentration of C-reactive protein and

D-dimers in patients with SARS-CoV-2 infection. Studies conducted in non-SARS-CoV-2-infected acute ischemic stroke patients demonstrated a higher rate of death or disability and post-thrombolytic intracerebral hemorrhages in patients with elevated concentration of C-reactive protein and D-dimers.^[25,26] Another point is that hepatic dysfunction manifesting as elevation in serum transaminases (elevated PT, international normalized ratio, activated partial thromboplastin time, or reduced platelet count) can occur in patients with SARS-CoV-2 infection and increase the risk of intracerebral hemorrhages.^[25,26] Thus, to the management of ischemic stroke patients with SARS-CoV-2 infection, a detailed assessment of coagulation profile is crucial to decision regarding IV thrombolysis in these patients. Endovascular thrombectomy should be evaluated according with current guidelines.^[26]

The era of COVID-19 has brought about significant changes regarding hospital management, at stroke, there was a change in the etiology investigation protocol, according to Jin *et al.*, 2019. Serum D-dimer level is generally increased, being able to reflect in stroke, it is well known that many of these patients may already have other cerebrovascular risk factors, such as hypertension, diabetes mellitus, hyperlipidemia, smoking, or a previous history of stroke.^[27]

If a patient with acute ischemic stroke with a suspected or confirmed diagnosis of COVID-19 is admitted, emergency treatment could be offered, if the D-dimer level is high, but additional studies should be performed to affirm this management. In our systematic review with 22

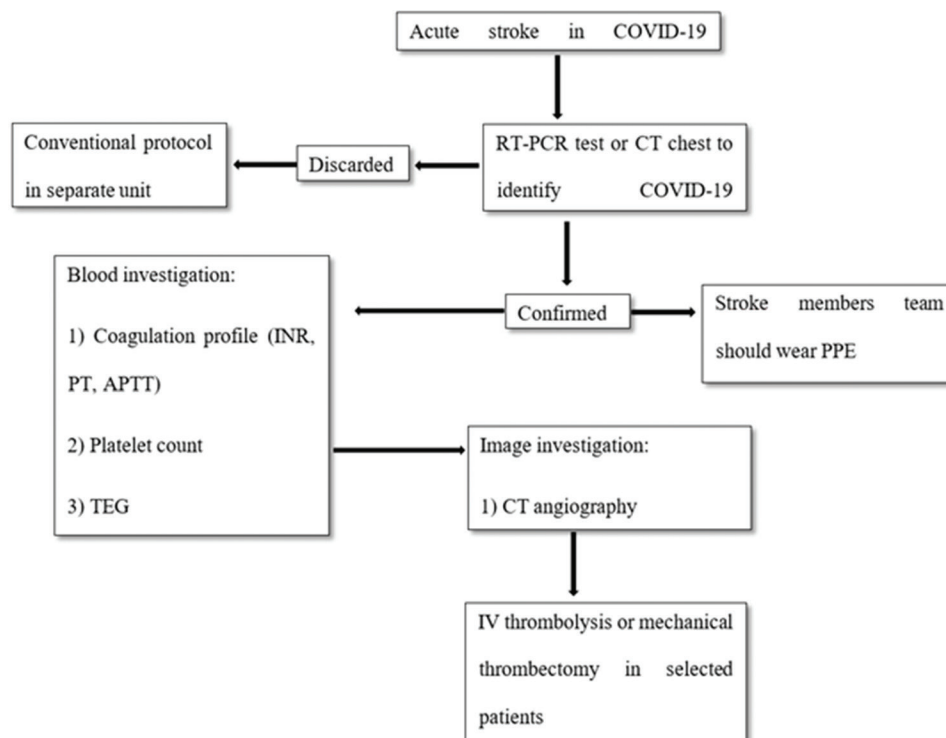


Figure 4: Our algorithm proposed to management COVID-19 patients with ischemic stroke. RT-PCR: Reverse transcription polymerase chain reaction test, PPE: Personal protective equipment, PT: Prothrombin time, INR: International normalized ratio, APTT: Activated partial thromboplastin time, TEG: Thromboelastography, CT: Computerized tomography, IV: Intravenous.

patients included, 21 patients had an ischemic stroke and anticoagulant was instituted in all of the cases, reflecting a better prognosis.^[6-15]

In the context of the current COVID-19, a necessary point for futures studies is the possibility of coexistence of stroke and refractory hypoxemia, in mechanically ventilated patients. So far, too little is known about how to better manage the association of both, especially in large size stroke under risk of elevated intracranial pressure.

The ability to deliver timely and efficacious care for the stroke in itself must be balanced with the risk of potential elevated intracranial pressure that happens as a result of “permissive hypercapnia” during the well-established “protective-lung ventilation strategy.”^[28] Rescue approaches such as extracorporeal membrane oxygenation (ECMO) coupled with extracorporeal carbon dioxide removal (ECCO2R) may be applied to avoid lung disease worsening and protect the brain from herniation simultaneously.^[29] Surgical decompressive craniectomy should also be taking into consideration in selected cases either in combination with ECMO/ECCO2R or alone, especially in low-resource centers.^[30]

Other particular point in COVID-19 pandemic and stroke is that patients with mild stroke symptoms will possibly be

discharged prematurely without a complete stroke evaluation or a secondary stroke prevention strategy. It can occur because the health-care system has focused on identifying patients with COVID-19 and preserving health-care resources.^[31]

The National Institutes of Health (NIH) StrokeNet was created in 2013 to facilitate the rapid initiation and efficient implementation of small and large multisite exploratory and confirmatory clinical trials of stroke management. COVID-19 pandemic also provided specific impacts and solutions in NIH. Solutions such as increased use of telemedicine and digital technologies, a centralized approach to electronic and remote consent across all trial sites rather than each individual site, innovative approaches to online survey and focus groups for studies using exemption from informed consent.^[32]

Prognosis

The poor prognosis to patients with COVID-19 and stroke not yet is completely elucidated, however, are many possibilities that can suppose this, such as the patients who are in risk factor group develop a virus form more severe. Risk factors are the same to factors to stroke and cardiovascular diseases, so patients with COVID-19 may have cardiovascular manifestations and that cardiovascular morbidities probably result in worst outcomes. Patients with severe infection are

more susceptible to develop acute cerebrovascular events than those with less severe infection.^[33]

The majority of patients of our revision had previous cardiovascular comorbidities, such as hypertension, cardiac diseases, and diabetes mellitus, therefore, they were in fact in the risk group of COVID-19 and this could contribute to a poor prognosis.^[34]

The studies showed an increased inflammatory response and hypercoagulation disturb state was found in patients that had cerebrovascular events. This information was proved that the risk for worse outcome was higher in patients who are with prolonged PT, thrombin time, and D-dimer high.^[16,17,33] This situation of coagulopathy could turn patients more susceptible to thrombotic events, including stroke. The D-dimer levels are under the limit in only three patients of our revision, therefore, being in accordance with the literature. The possibility of COVID-19 can cause clotting in large vessels of patients without risk factors for stroke which are suggested by reported five cases of large-vessel stroke in young patients under 50 years old.^[33]

In our literature review, including 22 patients (7 women and 15 men), age ranged 33–88 years old, the outcome of these patients was four died, two in severe state, and the others were in moderate-to-good state until the publication of the articles. All of died patients had some risk factors, hypertension, diabetes, smoking, and others cardiac diseases and were severity state. In addition, older patients are vulnerable to poor prognosis.^[6-15]

Another factor worth mentioning in the analysis of factors predicting the worst outcome for patients with COVID-19 and stroke is hypercapnia caused by mechanical ventilators. The permissive hypercapnia, necessary during protective mechanical ventilation in patients with severe COVID-19, generally an accumulation of CO₂, which can determine a state of harmful cerebral hyperemia. This permissive hypercapnia is difficult to manage in patients with COVID-19, given that the patient needs to maintain good pulmonary ventilation, although attention is needed to the possible worsening of the neurological condition through this intervention.

When analyzing the characteristics of the patients in this review, it is noticed that the incidence of vascular involvement is of large caliber vessels, which makes the situation even more serious and therefore makes the outcome more unfavorable. Furthermore, it is observed that there are a greater number of cases in ischemic stroke compared to hemorrhagic stroke.^[10]

CONCLUSION

Although it is not yet possible to determine all the precise and specific characteristics of the infection by the coronavirus.

There is strong evidence that vascular complications may arise for the most part due to the well-recognized potentially fatal inflammatory storm, which reflects a hyperactivation of inflammatory factors and dysfunction of the coagulation system, especially D-dimer and platelet abnormalities. The prognosis of these patients is, therefore, linked to the inflammatory process, complicated by severe respiratory conditions, renal, cardiac, and hematological disorders.

Limitations

This review has several limitations. Few studies were available for inclusion. More detailed patient data were unavailable in most studies at the time of analyses. Futures studies are necessary to determinate protocol management and real prognosis in COVID-19 patients.

Authors' contributions

Conceptualization

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Writing – original draft

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Writing – review and editing

Nicollas Nunes Rabelo, Luiz Severo Bem Junior, Pedro Lukas do Rêgo Aquino, Hildo Rocha Cirne de Azevedo Filho, and Flávio Monteiro de Oliveira Júnior.

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Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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