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Review article

Hemorrhagic stroke in patients with COVID-19 infection: a systematic literature review

Acidente vascular encefálico hemorrágico em pacientes com infecção por COVID-19: uma revisão sistemática de literatura

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Abstract

Objective: to analyze, based on the literature, the impacts of the pandemic and the COVID-19 infection on the occurrence of hemorrhagic cerebrovascular events. **Materials and methods:** this is a systematic review of the literature, selecting articles in English, Portuguese and Spanish published between 2020 and 2022 available in the *Biblioteca Virtual em Saúde*, LILACS, SciELO and PubMed databases using the descriptors: "Hemorrhagic Stroke or Intracranial hemorrhage", "Covid-19 or Sars-CoV-2" AND "Nervous system or Neurologic Manifestations" AND "Cerebrovascular Disorders". The inclusion of publications was based on the analysis of titles, abstracts and keywords. Abstracts, expert opinions, editorials and case reports were excluded. **Results:** 12 articles from 115 publications were selected. Studies have shown an increase in the occurrence of hemorrhagic stroke in patients infected with COVID-19, especially in those with comorbidities. It predominantly affected blacks and Latinos and middle-aged patients. Intracranial hemorrhage was the most common subtype. The severity of the condition, reduced mobility and fear of contracting the infection directly affected the diagnostic and therapeutic approach of such patients. **Conclusion:** patients infected with SARS-CoV-2 had a higher risk of cerebral hemorrhage, especially those who already had previous cerebrovascular disease, in addition to high morbidity and mortality.
Keywords: Hemorrhagic Stroke. Covid-19. Neurologic manifestations. Cerebrovascular Disorders.

Resumo

Objetivo: analisar, baseado na literatura, os impactos da pandemia e da infecção pela COVID-19 na ocorrência de eventos cerebrovasculares hemorrágicos. **Materiais e Métodos:** trata-se de uma revisão sistemática da literatura, selecionando artigos em inglês, português e espanhol publicados entre 2020 e 2022 disponíveis nas bases de dados Biblioteca Virtual em Saúde, LILACS, SciELO e PubMed, usando os descritores: "*Hemorrhagic Stroke or Intracranial hemorrhage*", "*Covid-19 or Sars-CoV-2*" and "*Nervous system or Neurologic Manifestations*" and "*Cerebrovascular Disorders*". A inclusão das publicações foi baseada na análise dos títulos, resumos e palavras-chave. Foram excluídos resumos, opiniões de especialistas, editoriais e relatos de casos. **Resultados:** foram selecionados 12 artigos de 115 publicações. Os estudos mostraram um aumento na ocorrência de acidente vascular encefálico hemorrágico em paciente infectados pela COVID-19, principalmente naqueles que apresentavam comorbidades. Acometeu predominantemente negros e latinos e pacientes de meia idade. A hemorragia intracraniana foi o subtipo mais comum. A gravidade do quadro, a redução da mobilidade e o medo de contrair a infecção afetaram diretamente a abordagem diagnóstica e terapêutica de tais pacientes. **Conclusão:** pacientes contaminados pelo SARS-CoV-2 apresentaram maior risco de hemorragia cerebral, principalmente aqueles que já apresentavam doença cerebrovascular prévia, além de elevada morbimortalidade.
Palavras-chave: Acidente Vascular Encefálico Hemorrágico. Covid-19. Manifestações neurológicas. Distúrbios Cerebrovasculares.

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Introduction

In 2002/2003, in Asia, a pandemic caused by the coronavirus, responsible for Severe Acute Respiratory Syndrome (SARS-CoV), emerged. Years later, in 2019, in China, a similar virus emerged, then called coronavirus 2 or SARS-CoV 2, responsible for an epidemic of atypical pneumonia cases[1].

Due to it being a highly transmitted virus, the infection quickly took on pandemic proportions, so that, currently, Corona *Virus Disease* 2019 (COVID-19) has been responsible for an important impact on public health, affecting different social spheres, reaching numbers of cases and deaths higher than the rates caused by SARS-CoV in 2003[2-4].

The syndrome resulting from this RNA virus predominantly presents fever, fatigue, respiratory symptoms, including non-productive cough and shortness of breath. It can involve multiple organs, including cardiac, gastrointestinal, reticuloendothelial and neurological systems[5-7].

Study carried out by Accorsi *et al.*[8] observed that many of those infected ends up developing important neurological changes, this can be explained by the expression of Angiotensin Converting Enzyme type 2 (ACE 2) receptors, present in glial cells and neurons. From this, it is possible to justify the viral tropism for the nervous system, associated with the ability to rupture the blood-brain barrier due to infection.

The pro-inflammatory cytokines released to contain the infection are capable of destroying endothelial cells or causing a hypercoagulable state, justifying the presence of brain vascular disorders[8].

To date, there is a paucity of comprehensive research into the neurological manifestations of coronavirus viremia, but retrospective non-peer-reviewed cases have been documented, for example in convenience samples from three hospitals in Wuhan, China, up to 36% of patients with COVID-19 manifested neurological symptoms[9-10].

It is described, in some investigations, that around a third of infected patients present neurological manifestations, including myalgia, changes in taste, smell and vision, headache, dizziness, polyneuropathy and neuralgia. Furthermore, there are reports of serious neurological syndromes resulting from the infection, such as cerebrovascular disease, whether a vascular event due to ischemic or hemorrhagic brain disease, and encephalopathies, such as acute limbic and brainstem encephalitis, Guillain-Barré Syndrome, meningitis, ataxia, epilepsy and reduced consciousness, among other manifestations[8,11].

Although clinical data are not sufficient, there is still a lot of concern that COVID-19 may increase the risk or trigger the onset of hemorrhagic stroke, especially in the elderly [12]. Such

cerebrovascular disease, an entity reported as part of these manifestations, continues to be a global health problem, posing a great challenge to health professionals, since it has a significant incidence and prevalence, but above all because the vascular condition implies a high morbidity and mortality in all countries[13].

In order to contribute to current studies on the new coronavirus pandemic, this work aimed to analyze, based on the literature, the relationship between hemorrhagic cerebrovascular events and COVID-19 infection, so that, highlighting this knowledge of morbidity and mortality, the diagnoses are made early, optimizing treatment and improving prognosis conditions. Based on this assumption, it is important to record this review in the medical literature, given that there are few cases described, with scarce epidemiological data and research on its etiology and risk factors, with room for major advances in knowledge on this topic.

Materials and methods

This is an integrative systematic review of the literature, prepared following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA Statement) methodology, focusing on the following guiding question “What are the impacts of the pandemic and infection by the new Coronavirus in cases of hemorrhagic stroke?”

Scientific Electronic Library Online (SciELO) and PubMed were used, with the following descriptors indexed on the platform DeCS/MeSH used in combination (Boolean operators AND / OR): “Covid-19 or Sars-CoV-2”, “Hemorrhagic Stroke or Intracranial hemorrhage” AND “Nervous system or Neurologic Manifestations” AND “Cerebrovascular Disorders”.

Original studies available in full in English, Spanish and Portuguese were included, published between 2020 and 2022, which addressed adult and child patients with Hemorrhagic Stroke likely caused by COVID-19, infected confirmed by laboratory tests. Abstracts, letters to the editor, expert opinions, editorial articles, theses and dissertations, as well as duplicate studies were excluded.

The search was carried out on October 16, 2022. First, the titles were analyzed, followed by the abstracts and keywords of the selected studies. Those who did not meet the objective and guiding question of the research were excluded. The articles included from the summary were read in full after applying the inclusion and exclusion criteria discussed previously.

The references of the chosen articles were manually tracked in order to select relevant works. The studies were carefully analyzed by two independent researchers, considering approval or not between them based on reading the titles and abstracts and, after considering them appropriate, the

articles were evaluated in full. Figure 1 shows the general result of the search carried out and the number of articles considered in each database.

Using pre-determined collection instruments, it was possible to extract the study variables, which include type, year of publication, location, design, methodological summary, main results found and levels of evidence. This made it possible to analyze all the variables obtained in the data and evaluate the results. The studies were evaluated regarding the level of evidence, using parameters from the Oxford Center Evidence-Based Medicine tool[14].

Results

The studies were published in the years 2022 (n=5), 2021 (n=5) and 2020 (n=2). The authors of the articles were of American (n=6), Brazilian (n=2), Indian (n=1), Chinese (n=2) and Spanish (n=1) origin. The starting point was the study carried out with patients infected or not with COVID-19 who had a hemorrhagic cerebrovascular accident during the new Coronavirus pandemic period or previously.

Of the twelve articles selected, nine were cohort studies, two were case studies and one was a case-control study and, among these studies, a total population of 32,458 patients was obtained. In terms of level of evidence, the majority were level B (n=10), with 2 being level C. Table 1 presents the main characteristics of the articles comprising the final sample (n=12).

Discussion

The studies presented showed an increase in the occurrence of hemorrhagic stroke and greater stroke severity, with high morbidity and mortality during the pandemic, especially among patients with a stroke positive for COVID-19[15-19], and a reduction in the 10-year survival rate[15]. However, there was a significant drop in hospital care for acute stroke cases around the world [16], generating the impression that the incidence of stroke had decreased, but, in reality, this occurred due to patients not seeking care for fear of acquiring an infection in the hospital[17] and the decrease in public mobility during the pandemic[18]. This may explain the lack of apparent increase in stroke rates compared to historical controls[17].

Among the risk factors, reports reveal that the most affected patients have underlying chronic diseases, such as arterial hypertension, with emphasis on systolic pressure, and diabetes mellitus, which are two main risk factors for hemorrhagic stroke[16-17,20-24]; in addition to obesity, hyperlipidemia, chronic kidney disease[20-21,23-24], atrial fibrillation/flutter[20,21], cirrhosis, ischemic heart

disease, chronic obstructive pulmonary disease (COPD), dementia, heart failure [23] and tobacco consumption[23-24].

Regarding age group, in hemorrhagic stroke, the increase in mortality in 2020 was observed in younger patients[15,17,21] aged 50 years or younger, compared to 2019, associated with the increase in admissions to Intensive Care Units (ICU)[15]. The predilection of occurrence by sex varied between studies. Some showed a slight inclination of the indices towards the female sex[15,17,25], others towards the male sex[16,18,24,26] and some without statistically important differences[23].

Figure 1. Flowchart with representation from the selection of the studies for a systematic review on the impacts of the pandemic and Covid-19 infection on the occurrence of hemorrhagic stroke, 2023.

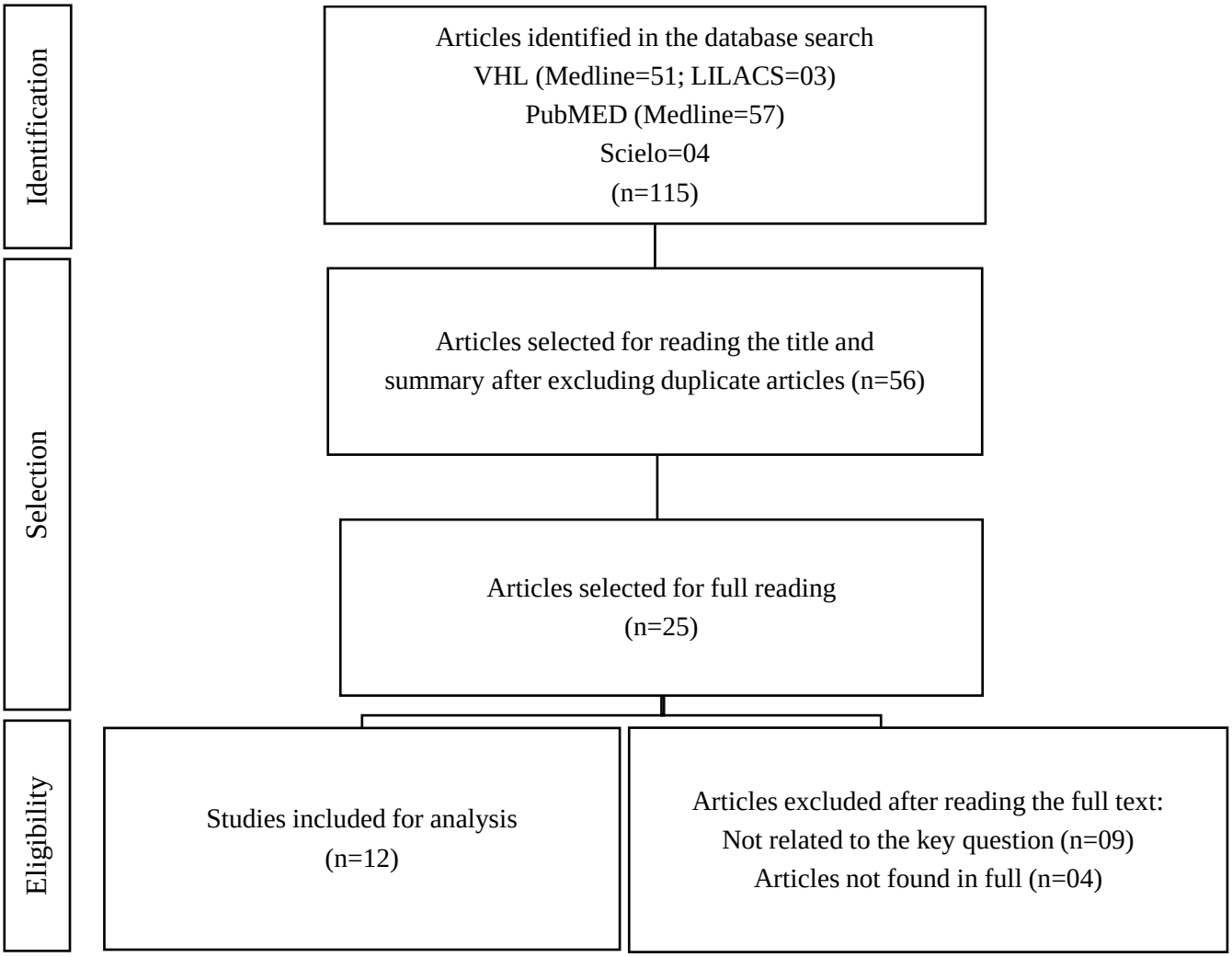

Chart 1. Characterization of studies on the association between Hemorrhagic Stroke and infection with the new Coronavirus, according to author, year, location, design, sample and scenarios, objective, results found and level of evidence. 2023.

Author and year	Design	Sample and Scenario	Objective	Main results	Level of Evidence
Altschul *et al*., 2020 [19]	Cohort	Retrospective cohort of 35 patients admitted to one of the three main hospitals of a health network, which treated patients with stroke during the period from March 1st to May 1st, 2020	Characterize the incidence, risk of mortality and identify risk factors for mortality in patients with hemorrhage and COVID-19.	Hemorrhagic presentations with COVID-19 are a rare but serious manifestation of the disease. Hemorrhagic stroke of the Acute Subdural Hematoma type demonstrated a higher number of cases and Multicompartmental Hemorrhage a higher mortality rate (74.1%).	B
Wang *et al*., 2020 [20]	Cohort	Study with 16 patients admitted to the intensive care unit with severe COVID-19, who underwent brain MRI to evaluate coma or focal neurological deficits.	To identify the potential contribution of coronavirus disease 2019 to hemorrhagic stroke in the elderly and propose possible mechanisms.	Cerebral microvascular lesions are common in patients with severe COVID-19. Radiologic-pathologic correlation suggests a combination of hemorrhagic and ischemic microvascular lesions that may reflect an underlying hypoxic mechanism of injury.	B
Ramos *et al*., 2021 [17]	Cohort	Study with 84 patients with acute ischemic or hemorrhagic stroke tested for COVID-19 and treated from March 13 to May 19, 2020; were analyzed retrospectively. COVID+ patients were compared to COVID- patients and a historical 2019 cohort of 152 patients.	Compare patients with COVID+ to patients with COVID- with radiological acute stroke.	COVID status, regardless of severity, was associated with higher mortality in stroke patients (54%, $p<0.0001$) and a greater tendency for hemorrhagic conversion of ischemic stroke (11%, $p=0.03$). Such patients were younger and less likely to use antiplatelet drugs, with higher rates of thrombocytopenia, suggesting a possible role for antiplatelet use in this population.	B

Castro *et al*., 2021 [22]	Case Series	Case reports of ischemic, thrombotic and hemorrhagic complications in six patients diagnosed with SARS-CoV-2 infection.	To report cases of ischemic, thrombotic and hemorrhagic complications in six patients diagnosed with SARS-CoV-2 infection.	Intracranial hemorrhagic lesions can also be seen in these patients. The mechanism causing hemorrhage may be associated with anticoagulant therapy or factors such as coagulopathy and endotheliopathy.	W
Mishra *et al.*, 2021 [24]	Case Series	Case series with 324 patients admitted with intracranial hemorrhage (ICH) between March and July 2020.	To describe the clinical, laboratory, temporal, radiographic and outcome characteristics of acute ICH in patients with COVID-19.	ICH associated with COVID-19 is often linked to at least one known risk factor for ICH and severe pneumonia. There was a relative increase suggestive of ICH among all types of stroke in the first peak of the pandemic.	W
Shkoukani *et al*., 2021 [25]	Cohort	A self-report registry of people with Brain Malformations infected by COVID-19 was launched in March 2020, with a final sample of 52 individuals.	Analyze the association between COVID-19, Hemorrhagic Neurovascular Disease and Cerebral Cavernous Malformation	Patients with Brain Malformations who contract COVID-19 have a more severe illness, including a potentially higher risk of hemorrhagic stroke.	B
Siegler *et al*., 2021 [26]	Cohort	Evaluation of 14,483 patients with SARS-CoV-2 admitted to 31 hospitals in 4 countries (February to June 2020), with 172 of these with an acute cerebrovascular event, 28 with intracranial hemorrhage.	To summarize findings from a multinational observational cohort of patients with SARS-CoV-2 and cerebrovascular disease.	There was a significantly higher mortality rate among COVID-19 positive patients with stroke plus intracranial hemorrhage (39%)	B
Kurtz *et al*., 2022 [15]	Cohort	Data collection in 165 Intensive Care Units in Brazil between 2011 and 2020. Of the 17,115 admissions for stroke, 3,481 were hemorrhagic.	To analyze clinical characteristics and mortality over a 10-year period and evaluate the impact of the pandemic on stroke outcomes.	In hemorrhagic stroke, a 26% increase in mortality was observed in patients aged 50 years in 2020 compared to 2019.	B

Ramachandran *et al*., 2022 [16]	Cohort	Single Center Retrospective Study in a Stroke Unit in India. 134 patients with imaging-confirmed acute stroke, presenting within 24 hours of symptom onset in May to July 2020 and May to July 2019, were included.	Investigate the impact of COVID-19 on the treatment of stroke patients.	There were more cases of intracerebral hemorrhage in COVID+ strokes when compared to non-COVID strokes (9:6). COVID+ strokes were more severe (higher NIHS) when compared to non-COVID strokes during the same pandemic period.	B
Nia *et al*., 2022 [18]	Cohort	Analysis of data from 45 healthcare organizations and creation of cohorts based on ICD-10 for various stroke subtypes, identifying 22,497 patients with a 10-year history of cerebrovascular diseases and a diagnosis of COVID-19.	To identify risk factors and stroke recurrence based on various subtypes in patients with previous cerebrovascular diseases and COVID-19.	Patients with a history of hemorrhage (subarachnoid, intracerebral, intracranial hemorrhage) or a history of ischemic stroke (cerebral infarction) were at increased risk (p=0.001) of intracranial hemorrhage after COVID-19 diagnosis compared to non-COVID patients.	B
Shoskes *et al*., 2022 [21]	Case-control	26 patients hospitalized with severe Acute Respiratory Distress Syndrome (ARDS) due to COVID-19 and 66 patients with ARDS due to another cause underwent brain Magnetic Resonance Imaging (MRI) to evaluate cerebrovascular injury.	To compare the frequency and patterns of cerebrovascular injury on brain MRI between patients with COVID-19 ARDS and non-COVID-19 ARDS.	The frequencies of hemorrhagic cerebrovascular lesions were higher among ARDS patients with COVID-19 than in those without COVID-19.	B
Lazcano *et al*., 2022 [23]	Cohort	Prospective study including 91,629 positive cases of COVID-19 between February 1 and July 31, 2020, 5752 cases of previous stroke.	Determine the association between previous stroke and mortality after COVID-19 disease according to sex, age groups and stroke subtypes.	Patients with a previous stroke had higher mortality rates (10.38%, p<0.001), especially in those under 80 years of age, including both ischemic and hemorrhagic strokes.	B

ICH: Intracranial Hemorrhage; MRI: Magnetic Resonance Imaging; ARDS: Acute Respiratory Distress Syndrome.

Discussion

The role of race and ethnicity in the progression of COVID-19 has shown emerging evidence suggesting that minority populations, including Black/African Americans, Hispanics/Latinos, are more affected and have higher mortality rates, but this occurrence related to the fact that which are a less assisted population[17-19].

Among the impacts of the pandemic, an increase in stroke cases with higher NIHSS *(National Institute of Health Stroke Scale) was observed*[16-17]. Blood glucose levels at hospital admission and blood pressure were higher, given insufficient control due to restricted access to healthcare facilities during the lockdown and fear of contracting COVID. Patients with a positive stroke for COVID-19 had more hemorrhagic strokes[15-17], more severe strokes with low ASPECTS CT (*Alberta stroke program early CT score*), high hospital mortality resulting from intracerebral hemorrhage (ICH) and worse functional outcome at discharge and after three months[16].

A greater number of cases of hemorrhagic transformation were also observed in repeated images within 24-36 hours of ischemic stroke, regardless of therapeutic anticoagulation[16], which would indicate coagulopathy and prothrombotic state associated with COVID infection[16-17,22,23] as a higher incidence of thrombocytopenia, leukopenia, elevated D-dimer [17,24], prolonged Active Thromboplastin Time (PTT), INR > 1.2[19] and lower rate of use of antiplatelet drugs were noted[17,19].

Regarding the subtypes of hemorrhagic stroke, ICH was more frequent in patients with COVID, resulting in higher mortality rates[15,18-19,24], especially in the multicompartmental (HMC) and multifocal (MFH) types, associated with failure of multiple organs, DIC (disseminated intravascular coagulation)[19] and iatrogenic use of anticoagulants[19,21-22,24]. Next, the subtypes with the worst outcomes included subarachnoid hemorrhage (SAH), focal intracerebral hemorrhage (ICHF) and, finally, acute subdural hematoma (ADHS). A greater lethality was also observed in strokes of spontaneous, non-traumatic origin[19].

In the body, ICH probably occurs through the negative regulation of angiotensin-converting enzyme (ACE) 2, leading to its accumulation in the blood, inducing an increase in blood pressure, greater permeability of the blood-brain barrier (BBB) and a reduction in vascular protection[16,18,20,25]. Furthermore, age- and/or disease-related immune dysfunction and exacerbated catecholamine release secondary to anxiety and stress can also aggravate CNS symptoms caused by SARS-CoV type 2 coronavirus infection[20].

Clinically, most cases had respiratory manifestations initially followed by neurological symptoms and in a smaller proportion the symptoms appeared simultaneously[18,24]. Some opened with

mild pneumonia (without severe pneumonia and without the need for oxygen therapy) and the rest had a severe form of the disease (fever or suspected respiratory infection, plus one of the other manifestations: respiratory rate > 30 breaths/ minute, severe respiratory distress, or desaturation ≤ 93% in room air), with many requiring a mechanical ventilator due to Acute Respiratory Distress Syndrome (ARDS)[25].

Patients with a previous diagnosis of cerebrovascular disease (CVD) had a higher risk of hospitalization, intubation, ICU admission and mortality, in addition to a higher chance of a new hemorrhagic stroke within 90 days in patients with ischemic or hemorrhagic stroke (subarachnoid, intracerebral, hemorrhagic intracranial) previous[18]. Patients with cerebral arteriovenous malformations (AVM) also presented a higher risk of symptomatic hemorrhage, manifesting an exacerbation or pre-existing clinical condition related to the AVM, such as seizures, neurological deficit, worsening of headache and visual blurring[25].

The severity of the systemic condition caused by COVID-19 directly affected the diagnosis and early therapeutic approach of patients with cerebrovascular events due to the decreased use of imaging exams in seriously ill patients considered unsafe for transport or in those in whom brain imaging was not possible. would significantly change its clinical trajectory[17,24]. Many strokes and hemorrhagic stroke conversions have been found during the evaluation of critically ill or intubated patients unable to provide a reliable neurological examination, therefore it is unclear when or if these strokes became symptomatic[17].

In imaging studies, ICH and its subtypes were predominant, generally more voluminous[15] and diffuse [19]. Furthermore, the MRI pattern of disseminated hemorrhagic leukoencephalopathy was unique to patients with COVID-19[21]. Another common, if not universal, characteristic of these hemorrhages is their location in deep areas, such as the basal ganglia or posterior circulation. These locations may represent “vulnerable areas” for SARS-CoV-2 selectivity for invasion or vascular compromise[24].

The unprecedented challenges during the novel coronavirus pandemic and subsequent lockdown have resulted in a delay in treatment metrics for acute stroke [16]. There were delays in door-to-tomography and door-to-needle times during the pandemic, resulting in lower rates of thrombectomy and intravenous thrombolysis[16,18], in addition to a reduction in the surgical approach[19]. Many stroke consultations received during the COVID era were for existing inpatients, especially those with COVID+, suggesting that there has been a decrease in the number of patients presenting to the emergency department due to stroke symptoms, hindering early treatment[18].

Studies demonstrate a delay in diagnostic and therapeutic approaches to assisting COVID+ patients with hemorrhagic cerebral manifestations in the midst of the pandemic, but it is worth highlighting that this is a new and unknown context that required sudden changes in daily activities, which could directly influence the results. of the study. Furthermore, there is a lack of adaptation of the literature to the Brazilian context and the differences in public and private health care were not considered. The need for more research and reflection on the role of health professionals in the early approach to patients suspected of hemorrhagic stroke is highlighted, in order to ensure greater survival for them.

Conclusion

Patients infected with SARS-CoV-2 were at higher risk of hemorrhagic stroke, especially those who already had previous cerebrovascular disease. The pandemic directly hampered the diagnosis and early management of patients suspected of having a hemorrhagic stroke, both due to the severity of the infectious condition and the difficulty in accessing hospitals, due to reduced mobility and fear of contracting the disease. Furthermore, there is a high morbidity and mortality rate in this population due to the greater number of intracerebral hemorrhages and systemic complications of COVID-19 infection. The medical team must be aware of the presence of risk factors and clinical manifestations in these patients, which may be associated with a higher rate of complications and directly interfere with treatment. The everyday findings of scientific research must be considered and adapted to the sociodemographic reality of each region.

Authors' contributions

The authors approved the final version of the manuscript and declared themselves responsible for all aspects of the work, including ensuring its accuracy and integrity.

Conflict of interest

The authors declare no conflicts of interest.

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