Ischemic stroke during COVID-19 infection: a retrospective case series

Acidente vascular cerebral isquêmico durante a infecção por COVID-19: uma série de casos retrospectivos

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ABSTRACT

Background: COVID-19 affects the upper respiratory tract and can lead to organ injuries. The SARS-CoV-2 virus binds to angiotensin 2 receptors, highly expressed in pulmonary, endothelial, and nervous tissues. Ischemic Stroke (IS) is a major neurological complication, linked to coagulation disorders, endothelial dysfunction, and hyper-inflammatory responses. The purpose of this study is to characterize the clinical features of ischemic stroke occurring in patients with SARS-CoV-2 infection.

Material and Methods: A case-series study at Hospital das Clínicas, Faculty of Medicine of Marília, Brazil. The study analyzed 2013 medical records of COVID-19 patients hospitalized between 2020 and 2023, selecting 10 cases of acute ischemic stroke (AIS) during COVID-19 infection. Variables such as age, sex, risk factors, comorbidities, manifestations, severity, treatments, neuroimaging, and outcomes were analyzed Clinical outcomes were analyzed both quantitatively and qualitatively.

Results and discussion: Out of 2013 hospitalized patients, 10 (0.50%) had AIS. The mean age was 63 years, with 70% female. 60% were smokers, and 30% had a stroke history. Most (90%) had severe COVID-19, associated with hypertension, diabetes, dyslipidemia, atrial fibrillation, and prior cerebrovascular disease. 89% required high-flow oxygen, and 22% developed delirium. The average time from COVID-19 to stroke was 7.6 days. 60% of AIS cases had cardioembolic or undetermined etiology. 80% presented partial anterior circulation syndrome, with a 30% mortality rate.

Conclusions: The severity of these cases highlights the importance of rigorous risk factor management and thorough diagnostic investigation, underscoring the need for continuous monitoring and treatment strategies to optimize outcomes.

Keywords: COVID-19. SARS-CoV-2. Ischemic Stroke. Cerebrovascular Disorders. Neurologic Manifestations.

RESUMO

Introdução: A COVID-19 afeta o trato respiratório superior e pode provocar lesões em diversos órgãos. O vírus SARS-CoV-2 liga-se aos receptores de angiotensina II, expressos nos tecidos pulmonar, endotelial e nervoso, sendo o Acidente Vascular Cerebral Isquêmico (AVCi) uma complicação associada a distúrbios de coagulação, disfunção endotelial e resposta inflamatória exacerbada. Este estudo tem como objetivo analisar as características clínicas de pacientes com AVCi durante a infecção por SARS-CoV-2.

Materiais e métodos: Estudo tipo série de casos, com análise de 2.013 prontuários de pacientes internados com COVID-19 entre 2020 e 2023, dos quais 10 apresentaram AVCi agudo. Avaliaram-se variáveis como idade, sexo, fatores de risco, comorbidades, manifestações clínicas, gravidade, tratamentos, achados em neuroimagem e desfechos.

Resultados e discussão: Dos 2.013 pacientes hospitalizados, 10 (0,50%) apresentaram AVCi. A média de idade foi de 63 anos, com predomínio do sexo feminino (70%). Desses, 60% eram tabagistas e 30% tinham histórico de AVC. A maioria (90%) apresentava COVID-19 grave, frequentemente associada a hipertensão, diabetes, dislipidemia, fibrilação atrial e doença cerebrovascular prévia. Cerca de 89% necessitaram de oxigenoterapia de alto fluxo e 22% desenvolveram delirium. O intervalo médio entre o início da COVID-19 e o AVC foi de 7,6 dias. Em 60% dos casos, a etiologia foi cardioembólica ou indeterminada. O tipo mais comum foi a síndrome de circulação anterior parcial (80%), com taxa de mortalidade de 30%.

Conclusão: A gravidade dos casos reforça a importância do controle rigoroso de fatores de risco, investigação diagnóstica adequada e monitoramento contínuo.

Palavras-chave: COVID-19. SARS-CoV-2. AVC Isquêmico. Transtornos Cerebrovasculares. Manifestações Neurológicas.

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INTRODUCTION

The Coronavirus Disease 2019 (COVID-19), declared a pandemic on March 11, 2020, by the World Health Organization (WHO), presents significant severity and complications. The infection is caused by the novel coronavirus associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), predominantly affecting the respiratory system of infected individuals. Of the five types of human coronaviruses (CoVs) discovered to date, SARS-CoV-2, although exhibiting a lower mortality rate, has the highest transmissibility among individuals, a characteristic that has enabled its rapid and widespread global transmission. SARS-CoV-2 is an enveloped virus with a lipid bilayer and a single-stranded positive-sense RNA genome, contained within a helical nucleocapsid.[1]

The clinical presentation of COVID-19 is highly variable, ranging from asymptomatic cases to severe instances that lead to the development of Acute Respiratory Distress Syndrome (ARDS). The most common manifestations of COVID-19 include fever, myalgia, headache, cough, sore throat, anosmia, and ageusia. SARS-CoV-2 infection typically begins in the upper respiratory tract but may subsequently affect the lung bases. Although the lungs are the most severely impacted organs, damage to other target organs may occur, particularly in the nervous, gastrointestinal, cardiovascular systems, as well as the liver and kidneys.[2]

Considering that cardiovascular and neurological complications are the leading causes of death (66%) resulting from COVID-19 infection,[3] the entry of the virus into host cells occurs through the binding of the viral spike glycoprotein (single domain) to the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in tissues and cells including pulmonary macrophages, respiratory epithelial cells, endothelial cells of arteries and veins, neurons, and microglia. Neurological manifestations, both central and peripheral, are reported in approximately 36.4% to 67% of COVID-19 patients, with a higher incidence in the advanced stages of the disease, either due to the infection itself, prolonged stays in Intensive Care Units (ICUs), or medication toxicity.[4]

SARS-CoV-2 neuroinvasion is explained through three primary pathways: hematogenous, endothelial, and transneuronal. In the hematogenous pathway, leukocyte and viral migration traverse the blood-brain barrier; in the endothelial pathway, viral spread occurs through the systemic circulation, infecting vascular endothelial cells; and in the transneuronal pathway, also known as transsynaptic transfer, the virus propagates between infected neurons, reaching higher regions of the Central Nervous System (CNS) via the cribriform plate and olfactory system. According to this mechanism, the endothelial pathway is considered the primary route for SARS-CoV-2 entry into the CNS, mediated by viral neurotropism via ACE2 receptors, whose expression may be upregulated in comorbidities such as diabetes mellitus and hypertension.[1,4]

The most commonly reported initial neurological symptoms include headache, myalgia, altered consciousness, and malaise. In contrast, severe neurological complications, notably cerebrovascular diseases such as stroke, are primarily caused by direct viral invasion, immunological disturbances, or metabolic disturbances, such as hypoxia.[5]

Stroke is defined as an acute focal neurological deficit resulting from brain injury secondary to a non-traumatic vascular event. Its forms of presentation are classified as ischemic or hemorrhagic. Ischemic Stroke (IS) may be lacunar, atherosclerotic, or embolic, while Hemorrhagic Stroke (HS) may be intraparenchymal or subarachnoid.[6]

Regarding its incidence, Acute Ischemic Stroke (AIS) was observed in approximately 1.3-4.7% of COVID-19 patients. In 26-48% of cases, no general or respiratory symptoms were reported before the ictus, while in symptomatic cases, stroke typically occurs 5 to 12 days after the onset of COVID-19 symptoms.[5]

Considering that AIS is more prevalent than HS, with respective rates ranging from 0.4% to 2.7% and 0.2% to 0.9% among hospitalized COVID-19 patients,[7] recent studies have identified several factors contributing to cerebrovascular accidents in COVID-19 patients, including: coagulopathy induced by infection, inflammatory hyperactivity, endothelial dysfunction, presence of comorbidities such as hypertension and diabetes mellitus, and alterations in blood pressure regulation due to the competitive blockage of ACE2 by the virus, leading to its dysregulation. [1,7]

Coagulopathy resulting from the infection is characterized by elevated levels of fibrin D-dimer and C-reactive protein (CRP), contributing to the risk of cerebral arterial/venous thrombosis.[8] Furthermore, aging is considered the main non-modifiable risk factor for cerebrovascular disease in COVID-19 patients, with an average age ranging from 65 to 71 years. Vascular risk factors account for approximately 77% of cases, compared to 15% in younger individuals under 40 years of age without comorbidities.[5]

In addition to these factors, it is crucial to highlight the influence of therapeutic interventions for COVID-19 and their potential correlation with cerebrovascular complications such as stroke. Regarding pharmacological treatment, antivirals, antiretrovirals, immunomodulators, anticoagulants, corticosteroids, and combination therapies have been notably used.[9]Additionally, the use of stroke medications during COVID-19 infection may offer potential benefits.[1]

Globally, over 770 million confirmed cases of COVID-19 have been reported, with more than 6.9 million deaths recorded by the WHO.[10] In Brazil, the incidence stands at over 18,000 per 100,000 inhabitants, with a

mortality rate approaching 336 per 100,000 inhabitants.[11]

Additionally, it is notable that 9.6% of COVID-19 deaths in Italy were attributed to stroke-related complications, a figure also estimated globally by the American Heart Association at around 5.9%, with an incidence of 1.3-4.7% for acute ischemic stroke in patients with COVID-19.[1]

Thus, ischemic stroke is considered one of the most common cerebrovascular complications observed in COVID-19 patients, associated with significant morbidity and mortality.[7]

Although many studies demonstrate the higher prevalence of ischemic stroke and its increased risk in severe SARS-CoV-2 infections, the literature reveals gaps regarding the investigation of traditional risk factors (such as age and sex) and vascular factors (hypertension, dyslipidemia, diabetes mellitus, cardiovascular diseases, cardioembolism, obesity, etc.) for the occurrence of ischemic stroke in COVID-19 hospitalized patients without a history of prior stroke. Moreover, few studies examine the correlation between standard risk factors for ischemic stroke, comorbidities, therapeutic and pharmacological interventions during hospitalization, inflammatory markers (C-reactive protein and ferritin), coagulopathy markers, and distinct neuroimaging patterns of stroke (focusing on the most affected vascular territories) with the severity of ischemic events across different age groups.

Characterizing the different phenotypes, clinical manifestations, treatments received during hospitalization, laboratory findings, and neuroimaging results in patients with ischemic stroke during COVID-19 infection is crucial for identifying potential pathophysiological variations, estimating the frequency and severity of ischemic events based on predominant clinical and topographic conditions, optimizing management strategies in hospitalized SARS-CoV-2 patients with an elevated risk of ischemic events, and adapting treatment protocols according to the identified pathophysiological mechanisms. Furthermore, many studies have analyzed the neurological complications of COVID-19 without adequately addressing ischemic stroke and its relationship with infection severity and the most affected vascular territories in different clinical and age profiles of infected patients.

Based on the pathophysiological mechanisms of COVID-19 and their association with ischemic brain events, the hypothesis arises that SARS-CoV-2-infected patients, depending on the severity of their clinical condition, are at a higher risk of ischemic stroke during hospitalization. Therefore, the primary research question is to investigate the clinical characteristics of patients who experienced ischemic stroke during SARS-CoV-2 infection.

The objective of this study is to analyze the clinical characteristics of patients who experienced ischemic stroke in the context of SARS-CoV-2 infection. More specifically, it aims to investigate the prevalence of established vascular risk factors, associated comorbidities, age distribution, severity of infection, the temporal relationship between the onset of COVID-19 symptoms and the ischemic event, neurological manifestations, neuroimaging findings, the main vascular territories affected, therapeutic strategies implemented during hospitalization, and clinical outcomes.

MATERIALS AND METHODS

This is a retrospective secondary documentary research with a cross-sectional approach, involving qualitative and descriptive quantitative analyses.[12] A series of ten cases of patients who developed acute ischemic stroke during COVID-19 infection were collected from the medical records at *Hospital das Clínicas*, Faculty of Medicine of Marília (*HCFAMEMA*), São Paulo, Brazil.[13]

A total of 2,013 (two thousand and thirteen) electronic medical records of patients hospitalized between March 14, 2020, and March 14, 2023, with a confirmed diagnosis of COVID-19 infection via positive SARS-CoV-2 RT-PCR test were reviewed. Only the medical records of patients who exhibited radiographic evidence of acute ischemic stroke during COVID-19 infection were included in this study, without restrictions regarding age or biological sex, totaling 10 cases. Records of patients whose ischemic stroke occurred after hospitalization for COVID-19, when the RT-PCR test for SARS-CoV-2 was already negative, were excluded.

Considering the objectives of this study, the clinical profile of the selected patients was categorized based on the retrospective collection of the following data from their medical records: age, sex, comorbidities, and risk factors for ischemic stroke, as well as the CHA2DS2-VASc score calculation for patients with atrial fibrillation (AF). Data on the severity of COVID-19 infection, such as the need for high-flow oxygen therapy and the occurrence of incident delirium during hospitalization, were also recorded. Additionally, the temporal relationship between the onset of SARS-CoV-2 symptoms and the ischemic event was analyzed. The Glasgow Coma Scale (GCS) score was assessed immediately following the ischemic stroke event. Signs and symptoms of ischemic stroke were classified using the Bamford Clinical Classification. Neuroimaging reports, including subtype/etiology of ischemic stroke according to the TOAST (Trial of Org 101072 in Acute Stroke Treatment) classification, ischemic patterns, and affected vascular territories were also reviewed, alongside large vessel exams, electrocardiograms, echocardiograms, and therapeutic approaches adopted for ischemic stroke and the clinical outcomes of these patients.

These clinical data were compiled into a data collection instrument, which was applied to all 10 included medical records and evaluated simultaneously by two independent examiners.

The Bamford Clinical Classification, which categorizes ischemic strokes into four main subtypes based

on symptom distribution and lesion location, was particularly emphasized: Lacunar Syndrome (LACI), Posterior Circulation Infarct (POCI), Total Anterior Circulation Infarct (TACI), and Partial Anterior Circulation Infarct (PACI). This classification is fundamental for guiding therapeutic strategies and patient management.[14]

The CHA2DS2-VASc score was applied to assess the need for anticoagulation in patients with atrial fibrillation, aiming to prevent stroke based on the presence and severity of certain risk factors.[15]

The most widely used method for classifying the pathophysiology of ischemic stroke is the TOAST classification, which organizes stroke etiology into five groups: large artery atherosclerosis, cardioembolism, small vessel occlusion (lacunes), infarcts from other etiologies, and infarcts of undetermined etiology.[16]

For data analysis, qualitative variables were described using absolute (f) and relative (%) frequency distributions, analyzed using Jamovi software.[17]

Subjective data, including the clinical presentation of COVID-19 and ischemic stroke, were interpreted and organized in Tables 1 and 2.

This study was approved by the Research Ethics Committee (REC) under the Certificate of Presentation for Ethical Appreciation (CAAE 75939223.9.0000.5413), on January 2, 2024. Furthermore, the REC granted an exemption from obtaining the Informed Consent Form (ICF) in accordance with Chapter IV, Item IV.8 of Resolution 466/12, for research involving medical records.[18]

RESULTS

Among the 2,013 patients hospitalized with COVID-19 between March 14, 2020, and March 14, 2023, ten (0.50%) patients developed ischemic stroke (IS) during hospitalization [Table 1]. The average age of the 10 selected patients was 63 years, with three (30%) patients being under 60 years of age. Regarding sex, 7 (70%) were female, and 3 (30%) were male.

In terms of smoking habits and stroke risk factors, six (60%) patients were smokers, and three (30%) had a personal history of ischemic or hemorrhagic stroke within a 3-16 years period prior to hospitalization for COVID-19. Additionally, three (30%) patients had a diagnosis of congestive heart failure associated with non-isolated atrial fibrillation (AF). Among the 10 patients with treatable chronic comorbidities, eight (80%) were undergoing regular treatment, with control of the underlying diseases.

In assessing the severity of COVID-19 infection during hospitalization, according to the Clinical Management Protocol for Severe Acute Respiratory Syndrome, nine (90%) patients were classified as having severe COVID-19, with eight (89%) requiring high-flow oxygen therapy, and two (22%) experiencing incident delirium during hospitalization. All 10 patients presented with the ischemic event during hospitalization for COVID-19. The average time between the onset of ischemic stroke and the onset of COVID-19 symptoms was 7.6 days, with the majority (60%) of patients experiencing this interval within 5 days.

Regarding the Glasgow Coma Scale (GCS), five (50%) patients had a score between 14 and 15 (mild), three (30%) had a score between 10 and 12 (moderate), and two (20%) had a score between 3 and 6 (severe). During data collection, only one of the 10 patients had NIHSS scale scores recorded in the medical record. Due to incomplete records, the analysis of this data was discontinued for patients who presented with IS during hospitalization for COVID-19.

Regarding the signs and symptoms of ischemic stroke, based on the BAMFORD Classification System, eight (80%) patients presented with partial anterior circulation syndrome (PACS), one (10%) had posterior circulation syndrome (POCS), and one (10%) had cerebral venous thrombosis syndrome. The vascular territory most affected by ischemia was the middle cerebral artery territory, with six (75%) cases involving this territory, as determined by imaging studies.

Other affected vascular territories included the basilar artery, the anterior cerebral artery, and the superior sagittal, transverse, and sigmoid venous sinuses, with each territory being affected in 12.5% of cases. Regarding stroke subtypes according to the SSS-TOAST classification, three (30%) cases were classified as having probable cardioembolic etiology (SSS-TOAST 2 probable); three (30%) as probable embolic etiology of undetermined origin (SSS-TOAST 5 probable); two (20%) as probable atherothrombotic etiology (SSS-TOAST 1 probable); one (10%) as other determined etiology (SSS-TOAST 4 probable); and one (10%) as cerebral venous thrombosis (SSS-TOAST 4 probable).

Among the 10 patients analyzed, 3 (30%) developed hemorrhagic transformation following the ischemic event, with an average interval of 5 days between ischemic onset and transformation.

Regarding the treatment of the ischemic event, all 10 (100%) patients received conservative therapy (anticoagulants/antiplatelets and statins), with no indication for thrombolytic therapy, mechanical thrombectomy, or bridging therapy (thrombolysis followed by endovascular therapy). The mortality rate was 30% among patients with IS, with an average interval of 10 days between the ischemic event and death. Seven (70%) patients were discharged with outpatient neurovascular follow-up. Table 1 and 2 presents the clinical characteristics of the 10 patients (P1-P10) who developed IS during SARS-CoV-2 infection.

Table 1. Clinical characteristics of 10 patients who had ischemic stroke (IS) during SARS-CoV-2 infection (P1-P5)

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age	71	79	64	55	75
Sex	F	M	F	F	M
Stroke subtype (SSS-TOAST)	Cardioembolic (SSS-TOAST 2 probable)	Atherothrombotic (SSS-TOAST 1 probable)	Embolic of undetermined origin (SSS-TOAST 5 probable)	Other undetermined etiologies (SSS-TOAST 4 probable)	Atherothrombotic (SSS-TOAST 1 probable)
Smoking	Non-smoker	Smoker	Non-smoker	Smoker	Smoker
Comorbidities and risk factors for stroke	Untreated hypertension and non-valvular atrial fibrillation (CHA2DS2-VASc score: 3)	Hypertension, dyslipidemia, hyperuricemia, prior IS 5 years ago, and basilar artery aneurysm (D=2.6 cm)	Type 2 DM non-ID and hypothyroidism	HIV with undetectable viral load	Hypertension, dyslipidemia, type 2 DM non-ID, obesity, and IS (right parietal lobe) 3 years ago.
Continuous medication	ASA, amiodarone, gabapentin, omeprazole	losartan, hydrochlorothiazide, simvastatin, clopidogrel, gabapentin, allopurinol	metformin, levothyroxine	none	losartan, atenolol, metformin, citalopram, dapagliflozin, simvastatin, ASA
Glasgow	15	10 (3-1-6)	11 (3-2-6)	15	12 (3-3-6)
Time between ictus and COVID-19 infection	IS during COVID-19 hospitalization (5 days after DSO)	1 month after DSO (IS after COVID-19 discharge)	IS during COVID-19 hospitalization (2 days after DSO)	IS during COVID-19 hospitalization (12 days after DSO)	IS during COVID-19 hospitalization (1 day after DSO)
COVID-19 Severity Assessment	Severe (hospitalization progressed to PE and IS)	Severe (SpO2 94% on Hudson mask 15L/min)	Severe (mild tachypnea on Hudson mask 10L/min, 75% lung involvement)	Mild (no oxygen therapy required)	Severe (SpO2 <91%, decompensation of underlying diseases)
High-flow oxygen therapy	Yes	Yes	Yes	No	Yes
Incident delirium	No	No	No	No	No
Stroke signs and symptoms	Dysarthria and right hemiparesis	Loss of consciousness, disproportionate right hemiparesis with brachiofacial predominance	Loss of consciousness, Broca's aphasia, right hemiparesis, left gaze deviation	Disproportionate right hemiparesis with brachial predominance	Confusion, drowsiness, disproportionate left hemiparesis with crural predominance, bilateral Hoffman sign
BAMFORD scale	PACS	PACS	PACS	PACS	PACS
Neuroimaging	CT and MRI	CT	CT	CT and MRI	CT and MRI
Vascular territory	Left middle cerebral artery (MCA) territory and superior cerebellar artery territory	Undetermined	Left MCA territory (M2, M3, M4 segments)	Left MCA and left PCA territory	Right MCA territory
CVT	No	No	No	No	No
Cervical and cerebral vessel investigation	Non-significant stenosis	Non-significant stenosis	No alterations	No alterations	Multiple microangiopathy foci
TTE	Left ventricular diastolic dysfunction grade I (mild). No other changes	Not performed	Not performed	Normal. Transesophageal echocardiogram performed later on outpatient basis	Not performed
ECG	Atrial fibrillation	Sinus rhythm	Sinus rhythm	Sinus rhythm	Sinus rhythm
Stroke treatment	ASA, Sinvastatin, Valproic Acid	Prophylactic Heparin	Prophylactic Heparin	ASA and Sinvastatin	ASA and Sinvastatin
Hemorrhagic transformation	Yes (5 months post-ictus)	No	Yes (10 days post-ictus)	No	No
Death/Outcome	Discharged	Death 13 days after ischemic event	Death 10 days after ischemic event	Discharged	Discharged

Legend: F = Female; M = Male; HTN = Hypertension; DM2 = Type 2 Diabetes Mellitus; ID = Insulin-dependent; COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Heart Failure; ASA = Acetylsalicylic Acid; DSO = Date of Symptom Onset; ECG = Electrocardiogram; PE = Pulmonary Embolism; SpO2 = Peripheral Oxygen Saturation; NOC = Nasal Oxygen Catheter; AA = Ambient Air; CVT = Cerebral Venous Thrombosis; TTE = Transthoracic Echocardiogram; TEE = Transesophageal Echocardiogram; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; MCA = Middle Cerebral Artery; PCA = Posterior Cerebral Artery; ACA = Anterior Cerebral Artery; SAH = Subarachnoid Hemorrhage; IJV = Internal Jugular Vein.

Table 2. Clinical characteristics of 10 patients who had ischemic stroke (IS) during SARS-CoV-2 infection (P6-P10)

Variable	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age	51	59	90	67	70
Sex	M	F	F	F	F
Stroke subtype (SSS-TOAST)	Embolic of undetermined origin (SSS-TOAST 5 probable)	Embolic of undetermined origin (SSS-TOAST 5 probable)	Cardioembolic (SSS-TOAST 2 probable)	Cerebral venous thrombosis (SSS-TOAST 4 probable)	Cardioembolic (SSS-TOAST 2 probable)
Smoking	Smoker	Smoker	Smoker	Non-smoker	Non-smoker
Comorbidities and risk factors for stroke	Type 2 DM non-ID, dyslipidemia	Type 2 DM non-ID, COPD	Hypertension, hypothyroidism, obesity, dyslipidemia, CHF, and paroxysmal non-valvular atrial fibrillation (CHA2DS2-VASc score: 4)	Hypertension, Type 2 DM ID, hyperthyroidism	Cerebellar stroke 16 years ago, chronic venous insufficiency, CHF, non-valvular atrial fibrillation (CHA2DS2-VASc score: 5)
Continuous medication	metformin, omeprazole, sinvastatin	metformin	ASA, bisoprolol, diosmin, hesperidin, furosemide, spironolactone, levothyroxine	losartan, NPH insulin, atenolol, hydrochlorothiazide, thiamazole	valsartan, hydrochlorothiazide, bisoprolol, rivaroxaban, spironolactone, hydralazine, atenolol, diosmin + hesperidin, cilostazol
Glasgow	6	3T	15	14	14
Time between ictus and COVID-19 infection	IS during COVID-19 hospitalization (5 days after DSO)	IS during COVID-19 hospitalization (7 days after DSO)	IS during COVID-19 hospitalization (3 days after DSO)	IS during COVID-19 hospitalization (10 days after DSO)	IS during COVID-19 hospitalization (1 day after DSO)
COVID-19 Severity Assessment	Severe (SpO2 < 90% in AA)	Severe (SpO2 < 92% with Hudson mask at 10L/min)	Severe (SpO2 < 91% in CN 5L/min)	Severe (decompensation of underlying diseases: hyperthyroidism and AF)	Severe
High-flow oxygen therapy	Yes	Yes	Yes	No	No
Incident delirium	Yes	No	No	Yes	No
Stroke signs and symptoms	Dysarthria, vertigo, imbalance, drowsiness, confusion, multidirectional bilateral nystagmus, left-sided central facial paralysis, and mild global paresis	Left-sided facial paralysis, dysphagia, and dysarthria	Broca's aphasia, right hemiplegia, left-sided gaze deviation	Confusion, loss of consciousness, dysphagia, dyslalia, and Broca's aphasia	Confusion, dysarthria, disproportionate hemiparesis with bilateral crural predominance
BAMFORD scale	POCS	PACS	PACS	CVT syndrome	PACS
Neuroimaging	CT	CT	CT	CT, MRI, and Angio MRI	CT
Vascular territory	Basilar artery branches territory	MCA territory	Anterior Cerebral Artery (ACA) territory	Superior sagittal sinus, transverse, sigmoid sinus, and left internal jugular vein territory	Undetermined
CVT	No	No	No	Yes	No
Cervical and cerebral vessel investigation	Non-significant stenosis	No alterations	Non-significant stenosis	Irregularities in the M1 and M2 segments of the middle cerebral arteries. Filling failure of the superior sagittal sinus, transverse, sigmoid sinuses, and left internal jugular vein, compatible with thrombus	Non-significant stenosis
TTE	Not performed	Not performed	Left ventricular diastolic dysfunction grade I (mild). No other changes.	Not performed	Not performed
ECG	Sinus rhythm	Sinus rhythm	Sinus rhythm	Sinus rhythm	Atrial fibrillation
Stroke treatment	Prophylactic Heparin	ASA and Sinvastatin	ASA and Sinvastatin	Enoxaparin, Sinvastatin, and Valproic Acid	ASA, Rivaroxaban, and Sinvastatin
Hemorrhagic transformation	No	No	No	Yes (SAH secondary to CVT)	No
Death/Outcome	Discharged	Death (severe and irreversible ischemic injury, absence of brainstem reflexes after 7 days of ictus)	Discharged	Discharged	Discharged

Legend: F = Female; M = Male; HTN = Hypertension; DM2 = Type 2 Diabetes Mellitus; ID = Insulin-dependent; COPD = Chronic Obstructive Pulmonary Disease; CHF = Congestive Heart Failure; ASA = Acetylsalicylic Acid; DSO = Date of Symptom Onset; ECG = Electrocardiogram; PE = Pulmonary Embolism; SpO2 = Peripheral Oxygen Saturation; NOC = Nasal Oxygen Catheter; AA = Ambient Air; CVT = Cerebral Venous Thrombosis; TTE = Transthoracic Echocardiogram; TEE = Transesophageal Echocardiogram; CT = Computed Tomography; MRI = Magnetic Resonance Imaging; MCA = Middle Cerebral Artery; PCA = Posterior Cerebral Artery; ACA = Anterior Cerebral Artery; SAH = Subarachnoid Hemorrhage; IJV = Internal Jugular Vein. ,

DISCUSSION

Stroke, though an uncommon complication in the context of COVID-19, is notably more prevalent as ischemic stroke (IS) than as hemorrhagic stroke.[19] This study aimed to investigate the incidence and characteristics of ischemic stroke in patients hospitalized with COVID-19 over a three-year period.

The incidence of ischemic stroke among patients in our cohort was 0.50%, which is significantly lower than the 5% frequency reported in studies from China.[20] However, this finding is consistent with recent retrospective cohort studies conducted in various countries, including China, Spain, and the United States, which reported ischemic stroke incidences ranging from 0.4% to 2.7% in COVID-19 patients.[21] This discrepancy may be attributed to differences in the inclusion criteria, particularly regarding the interval between the onset of COVID-19 symptoms and the occurrence of ischemic stroke. Additionally, this study excluded cases of ischemic stroke with nonspecific symptoms or without neuroimaging evidence, as well as cases where the ischemic event occurred after hospitalization for COVID-19.

In our cohort, the majority of patients with ischemic stroke (90%) had severe COVID-19 infection, which was associated with significant risk factors such as hypertension, diabetes mellitus, dyslipidemia, atrial fibrillation, and a history of cerebrovascular disease. The severity of infection was particularly notable, with 89% requiring high-flow oxygen therapy and 22% developing delirium during hospitalization. These findings align with data from several studies,[1,5,22,23,24,25] which have linked severe COVID-19 infection, irrespective of the need for intensive care, to an increased risk of ischemic stroke. Conversely, some studies suggest that COVID-19 may act as an independent risk factor for hospital-associated stroke,[26] with mechanisms such as hypoxia, hypercoagulability, and inflammation contributing to stroke occurrence, progression, and prognosis in COVID-19 patients.[5]

The average time between the onset of COVID-19 symptoms (date of symptom onset, DSO) and the ischemic event in our study was 7.6 days, with 60% of patients experiencing the stroke within 5 days of symptom onset. These results are in line with most studies, which report an interval of 1 to 3 weeks between the onset of COVID-19 symptoms and the occurrence of ischemic stroke.[26,27]

Regarding the etiological classification of ischemic stroke, the SSS-TOAST scale revealed that the most frequent subtypes were cardioembolic (SSS-TOAST 2 probable) and embolic of undetermined origin (SSS-TOAST 5 probable), each accounting for 30% of cases. These findings support the existing literature, which indicates that the hypercoagulability associated with COVID-19 increases the risk of cardioembolic strokes.[20] Moreover, the high proportion (30%) of strokes of undetermined origin is consistent with recent studies,[21,23,25] which have reported a high frequency of cryptogenic strokes in COVID-19 patients, a subtype that accounts for 10–30% of ischemic strokes directly linked to SARS-CoV-2 infection.

Given the prevalence of cryptogenic strokes, a thorough diagnostic investigation is warranted for these patients, including evaluation of large vessels and initial transthoracic echocardiogram (TTE), with transesophageal echocardiogram (TEE) as a follow-up if necessary. This is crucial for accurate stroke etiology determination and to avoid misclassifying strokes as of undetermined origin.

Atrial fibrillation (AF), the most common cardiac arrhythmia, is significantly associated with an increased risk of stroke, mortality, and hospitalization due to heart failure. In our cohort, all patients classified with probable cardioembolic etiology (SSS-TOAST 2 probable) had non-valvular AF and elevated CHA2DS2-VASc scores (ranging from 3 to 5), indicating a high stroke risk. However, 66.7% of these patients were not using non-vitamin K oral anticoagulants (NOACs), which are recommended for stroke prevention in non-valvular AF.[28] AF significantly contributes to embolic events, and strokes associated with this arrhythmia tend to be more fatal and disabling, with lower chances of recovery and hospital discharge. These observations underscore the need for proactive stroke prevention strategies in AF management. Risk stratification, such as using the CHA2DS2-VASc scale, is essential to identify patients who would benefit from anticoagulation.[26] Thus, the combination of COVID-19-induced hypercoagulability and arrhythmias like AF highlights the importance of timely intervention for stroke prevention in high-risk patients.

Regarding hemorrhagic transformation, 30% of patients in our cohort experienced this complication, with an average interval of 5 days between the ischemic event and transformation. The mortality rate among these patients was 30%, with the average time from ischemic event to death being 10 days. These findings are consistent with the literature, including a study by Nannoni et al. [20], which analyzed 1,655 patients across 44 studies and reported a hospital mortality rate of 31.5%. The proximity of our mortality rate to this figure emphasizes the severity of outcomes in stroke patients with COVID-19.

In terms of treatment, all patients received conservative therapy, including anticoagulants, antiplatelet agents, and statins, with no indications for thrombolytic therapy, mechanical thrombectomy, or bridge therapy (thrombolysis followed by endovascular therapy). Hospital discharge occurred for 60% of patients, who continued with outpatient neurovascular follow-up. These results suggest potential for recovery in some patients, but also highlight the importance of ongoing care and long-term monitoring to optimize clinical outcomes.

CONCLUSION

Considering the objectives of this study, based on the evaluations of medical records, it is possible to conclude that, although the incidence of stroke (CVA) in patients with COVID-19 is relatively low (0.50%), the severity of the cases is considerable.

It was observed that the majority of patients with ischemic strokes in the sample were associated with severe COVID-19 infections and significant risk factors, including hypertension, diabetes, and a history of cardiovascular disease.

The high rate of cardioembolic strokes and the occurrence of hemorrhagic transformations underscore the necessity of rigorous management of risk factors, particularly regarding the stratification and prophylaxis of patients with atrial fibrillation. The elevated proportion of strokes of undetermined origin emphasizes the importance of thorough diagnostic investigations, including neuroimaging and echocardiography, to avoid overestimating cryptogenic subtypes.

Ultimately, the high mortality rate observed, which is consistent with the literature, highlights the need for continuous monitoring and the implementation of effective treatment and prevention strategies for ischemic strokes, in order to optimize clinical outcomes in a population vulnerable to the severe complications associated with COVID-19.

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