Stroke Risk Related to Coronavirus Disease-2019

What Have We Learned?

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KEYWORDS

• Ischemic stroke • Risk • COVID-19 • SARS-CoV-2

KEY POINTS

- Coronavirus disease-2019 (COVID-19) and stroke risk.
- Stroke risk in severe acute respiratory syndrome coronavirus 2.
- Ischemic stroke in patients with COVID-19.

INTRODUCTION

Since its initial outbreak in December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (coronavirus disease-2019 [COVID-19]) virus with its associated severe acute respiratory disease and pneumonia began to spread worldwide (**Fig. 1**, **Tables 1** and **2**).[1] Though COVID-19 is primarily associated with the pulmonary system, the virus can lead to damaging diseases that affect multiple organ systems including the central nervous system. Various neurologic manifestations and disorders associated with COVID-19 can range from mild symptoms such as headache or myalgias to more severe disorders including Guillain–Barre' syndrome, seizures, and psychosis. Though some of these neurologic associations are mild and likely reversible, significant numbers of patients with COVID-19 experience a stroke.[1]

On March 11, 2020, the World Health Organization declared COVID-19 to be a pandemic and since then, reports of increased risk for acute ischemic stroke (AIS) in those with COVID-19 began to emerge and continue to evolve.[2]

DISCUSSION

Stroke care is based on the American Stroke Association Guidelines.[3,4] Timely presentation to the nearest hospital reduces the delay of care to potentially offer

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Crit Care Nurs Clin N Am 35 (2023) 53–65
https://doi.org/10.1016/j.cnc.2022.10.001
ccnursing.theclinics.com

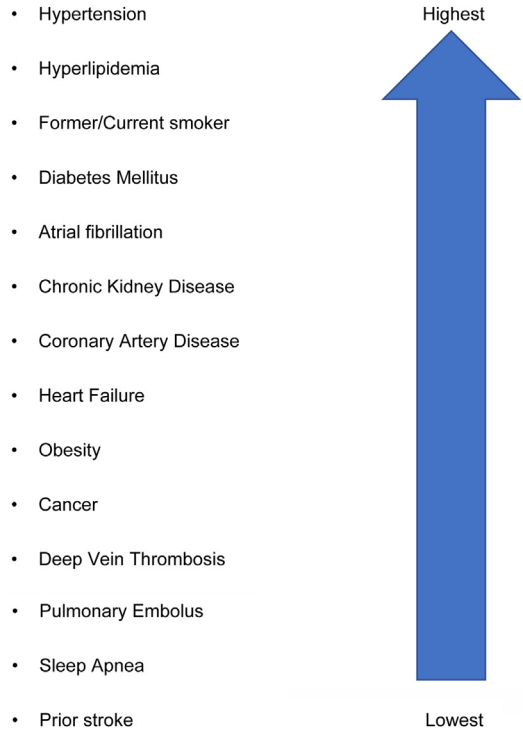

Fig. 1. Vascular risk factor prevalence in patients.[32]

interventions such as intravenous thrombolytic or cerebral thrombectomy. Delay of care increases the likelihood of being ineligible for these interventions, thereby increasing mortality and morbidity related to stroke. The COVID-19 pandemic caused a tremendous stain on the health care system worldwide because of the lack of treatment methods for patients infected with COVID-19. It overburdened emergency rooms and overwhelmed medical staff which impacted stroke care. Patients with transient ischemic attacks or those with mild stroke symptoms refrained from presenting to the emergency room or declined admission out of fear.[5]

At the beginning of the pandemic, The World Health Organization had recommended the reduction of exposure with the use of protective personal equipment, social distancing, avoiding crowds, home confinement, and for health care systems to cease all nonessential services and elective surgeries to reduce the spread of the virus.[6] Studies suggested that because of the isolation requirements, people with stroke symptoms either did not know they were experiencing a stroke or delayed seeking care thereby limiting interventions.[5]

Research

Early in the pandemic, COVID-19 began to become associated with AIS. Patients with the COVID-19 infection in China were noted with coagulopathy and antiphospholipid antibodies. They were elderly patients with severe infection prone to cerebrovascular events and younger patients, less than 50 years of age with large vessel strokes.[7] A study in the United States confirmed a significant incident of acute stroke in patients with COVID-19 infection and found COVID-19 to be an independent risk factor for AIS. Therefore, patients with COVID-19 should have continuous monitoring for AIS.[8]

Table 1
Correlation of cerebrovascular disease with coronavirus disease-2019

Study Methodology	Neurologic Manifestations	Total Number	Number of Strokes	%	Authors
Retrospective observational	Cerebrovascular disease Ischemic stroke – 5 Hemorrhagic stroke – 1	214	6	2.8	Mao et al,[10] 2020
Single-center retrospective, observational	Cerebrovascular disease Ischemic stroke – 10 Hemorrhagic stroke – 1	219	11	5	Li et al,[13] 2020
Multicenter, multinational, observational, systematic review, meta-analysis	Strokes Ischemic stroke – 123 Hemorrhagic stroke – 27 Cerebral venous thrombosis – 6	17,779	156	0.9 (Pooled risk)	Shahjouei et al,[14] 2020
Systematic review, meta-analysis	Ischemic stroke	8577	226	2.6	Huth et al,[15] 2021
Multicenter, retrospective	Ischemic stroke	41,971	1143	2.7	Srivastava et al,[16] 2021
Multicenter, retrospective	Ischemic stroke Hemorrhagic stroke Cerebral venous thrombosis	725	34 6 2	4.7 0.8 0.3	Mahedmmedi et al,[17] 2020
Retrospective, observational	Ischemic stroke Hemorrhagic stroke	841	11	1.3	Romero-Sanchez et al,[18] 2020
Systematic review, meta-analysis	Acute cerebrovascular disease Acute ischemic stroke—1329 Intracerebral hemorrhage—180	108,571	1409	1.3	Nanooni et al,[19] 2021

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Table 1
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Study Methodology	Neurologic Manifestations	Total Number	Number of Strokes	%	Authors
Retrospective cohort	Acute cerebrovascular disease Acute ischemic stroke/TIA—160 Intracerebral hemorrhage—44 Subarachnoid hemorrhage—33 Epidural/subdural hemorrhage—21 Central venous thromboses—2 Not otherwise classified—24	21, 073	284	1.4 (Pooled risk)	Shakil et al,[20] 2022
Retrospective cohort	Acute ischemic stroke	8163	103	1.6	Qureshi et al,[21] 2021
Retrospective observational cohort	Ischemic stroke	14,483	156	0.8	Siegler,[22] 2021

Table 2
Features of stroke in coronavirus disease-2019

Common Findings Across Studies Reviewed	References
More common in younger patients (mean < 55 years) without classic vascular risk factors	Shahjouei et al,[24] 2021; Jabbour et al,[25] 2022; Zhang et al,[7] 2020
More common among younger (ages 65 to 74 years) Medicare beneficiaries and among Medicare beneficiaries without prior history of stroke.	Yang et al,[26] 2022
Higher prevalence of cryptogenic stroke	Shahjouei et al,[24] 2021; Yang et al,[26] 2022; Stein et al,[27] 2021; Siegler et al,[22] 2021
Increased incidence of large vessel occlusion stroke	Lee et al,[28] 2020; John et al,[29] 2020; Shahjouei et al,[24] 2021 Shahjouei et al,[30] 2021; Roman et al,[23] Li et al,[13] 2020; Nanonni,[19] 2021
Smaller incidence of small vessel occlusion stroke and lacunar stroke	Shahjouei et al,[24] 2021
Stroke more severe	Ntaios,[31] 2020
Patients more critically ill, on mechanical ventilator, with ischemic heart disease	Li et al,[10] 2020
Higher mortality (in-hospital)	Nanonni et al,[19] 2021; Quereshi,[21] 2021; Siegler,[22] 2021
Increased morbidity and mortality	Stein et al,[27] 2021; Ntaios,[31] 2020; Jabbour et al,[25] 2022
Worse functional outcomes	Ntaios,[31] 2020
Increased incidence of stroke with severe COVID-19	Mao et al,[10] 2020; Nanonni et al,[19] 2021
Increased incidence of multi-territory strokes	Nanonni et al,[19] 2021; Yang et al,[26] 2022

Reports of neurologic involvement in 30% to 50% of all individuals with SARS-CoV-2 infection have been defined, with almost half of these attributable to stroke.[9] According to Mao and associates, early reports from Wuhan ascertained that more than 36% of patients with COVID-19 had some degree of neurologic involvement, most commonly affecting the central nervous system.[10] Maury and colleagues[11] found that up to 73% of hospitalized patients with COVID-19 experienced some type of neurologic symptom. These same authors also reported that acute cerebrovascular diseases, predominately AIS, have been found in 0.7% to 5.8% of hospitalized patients with COVID-19. The increased risk of ischemic stroke and intracranial hemorrhage with or post-COVID-19 was evident in study after study. An alarming finding by Taquet and colleagues[12] showed that the incidence of ischemic stroke was almost one in 10 or (three in 100 for a first stroke) in patients with encephalopathy (n = 236, 379).

In one of the earliest studies, with data collected from January 16, 2020, to February 19, 2020, from three special care centers in Wuhan, China, Mao and colleagues[10] found that of the 214 patients, 36.4% or 78 patients had neurologic sequelae. Severe infection, characterized by respiratory status, was seen in 88 patients (41.1%) and of those, 5.7% had an acute cerebrovascular disease and 14.8% showed impairment of consciousness. Those with severe infection were older and had more comorbidities, specifically hypertension.[10]

A review of 11 studies outlines the frequency that cerebrovascular disease is shown to correlate with COVID-19, with the focus being ischemic stroke.

Roman and colleagues[23] found that central nervous system manifestations such as headache, partial or total loss of smell (hyposmia, anosmia) and distorted (dysgeusia), diminished (hypogeusia), or loss (ageusia) of taste perception to be common early symptoms of COVID-19 infection. In fact, changes in taste and smell sensation were often used as primary screening symptoms for COVID-19. Considering the anatomy of the olfactory nerve and cribriform plate, this might suggest how the virus gains access to the brain. Respiratory failure is often the main cause of death related to COVID-19 and this pathway may explain how the COVID-19 virus gains access to the rhinencephalon and brainstem centers.[23]

Cerebrovascular disease, primarily large vessel ischemic strokes, and to a lesser degree cerebral venous thrombosis, intracerebral hemorrhage, and subarachnoid hemorrhage, are thought to occur as part of a thrombotic state generated by the virus attaching to ACE2 endothelial receptors leading to extensive endothelial inflammation, coagulopathy, as well as arterial and venous thromboses.[23]

Below is a table of common stroke features obtained from a variety of research studies primarily, from data procured in 2019 - early 2021.

Yang and colleagues[26] in their systematic review and meta-analysis of Medicare beneficiaries 65 years and older, examined the characteristics and outcomes of patients with COVID-19 and stroke and found a pooled incidence of 1.4% of acute cerebrovascular disease. In their study, they found that most patients admitted with COVID-19 symptoms developed stroke a few days later. The strokes were usually ischemic in nature, cryptogenic in cause, and often distinguished by multiple cerebral infarctions.[26]

When determining risk factors for stroke incidence in patients with COVID-19, Nannoni and associates[19] examined four studies. These researchers were able to compare clinical characteristics of patients with both COVID-19 and cerebrovascular disease (n = 113) and those without cerebrovascular disease (n = 11,683). Patients with COVID-19 who also had cerebrovascular risk factors such as hypertension, diabetes mellitus, and coronary artery disease showed an increased risk for stroke. The patients were also older and there were no differences in male versus female. Interestingly, their research did not show any significant difference between smokers and nonsmokers.[19]

In their meta-analysis of clinical characteristics of patients with both COVID-19 and acute cerebrovascular disease, the above authors[19] examined 50 studies. The authors found that median age was 65.3 years with the majority being male. Hypertension, diabetes mellitus, and dyslipidemia were the most common vascular risk factors. Severe COVID-19 was seen in 61% of the patients with 86.7% demonstrating radiologic evidence of pneumonia and 14.8% of patients were afflicted with pulmonary embolism.[19]

Clinical implications for the above study[19] include:

- Incidence of stroke could complicate the course of COVID-19 with those older and having more severe infection presenting a higher risk
- Though incidence of stroke in COVID-19 population was less than 2%, this would have a global impact because of sheer numbers of people infected by the virus
- Clinicians, including nurses, should be vigilant in their bedside assessments observing for acute neurologic symptom development in patients with COVID-19
- Patients who are intubated and/or sedated require close monitoring incorporating assessment of pupillary reactivity and utilization of the Glasgow Coma Scale which might render discovery of abnormal neurologic manifestations

- Patients who have abnormal coagulation studies or other thrombotic complications deserve close observation for development of sudden abnormal neurologic dysfunction
- Providers should follow a protected stroke pathway for patients with stroke presentation who also have suspected or confirmed COVID-19 infection.

Another study by Qureshi and peers found that in patients with COVID-19, the proportion of patients with hypertension, diabetes mellitus, hyperlipidemia, atrial fibrillation, and congestive heart failure was significantly higher among those with AIS.[21]

Xu and colleagues[32] in 2021 found some similarities in risk factor prevalence, specifically with hypertension, hyperlipidemia, diabetes mellitus, atrial fibrillation, and heart failure, in their study as outlined below:

- Hypertension highest
- Hyperlipidemia
- Former/current smoker
- Diabetes mellitus
- Atrial fibrillation
- Chronic kidney disease
- Coronary artery disease
- Heart failure
- Obesity
- Cancer
- Deep vein thrombosis
- Pulmonary embolus
- Sleep apnea
- Prior stroke lowest

In an international multicenter retrospective study including 50 comprehensive stroke centers with a cohort of 575 patients with large vessel occlusion, Jabbour and colleagues[25] found that 194 of the patients were positive for COVID-19. The group members were younger (62.5 years), had fewer risk factors for cerebrovascular disease, and experienced higher morbidity and mortality rates.

Mechanisms of Hypercoagulability in Coronavirus Disease-2019

The specific process through which COVID-19 lends to a hypercoagulable state in the infected population is unknown but understanding the pathophysiology of the hypercoagulable state is key to optimizing treatment to those with COVID-19-induced ischemic stroke and for the prevention of ischemic stroke in those with COVID-19 infection. Inflammation and hypercoagulability are influenced by a cytokine storm that interacts with the coagulation cascade. Studies show cytokines cause neutrophil extracellular traps (NETs), which turn on the extrinsic and intrinsic coagulation pathways creating thrombin that promotes coagulation and leads to AIS.[33]

COVID-19 invades endothelial cells in vessels, tissues, and organs through the angiotensin-converting enzyme 2 (ACE 2), which can damage renal, intestine, and lung tissue. It is a known fact that damaged endothelial cells are related to ischemic stroke. Interestingly, cerebral neurons and vascular smooth muscle cells have the ACE 2 receptor that allows the virus to cross the blood–brain barrier creating central nervous system damage and promote central thrombosis.[33]

Patients with severe cases of COVID-19 have low platelet and lymphocyte counts and increased neutrophils, D-dimer and C-reactive protein levels. It has been hypothesized the virus interferes with lymphocytes by decreasing platelet production,

increasing platelet destruction, and then possibly to thrombosis leading to platelet consumption. Platelet activation related to a hypercoagulable state in patients with COVID-19 may increase the risk of AIS.[33]

During the inflammatory cascade, neutrophils use NETs to capture bacteria. These NETs are made from DNA and proteins which are possibly related to diseases in a hypercoagulable state promoting thrombosis, which in turn may contribute to AIS.[33]

Activated platelet release particles (MPs) result from apoptosis of cells. They are the result of various cells such as erythrocytes, platelets, and endothelial cells. MPs are suspected to cause hypercoagulability in many disease states including stroke.[33]

The immune system uses the complement system for protection against viruses. Lack of an adequately functional complement system can cause a system wide inflammatory response creating tissue damage. Coagulation and micro-thrombosis are also associated with the activation of the complement system.[33]

Patients who become hypoxic from the development of acute respiratory distress syndrome with severe COVID-19 infection trigger pathways leading to thrombosis. It is suspected that bacteria or viruses promote antiphospholipid antibodies thereby patients with COVID-19 promoting antiphospholipid production are at risk for hypercoagulability state-induced ischemic stroke.[33]

MBonde and colleagues[9] proposed the pathophysiology of AIS with.

COVID-19 involves:

- Inflammatory response
- Coagulopathy
- Endothelial dysfunction
- Platelet activation
- Cardioembolic phenomenon

Implications for Future Research

COVID-19 vaccination status is one cohort for new researchers to consider when collecting data and looking at the relationship between COVID-19 and stroke risk. Kakovan and associates indicate that vaccine-induced thrombotic thrombocytopenai (VITT) may be associated with stroke post-COVID-19 vaccine.[34] Clinicians should be aware of possible stroke after COVID-19 vaccination to ensure rapid diagnosis and treatment. Should a patient develop any new neurologic symptoms, especially constant headaches, within a month of receiving a COVID-19 vaccine, moderate suspicion for stroke should be considered. Laboratory testing for possible VITT could include platelet count, D-dimer, anti-PF4 antibody, fibrinogen level, and brain imaging. In addition, those with VITT should be evaluated for concurrent thrombotic diagnoses such as deep vein thrombosis, pulmonary thromboembolism, and venous thrombosis.[34]

Stroke and cerebral venous thrombosis have been reported in the Vaccine Adverse Event Reporting System (VAERS) specific to the Pfizer-BioNTech, Moderna, and J&J/Janssen COVID-19 vaccines.[16] Though there is not yet a plethora of data supporting this, consideration of COVID-19 vaccine status is not unreasonable.

Huth and colleagues[15] concluded that more robust studies using standardized screening and case definitions are warranted. This was certainly apparent with our literature review and review of studies.

In their retrospective study ($n = 368$), Oates and associates[35] found support for the use of transthoracic echocardiography (TTE) in patients with COVID-19 to assist in risk detection of ischemic stroke. The authors developed a composite risk score using clinical and echocardiographic characteristics:

- Age less than 55 years
- Systolic blood pressure greater than 140 mm Hg
- Anticoagulation before admission
- Left atrial dilation
- Left ventricular thrombus

The researchers[35] found an increased incidence of left atrial dilation and left ventricular thrombus (48.3% vs 27.9%, $P = .04$:4.2% vs 0.7%, $P = .03$) in patients with ischemic stroke. TTE is currently used as a part of the diagnostic workup for stroke and TIA. This non-invasive diagnostic test could be used more in those with severe COVID-19 with suspected stroke.[35]

CLINICS CARE POINTS

- Worldwide research examining comparisons of coronavirus disease-2019 (COVID-19) positive and COVID-19 negative stroke cohorts show a relationship between COVID-19 and ischemic stroke.
- Providers must address control of risk factors such as hypertension, high coagulability states, and diabetes mellitus in patients with COVID-19.
- Public health campaigns focusing on stroke recognition and emphasizing the need to seek care for stroke, even during a pandemic, are needed.
- COVID-19 best practice guidelines should be incorporated within the American Heart Association/America Stroke Association Stroke guidelines.
- COVID-19-associated stroke can affect the young, with or without cerebrovascular risk factors.
- Morbidity and mortality are much worse in patients with COVID-19 and stroke as compared with patients with only stroke
- Hypercoagulability studies should be considered and completed on younger patients with stroke, with or without COVID-19 symptoms
- On patients with suspected stroke, a full stroke workup is warranted, even if done post-discharge through an outpatient setting
- More robust research is needed for the prevention and treatment of COVID-19

Clinical Relevance

In summary, there are many elements that participate in the activation of the immune system in patients infected with COVID-19 leading to a hypercoagulable state beginning with the trigger of a cytokine storm that creates subsequent endothelial cell damage and the production of NETs, distribution of MPs, platelet activation, and the initiation of the complement system. It is also important to understand hypoxia is a causal factor in COVID-19-related stroke. The cerebrum is sensitive to changes in oxygenation, so hypoxia can not only cause interstitial cerebral edema but also initiate the coagulation cascade.[33]

Antithrombotic therapy targeting the various mechanisms that lead to thrombosis should be considered in COVID-19-infected patients. Antithrombotic therapy increases oxygen saturation levels in the blood and the coagulopathy. Complications of COVID-19 lead to increased risk for AIS. Therefore, anticoagulation should be initiated early during the initial phase of COVID-19 to prevent AIS.[33]

Since the pandemic, studies have alluded to stoke patients with COVID-19 being younger and having a higher initial admission National Institutes of Health Stroke Scale (NIHSS) than those without COVID-19 infection. Laboratory data to assess for hypercoagulation or inflammation such as d-dimer, interleukin-6, C-reactive protein, fibrinogen, and platelets are usually elevated in the COVID-19 patient. All efforts should be made to adhere to national guidelines for stroke care.[36]

The COVID-19 pandemic created a greater opportunity for telemedicine. Utilization of telemedicine enabled social distancing and the ability to maintain isolation between patients and providers. Tele-Neurology is available to allow vascular neurologists to oversee stoke activations in remote facilities or where expertise is unavailable. It also provides quick use of the NIHSS to provide an assessment from symptom onset to treatment and management more efficiently.[37]

Patient evaluation for symptoms of an ischemic stroke should result in a full stroke workup. Typically, an initial neurologic evaluation is performed to assess deficits followed by cerebral and vascular imaging is performed. A cardiac workup and coagulation panel are included. Results of the imaging and patient eligibility as per stroke guidelines[3,4] determine interventions of intravenous thrombolytic or mechanical thrombectomy.[37]

Clinicians may assume stroke symptoms typically occur in the elderly population, but what we have seen since the COVID-19 pandemic are younger people including children experiencing stroke symptoms.[37,38] Stroke in the young usually includes further workup to explain their hypercoagulable state or cause for stroke. It is important for nursing to use a standardized tool such as the NIHSS to monitor for subtle neurologic changes in patients which may not be otherwise explained and advocating for neuroimaging. A standardized inpatient stroke code protocol should be implemented and familiar. As clinicians, identifying patient risk factors for stroke and being able to identify neurologic changes early, and knowing the time when the patient was last known normal are essential for timely stroke intervention.[39]

SUMMARY

In January 2022, for the 20th year in a row, nurses were ranked number one as the most trusted profession[40] despite the pandemic and its related critical staffing and equipment shortages, threat to their personal safety and that of their patients, coworkers, and families, and extreme physical and mental duress. Data and quality of care have long been linked to promote optimum patient outcomes. Accuracy of that data is crucial. As nurses are the largest group of health care professionals and play a key role in patient safety and quality outcomes, it is imperative that they have access to quality, robust data and be knowledgeable about its interpretation so that they can make informed practice decisions.[41]

Three years into the COVID-19 pandemic, there is growing evidence that the increased incidence of vascular risk factors with concomitant proinflammatory and procoagulation biomarkers show a distinct relationship of ischemic stroke risk in patients with SARS-CoV-2 infection.[7] Despite governmental assurances that the pandemic is over, long-term effects of COVID-19 continue to evolve. Other than vaccination, academic literature is still lacking with respect to prevention and early treatment of COVID-19 as well its long-term effects.

DISCLOSURE

The authors have nothing to disclose.

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