Discover Medicine

Review

Stroke risks in patients with COVID-19: multiple mechanisms of SARS-CoV-2, impact of sex and age, vaccination, and long-term infection

Moawiah M. Naffaa[1,2] · **Ola A. Al-Ewaidat**[3]

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Abstract
The COVID-19 pandemic has presented unprecedented challenges to the healthcare system, encompassing a spectrum of clinical presentations from asymptomatic cases to severe manifestations such as acute respiratory distress and multi-organ failure. A particular focus has emerged on the notable increase in ischemic strokes affecting both adults and pediatric populations. The virus's impact on the cardiovascular, hematologic, and immunologic systems contributes to the occurrence of ischemic cardiovascular events. Notably, individuals with COVID-19 have a significantly higher likelihood of experiencing strokes compared to those without the virus. This article explores the correlation between COVID-19 and strokes, underscoring the importance of understanding risk factors, multiple mechanisms, effects on pediatric populations, vaccination implications, and long-term consequences. The overarching goal is to enhance our understanding of how to mitigate stroke risk in COVID-19 patients, potentially leading to improved treatment options and outcomes. By discussing these aspects, we aim to provide comprehensive insights that could inform clinical practices and public health strategies.

Keywords Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) · Coronavirus disease 2019 (COVID-19) · Ischemic stroke (IS) · Vaccination · Long COVID-19

1 Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), responsible for Coronavirus Disease 2019 (COVID-19), exhibits unique tissue tropism and manifests in various clinical forms, from asymptomatic to severe cases leading to multi-organ failure and death [1]. The pandemic has posed unprecedented challenges to healthcare systems globally, marking one of the most significant crises in recent history. Our understanding of COVID-19 has rapidly evolved, recognizing its systemic impact, particularly on the nervous system through both direct viral invasion (neurotropism) and secondary effects on other organ systems [2, 3].

Stroke, a major cause of mortality and disability, has seen a significant rise in prevalence. Ischemic stroke (IS) constitutes approximately 60% of all strokes, followed by intracerebral hemorrhage (ICH) at 25%, and subarachnoid hemorrhage (SAH) at about 10% [4].

✉ Moawiah M. Naffaa, Moawiah.naffaa@duke.edu | [1]Department of Psychology and Neuroscience, Duke University, Durham, NC 27708, USA. [2]Department of Cell Biology, Duke University School of Medicine, Durham, NC 27710, USA. [3]Department of Internal Medicine, Ascension Saint Francis Hospital, Evanston, IL 60202, USA.

COVID-19's influence on stroke, especially ischemic strokes, is well-documented. The virus impacts the cardiovascular, hematologic, and immunologic systems, increasing rates of arterial and venous thromboses in both pulmonary and systemic vasculature [5, 6]. This results in ischemic events, including myocardial infarction (AMI) and stroke, which are recognized complications of COVID-19 [1, 7, 8]. Compared to influenza, COVID-19 patients have a significantly higher risk of stroke, persisting for up to a year post-infection [9–11].

Strokes are the most common neurological complications among hospitalized COVID-19 patients [12]. Initial reports indicated high rates of neurological symptoms in COVID-19 cases, with significant instances of cerebrovascular disease in severe cases [13]. The incidence of such events has varied, decreasing as treatment numbers increased. A history of stroke in infected patients is associated with poor outcomes, including higher in-hospital mortality [14, 15].

Studies from different regions, including the USA, highlight the link between COVID-19 and ischemic strokes, showing varying rates and outcomes. In New York, 0.9% of hospitalized COVID-19 patients had ischemic strokes, with a high mortality rate [16]. Cryptogenic stroke is notably more frequent in COVID-19 patients, emerging as a distinct mechanism and predictor of mortality [14, 16]. Reports indicate that COVID-19 patients are experiencing strokes and large vessel occlusions at pediatric ages [17, 18]. Independent risk factors for ischemic stroke and large vessel occlusion have been identified in COVID-19 patients [19–21].

Elevated D-dimer levels, indicating coagulation and immune activation, are a recurring finding in COVID-19 patients with ischemic strokes, especially in severe cases, highlighting an increased stroke risk even in less severe cases. Some patients present with strokes before COVID-19 symptoms, indicating an early thrombosis risk [22, 23].

The link between COVID-19 and different stroke types is a significant concern. This review aims to elucidate key risk factors, mechanisms, pathophysiology, pediatric impacts, vaccination implications, and long-term effects of SARS-CoV-2, aiming to improve our understanding and mitigate stroke risk in COVID-19 patients, and to explore potential treatments for those at risk.

2 Stroke dynamics in COVID-19: from acute phase intensity to age and sex disparities

COVID-19 has been linked to an elevated risk of cardiovascular diseases, including myocardial infarction, myocarditis, acute ischemic stroke (AIS), and intracerebral hemorrhage (ICH) [24–26]. Although ICH is rare in hospitalized COVID-19 patients, it is associated with higher mortality rates [27]. AIS, particularly attributed to large vessel occlusion due to systemic hypercoagulability induced by SARS-CoV-2 [28], is most prevalent during the first few days to two weeks following a COVID-19 diagnosis [29, 30]. A meta-analysis revealed a pooled AIS prevalence of approximately 2% in COVID-19 patients [31, 32], with an overall stroke incidence of 1.6% in hospitalized patients and 3.7% in critically ill patients [33].

The likelihood of experiencing a stroke, particularly an AIS, is higher among individuals hospitalized with COVID-19 compared to those recovering as outpatients [34]. Research indicates that the risk of ICH in hospitalized COVID-19 patients ranges from 0.14 to 0.86% [35]. Notably, a significant proportion (57%) of strokes occurs within the initial three days following a COVID-19 diagnosis, with the risk diminishing over time [36]. This observed risk of stroke, encompassing both AIS and ICH, during the acute phase of COVID-19 aligns with findings from earlier studies [8, 29, 30, 37].

It is crucial to emphasize that the increased risk of AIS and ICH during the acute phase of COVID-19, particularly in hospitalized patients with severe disease, can be attributed to distinct pathophysiological mechanisms. This evidence underscores that the acute phase of COVID-19 represents a high-risk period for stroke. To mitigate the elevated stroke risk in COVID-19 patients, particularly the prevalence of AIS and ICH, it is crucial to address both disease-specific and patient-specific risk factors. This approach will facilitate the development of individualized treatment plans, including appropriate medications.

Various cardiovascular risk factors, such as hypertension, atrial fibrillation (AF), diabetes, and a history of prior strokes, independently increase the risk of stroke in COVID-19 patients [10, 38, 39]. AF, which is often treated with anticoagulation therapy, is associated with a higher risk of ICH in COVID-19 patients [35, 36]. It is imperative to explore the intricate interplay between SARS-CoV-2 and diabetes mellitus, which may culminate in ICH, given that diabetes mellitus and hyperglycemia are well-recognized for their propensity to increase the risk of bleeding [40]. Close monitoring of cardiovascular risk factors such as hypertension, diabetes, and prior stroke history is essential, given their independent association with heightened stroke risk in COVID-19 patients. This monitoring supports the implementation of more effective treatment options.

Age and biological sex are crucial determinants of stroke risk and pathophysiology, influencing both the severity and mortality associated with COVID-19 [41–44]. A study examining sex- and age-specific stroke risk in COVID-19 patients over a six-month period found that men had a 32% higher risk of ischemic stroke compared to women, and overall stroke incidence remained elevated in men throughout the follow-up period [36, 45]. Significant age-specific sex differences were observed for both AIS and ICH in older patients [36].

Age has been associated with an increased risk of stroke, with some studies indicating that individuals who experience strokes in conjunction with COVID-19 are generally younger than those who are COVID-19-negative [25]. Conversely, other findings suggest that COVID-19 patients who suffer strokes are significantly older and exhibit a higher prevalence of concurrent cardiovascular risk factors compared to those who do not experience strokes during COVID-19 infection [36]. Future studies should be robust and well-designed to investigate the incidence of stroke across different adult age groups in COVID-19 patients compared to non-COVID-19 patients. Such studies can enhance our understanding of age-related risk factors for stroke in COVID-19 patients and provide further insights into the relationship between SARS-CoV-2 infection and stroke incidence across various age groups.

While sex differences in the incidence of AIS are well-established, studies on sex differences in the incidence of ICH remain inconclusive. A cohort study of COVID-19 patients suggested that men had an 83% higher risk of ICH compared to women; however, this trend was not significant in patients aged 75 years or older [36]. In contrast, a previous study conducted in Southeast Asia found an increased incidence of ICH in women aged 80 years or older, which may be associated with a higher use of anticoagulation therapy in this demographic [46]. Further investigations are needed to explore the underlying mechanisms that contribute to these sex differences in ICH incidence.

Recognizing variations in stroke risk across different age groups and sexes can lead to tailored treatment strategies, enhancing stroke prevention and ultimately reducing morbidity and improving outcomes in this vulnerable population.

3 From endothelial dysfunction to cytokine storms: understanding the complex pathways of COVID-19-associated stroke

Numerous viruses are linked to an increased risk of ischemic stroke [47], typically originating from infections in peripheral tissues without detectable viral presence in the central nervous system (CNS). Despite this, these infections elevate the incidence of stroke. Case–control studies consistently demonstrate that systemic infections frequently precede strokes, often within a few days of symptom onset [48, 49]. This association is believed to result from systemic immune activation, which, along with hypercoagulability and endothelial dysfunction, may lead to vascular injury or thromboembolism [50].

Several respiratory infections can invade the CNS either through direct invasion, as seen with herpesviruses (e.g., varicella-zoster virus) [51], or through hematologic spread. A large prospective study found that respiratory infections occurring within three days prior were associated with a 3.2-fold increase in stroke incidence [52]. Viral respiratory pathogens, such as Parvovirus B19, may also elevate stroke risk by causing arteriopathy [53]. Similarly, influenza-like illnesses are linked to a heightened risk of stroke. A large cohort study of ischemic stroke patients showed that those who experienced an influenza-like syndrome within the previous 15 days had a significantly increased stroke risk [54].

The current consensus recognizes that COVID-19 is associated with severe complications extending beyond the respiratory system. This association increases the risk of deep vein thrombosis, myocardial infarction, stroke, and various neurological effects, underscoring the significant impact of COVID-19 on the vascular system [55]. Critically ill patients with COVID-19 exhibit a higher incidence of stroke (5.7%) compared to those with milder cases (0.8%), highlighting the complexity of ischemic stroke in COVID-19 and the involvement of multifaceted risk factors and mechanisms [13].

Severe disease is more prevalent among older individuals with comorbidities, increasing their susceptibility to stroke [56]. Interestingly, COVID-19-positive patients with large vessel occlusion (LVO) tend to be younger and show lower rates of pre-existing cardiac comorbidities [16]. The heterogeneity of stroke in COVID-19 is attributed to multiple mechanisms, including cytokine storms, activation of the innate immune system, arrhythmia-related embolic events, hypoxia-induced ischemia, thrombotic microangiopathy, endotheliopathy, and coagulation activation [31, 57].

Investigating the precise pathogenic mechanisms that link SARS-CoV-2 infection to the development of ischemic stroke necessitates research at the molecular, cellular, and clinical levels. Chronic autoimmune diseases such as rheumatoid arthritis have been the subject of extensive study, revealing their association with increased susceptibility to stroke incidents. The pathophysiological mechanisms underlying strokes in autoimmune conditions are intricate and multifaceted, often involving chronic inflammation, immune system dysregulation, and endothelial dysfunction [58].

The pathophysiological pathways implicated in autoimmune-related strokes may intersect with those exploited by viral infections, such as SARS-CoV-2.

Early evidence indicates that COVID-19-associated stroke predominantly affects males and targets the anterior cerebral circulation. This observed association likely arises from a complex and multifactorial pathophysiological process [45, 59, 60]. COVID-19 has been observed to impact the endothelium, leading to endothelial dysfunction, which correlates closely with more severe manifestations of the disease [61]. Initially, there was a hypothesis that SARS-CoV-2 could directly infect the endothelium [62]. Elevated levels of Angiotensin Converting Enzyme-2 (ACE-2), a ubiquitous receptor in vascular endothelium and the virus's entry point into cells, were found in the lung endothelial cells of COVID-19 fatalities. This finding suggests a potential link between viral infection and endothelial damage **(**Fig. 1**)** [63, 64]. Furthermore, COVID-19-induced inflammation in adjacent blood vessels has also been identified [65]. Therefore, the increased risk of stroke associated with COVID-19 is proposed to involve ACE-2 receptor expression, viral entry into brain endothelial cells, and potential ACE-2 receptor inhibition or depletion [16, 66, 67].

Moreover, COVID-19 induces a hypercoagulable state, leading to vasculopathy and cardiomyopathy. Upon attaching to ACE-2 receptors and entering host cells, the virus triggers a cascade of cytolytic immune responses, activating both cellular and humoral defenses. The complex interplay between viral effects and host response results in systemic manifestations that heighten the risk of ischemic strokes. These include endothelial damage, platelet activation, and coagulopathy **(**Fig. 1**)** [68].

Under normal conditions, the intact vascular endothelium maintains inherent anticoagulant properties. However, when damaged, it transforms into a platform for platelet activation and initiation of the coagulation cascade, creating a highly procoagulant environment conducive to thrombus formation [69]. This clinical phenomenon has also been observed in pediatric cases of cerebral arterial and venous thrombosis [70].

Additional reports emphasize inflammation of the arterial vessel wall, particularly central nervous system (CNS) vasculitis or vasculopathy **(**Fig. 1**)** [71–73]. Proposed mechanisms suggest that endothelial dysfunction may result from structural and functional changes in endothelial cells, leading to arterial stiffness and morphological alterations in capillaries [74]. Another study highlights an increased risk of atherosclerosis due to inflammatory cascades and alterations in ACE-2 activity, disrupting the renin-angiotensin system [75].

A central aspect of COVID-19-associated prothrombotic states is endothelial cell infection and disruption, resulting in activated tissue factor (TF) expression and elevated von Willebrand factor (vWF) levels [62, 76]. This association between COVID-19 and endothelial effects may explain the heightened risk among individuals with heart and circulatory conditions [77]. Endothelial dysfunction may persist post-recovery, potentially contributing to long-term complications [78, 79]. Further research is warranted to ascertain whether persistent endothelial dysfunction directly correlates with enduring

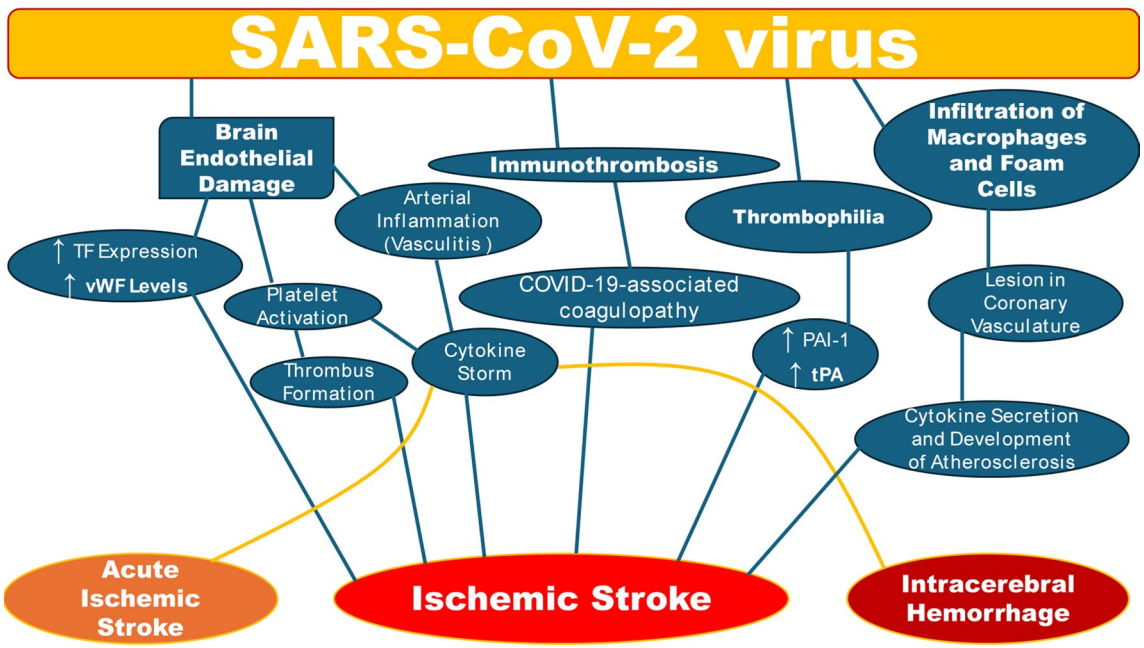

Fig. 1 Pathophysiological mechanisms of stroke induced by invasion of the SARS-CoV-2 virus

COVID-19 symptoms, suggesting existing treatments that enhance endothelial function could benefit individuals with long COVID.

Thrombosis initiation in response to viral pathogens involves innate immune system activation, termed 'immunothrombosis' (Fig. 1) [80]. This intricate process involves interactions among intravascular TF, innate immune cells, platelets, endothelial cells, and release of neutrophil extracellular traps (NETs), activating the contact pathway of coagulation. This underpins the primary hypothesis of COVID-19-associated coagulopathy (CAC) [80, 81].

Pathological thrombosis in COVID-19 patients is initiated by a hyper-inflammatory response known as a 'cytokine storm' (Fig. 1) [82]. Elevated interleukin-6 (IL-6) and C-reactive protein levels contribute to the hypercoagulable state associated with the disease [6, 83]. These markers are also linked to increased risks of stroke and myocardial infarction in healthy individuals [84]. Immune system activation and heightened inflammatory cytokines at the infection site prompt the expression of TF on endothelial cells, infiltrating macrophages, and neutrophils, leading to elevated TF levels in the lungs [82]. TF-induced coagulation involves the formation of the TF–factor VIIa complex enzyme, initiating blood coagulation. Subsequent assembly of factor Xa into prothrombinase leads to the conversion of prothrombin to thrombin, activating fibrinogen to fibrin and forming a fibrin-based clot, accompanied by platelet activation [85, 86].

Platelets play a critical role in the development of acute thrombosis in COVID-19 by inducing platelet expression of adhesion receptors and releasing chemokines, which facilitate the recruitment of innate immune cells [80]. Platelet activation can occur through various mechanisms, including direct infection, inflammatory molecules, NETs, vWF, and COVID-19-induced endotheliopathy [87].

The proposed mechanism for COVID-19-induced endotheliopathy and vasculopathy centers on endothelial cell injury, either directly through SARS-CoV-2 invasion or indirectly via acute systemic inflammation [88]. Studies have documented increased levels of markers associated with endothelial injury, such as plasminogen activator inhibitor-1 (PAI-1), vWF, syndecan-1, and thrombomodulin (Fig. 1) [89]. This dysfunctional endothelium contributes to the severity of COVID-19 [90].

Moreover, COVID-19 infection is characterized by minimal prolongation of prothrombin time (PT) and activated partial thromboplastin time (aPTT), along with mild thrombocytopenia, indicating a mechanism distinct from classic sepsis-induced coagulopathy [91, 92]. Elevated levels of plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA) suggest disruptions in fibrinolytic pathways, reflecting the hemostatic system's response to COVID-19-induced thrombophilia [93]. These molecular pathways warrant further study in the context of stroke in COVID-19 patients to better understand the multifactorial mechanisms of stroke incidence.

The mechanisms underlying AIS in COVID-19 patients involve the influence of the inflammatory storm and hypercoagulable state, which significantly contribute to thrombotic events. Additionally, vasculitis and cardiomyopathy play roles in these processes [31, 57, 94]. ICH in COVID-19 patients results from endothelial injury and inflammation due to viral invasion, which increases vessel wall fragility and leads to hemorrhage [35, 95]. Importantly, anticoagulation therapy used to prevent thrombosis in COVID-19 patients has been associated with an increased risk of ICH [96].

Furthermore, the heightened risk of stroke in COVID-19 patients is particularly notable among men across various age groups [36], possibly due to more pronounced inflammation and cytokine storms in infected men compared to women [97]. Biological mechanisms of cell death in the ischemic brain are influenced by sex, with factors such as coagulation, sex hormones, reproductive factors, and social factors impacting stroke outcomes [98, 99]. While the age-adjusted incidence of stroke is generally higher in men, women aged over 85 years exhibit higher stroke-related mortality and disability rates [99–101]. These observations underscore the critical role of age and gender in determining the impact of COVID-19 on stroke outcomes.

4 Unraveling a distinct connection between SARS-CoV-2 and stroke: coronary lesions and macrophage responses

The robust activation of inflammasomes in macrophages, triggered by the presence of SARS-CoV-2 in the lungs, exacerbates tissue damage [102]. Recent research has identified SARS-CoV-2 in the coronary vasculature tissue of eight COVID-19 patients, with higher concentrations of viral RNA in arterial walls compared to adjacent adipose tissue [103]. Notably, the virus exhibits significant replication within pathological intimal thickening (PIT) coronary lesions, indicative of early-stage lesions progressing to advanced atherosclerotic plaques [103].

Within the coronary vasculature, macrophages—specific white blood cells responsible for pathogen ingestion—are the primary cells infected by the virus [103]. This finding suggests that macrophages infiltrating virus-affected arterial vessels undergo a simultaneous inflammatory response, potentially exacerbating plaque inflammation and increasing the

risk of acute myocardial infarction (AMI) and stroke in COVID-19 patients [103]. The macrophage response thus emerges as a critical factor in the ischemic cardiovascular complications associated with COVID-19.

During the development of lesions, macrophages and foam cells, which specialize in addressing fatty deposits on blood vessel walls, encounter dysfunction due to prolonged exposure to an inflammatory microenvironment and lipids (Fig. 1) [104, 105]. In the initial stages of PIT lesions, macrophages exhibit increased susceptibility to SARS-CoV-2 infection, attributed to the accumulation of excessive triglycerides and cholesterol within lipid droplets [105].

Previous studies have reported the presence of SARS-CoV-2 in the heart, aorta, and other distant organs [106–109]. This evidence firmly establishes that SARS-CoV-2 can infect and replicate within macrophages located in the coronary vasculature of COVID-19 patients. Furthermore, the virus demonstrates a propensity to replicate in foam cells over other types of macrophages, potentially serving as a reservoir for viral debris within atherosclerotic plaques. Despite the prolonged increase in type I interferon (IFN) response in infected macrophages, infected foam cells displayed only a temporary activation of type I IFN gene expression [103]. This, coupled with a reduced inflammatory response, might facilitate the prolonged presence of SARS-CoV-2 in atherosclerotic autopsy samples.

Macrophages within vascular tissue have the capacity for self-renewal, potentially serving as enduring repositories of SARS-CoV-2 RNA within atherosclerotic plaques [110]. Additionally, viral RNA from SARS-CoV-2 has been detected in infected vascular smooth muscle cells (VSMCs) in autopsy samples from coronary arteries, suggesting a possible role in the persistence of the virus within the arterial wall [103, 111].

The invasion of macrophages and foam cells by SARS-CoV-2 induces a vigorous inflammatory response, leading to the secretion of cytokines associated with atherosclerosis development and increasing the likelihood of cardiovascular incidents [112–114]. Experiments conducted with a model simulating viral infection ex vivo validated the direct infection of atherosclerotic tissue by SARS-CoV-2 [103].

Inflammation triggered by SARS-CoV-2 invasion of vascular tissue, as demonstrated in cultures of macrophages and foam cells, results in the release of pro-atherogenic cytokines such as IL-6 and IL-1β [103]. This provides a molecular basis for understanding how SARS-CoV-2 infection of coronary lesions could exacerbate acute cardiovascular symptoms in COVID-19, such as AMI and stroke [8, 10].

Enhancing our comprehension of the mechanisms underlying stroke incidents in COVID-19 patients can also advance our understanding of traditional stroke etiologies. This knowledge has the potential to catalyze innovations in future treatment strategies by offering profound insights into diverse stroke mechanisms.

5 Ischemic strokes associated with COVID-19 in pediatric

Our understanding of ischemic strokes in pediatric patients affected by COVID-19 remains limited due to a paucity of data. Typically, children exposed to SARS-CoV-2 exhibit either asymptomatic cases or milder symptoms compared to adults [115, 116].

During the early stages of the pandemic (March to May 2020), research from multiple countries indicated that only 0.8% of pediatric SARS-CoV-2 cases involved ischemic strokes. Notably, the incidence of confirmed ischemic strokes associated with COVID-19 in children was remarkably low. For instance, none of the 33 documented cases of neonatal cerebral sinovenous thrombosis (CSVT) were linked to COVID-19, while only 3.6% of the 166 documented cases of childhood arterial ischemic strokes (AIS) were associated with the virus [117].

Despite lower exposure risks and less frequent screenings compared to adults, the prevalence of COVID-19 infection in children mirrors that seen in the adult population. While pediatric infections are often asymptomatic or present with milder clinical courses, children can still exhibit symptoms similar to those seen in adults, encompassing respiratory, cardiovascular, gastrointestinal, hematologic, and neurologic manifestations [115, 116, 118, 119]. Of particular note is the emerging association between COVID-19 and an increased propensity for ischemic strokes among neurological symptoms [60].

Unlike ischemic strokes in adults, which have been shown to result from various pathophysiological mechanisms (Fig. 1), ischemic strokes in pediatric COVID-19 cases often manifest as either AIS or CSVT. A cross-sectional analysis revealed that SARS-CoV-2 infection was most commonly associated with cases diagnosed as AIS among pediatric patients with ischemic strokes [70]. Additionally, a review indicated a significant proportion of childhood AIS cases occurring concurrently with CSVT, and the incidence of childhood CSVT exceeded that of neonatal AIS cases [70].

Recent data challenges the traditional notion that the highest risk of ischemic stroke occurs within the first week of life [120, 121]. Instead, the prevalence of ischemic strokes in children with COVID-19 remains consistent across all age groups [116]. This shift suggests a deviation from the typical early-life risk factors, with recorded ischemic strokes in older children highlighting a unique pattern of stroke occurrence associated with COVID-19 compared to the usual risk factors present within the first week of life [122, 123]. Furthermore, neonates infected with COVID-19 might exhibit mild or no clinical symptoms despite experiencing ischemic strokes, potentially leading to underreporting and reduced detection [124].

Several recognized risk factors contribute to the onset of AIS in pediatric patients, including congenital heart defects, infections, cancer, autoimmune disorders, genetic anomalies, and conditions that promote thrombosis [125]. Multiple studies have identified specific risk factors associated with ischemic stroke in pediatric COVID-19 patients, such as structural cardiovascular anomalies [126], anemia [117, 127], hemoglobinopathies, prior varicella infection [117], hematologic malignancies [128, 129], and systemic and central nervous system bacterial and tuberculous infections [130, 131].

Major cardiac issues were predominantly observed in pediatric patients experiencing Multisystem Inflammatory Syndrome in Children (MIS-C), often presenting with signs of cardiogenic shock. Echocardiographic evaluations revealed markers of cardiac dysfunction and the presence of intracardiac thrombi (cardioembolism) in these individuals [126, 132–134]. This underscores that COVID-19-related cardiac complications can serve as a potential pathway for arterial ischemic events in this pediatric cohort. Several hypotheses have been proposed to explain cardiac injury in the context of SARS-CoV-2 infection, including myocardial cell damage caused by elevated cytokine levels during systemic inflammation, direct viral-induced myocardial damage (viral myocarditis), and other factors such as abnormal heart rhythms resulting from electrolyte imbalances during the critical stage of the illness. Additionally, treatments involving drugs such as antivirals, immunotherapies, and steroids may also contribute to cardiac complications [135, 136].

Further research specifically focused on pediatric populations susceptible to stroke related to SARS-CoV-2 infection is necessary, incorporating both clinical investigations and laboratory experiments. This research is essential to understand the critical clinical parameters and outcomes, as well as the molecular and cellular mechanisms contributing to stroke occurrence in pediatric patients with COVID-19. Uncovering these details is crucial for enhancing early stroke diagnosis, preventing its occurrence, and developing effective management strategies.

6 Evaluating stroke risks and vaccination impact amidst COVID-19

The administration of COVID-19 vaccines has significantly reduced severe infections caused by the SARS-CoV-2 virus, with documented reductions of over 90% in hospitalizations and mortality rates [137, 138]. Despite these successes, persistent vaccine hesitancy characterized by indecision and uncertainty continues to hinder vaccination coverage [139]. Several factors contribute to this hesitancy, including the rapid development of vaccines, insufficient public knowledge, and concerns about side effects, which are typically mild and temporary [140]. As a result, there has been a concerted effort to investigate post-vaccination events, enabling healthcare providers to promptly assess vaccination risks and rebuild public confidence in COVID-19 vaccines.

A study in France highlighted an increased likelihood of hemorrhagic stroke (HS) within 28 days following Pfizer BNT162b2 vaccination and SARS-CoV-2 infection [141]. Similarly, a study in England examined the risk of ischemic stroke (IS) and CVST after COVID-19 vaccination, revealing uncertainties regarding the association between vaccination and stroke onset [142]. Subsequent systematic reviews of real-world data using cohort studies, self-controlled case series (SCCS), and case-crossover study (CCOS) methodologies produced conflicting findings. Cohort studies suggested a reduced risk of IS and HIT following vaccination, while SCCS indicated an elevated risk, particularly for CVST [143].

Longitudinal studies, comprising vaccinated and unvaccinated cohorts, compared outcomes over similar time frames to assess vaccine efficacy and safety [144, 145]. Although some studies noted disparities in demographic characteristics between groups, efforts were made to minimize biases through adjustments. Exclusion of SARS-CoV-2-positive individuals, with some exceptions due to testing limitations, demonstrated a significant protective effect of vaccines against infection and associated strokes [144–146].

In the first 21 to 28 days post-vaccination, SCCS studies identified an increased incidence of stroke subtypes, aligning with physiological responses triggered by vaccination, including immune activation and adaptive responses. The emergence of vaccine-induced immune thrombotic thrombocytopenia provided a plausible pathophysiological mechanism linking vaccination to IS and HS [147–150]. Different vaccine platforms showed varying risks, with mRNA vaccines associated with higher risks of IS and HS compared to the inactivated virus vaccine CoronaVac, which showed a reduced risk of HS within 2–3 weeks [151, 152].

Despite assumptions of no relationship between event occurrence and exposure in SCCS-designed studies, real-world applications may introduce selection biases. Cohort studies, which closely mirror real-world conditions, suggested less bias. Individuals at higher risk of stroke are advised to make informed decisions regarding vaccine selection based on their specific immunity needs against SARS-CoV-2. During the at-risk period, minimizing exposure to additional stroke triggers such as strenuous physical activity and emotional stress is crucial for prevention efforts [153].

A comprehensive meta-analysis of real-world data from 80 million individuals yielded conflicting results regarding the association between COVID-19 vaccination and acute stroke incidents [143]. While no significant increase in reported cases of acute stroke was observed post-vaccination, individuals at higher risk should carefully weigh the benefits and risks of vaccination. The research underscored the adverse impact of concurrent AIS and COVID-19, offering insights from a nationally representative sample [143]. Increased mortality from stroke during the COVID-19 pandemic in the United States highlighted the importance of understanding these interactions in future pandemics and subsequent COVID-19 surges [154].

After the introduction of the ChAdOx1-S (Oxford–AstraZeneca) vaccine, Norway reported five cases of severe venous thrombosis with thrombocytopenia within 7–10 days post-vaccination. Four of these cases involved cerebral venous sinus thrombosis [150], now classified as vaccine-induced immune thrombotic thrombocytopenia (VITT) [150, 155, 156]. Hypercoagulability and cerebral venous thrombosis (CVT) have been observed following both COVID-19 infection and vaccination, particularly with ChAdOx1-S. This vaccine has been associated with antiplatelet factor 4 antibodies, low platelet counts, and elevated d-dimer levels, characteristic of VITT [157].

A case–control study using logistic regression identified a higher prevalence of blood group O among patients with VITT-associated CVT following ChAdOx1-S vaccination compared to unvaccinated individuals, independent of other CVT risk factors [158]. This underscores the role of blood group O in VITT occurrence post-ChAdOx1-S vaccination. However, additional large-scale studies are essential to assess the safety implications for other blood groups. Furthermore, further experimental investigations are needed to elucidate the underlying mechanisms contributing to VITT following vaccination.

7 The risk of long COVID-19 on stroke incidences

COVID-19 is a complex multisystem disorder prominently featuring vascular endothelial injury [159, 160]. This endothelial damage contributes significantly to persistent symptoms lasting beyond four weeks post-onset of COVID-19, collectively termed "long COVID-19," which can profoundly impact affected individuals' quality of life [161–165].

The SARS-CoV-2 virus enters the host through ACE-2 receptors present in organs such as the lungs, heart, endothelial cells, intestines, and kidneys, leading to systemic endotheliitis and enduring symptoms. These symptoms commonly include fatigue, respiratory difficulties, chest pain, joint pain, heart irregularities, loss of smell and taste, hair thinning, cognitive impairments, and emotional strain [165–167].

Persistent endothelial dysfunction is hypothesized to contribute to long COVID-19 symptoms, as SARS-CoV-2 infection of endothelial cells can induce structural changes and programmed cell death that persist beyond the acute phase [168]. Evaluating endothelial function in recovering patients is crucial for early detection and prevention of long-term cardiovascular complications [159].

Understanding the incidence of persistent COVID-19 symptoms and their association with endothelial dysfunction in recovered individuals is paramount [78]. Risk factors such as advanced age, severe clinical conditions, underlying health issues, oxygen therapy, and hospitalization during the acute phase may exacerbate long COVID-19 symptoms [169–171].

Findings from the TUN-EndCOV study underscore that enduring symptoms like chest discomfort, fatigue, and non-respiratory neurocognitive issues in long COVID-19 are significantly linked to endothelial dysfunction, independent of age, sex, comorbidities, and severity of acute COVID-19 illness requiring oxygen therapy [78]. Multivariate analysis confirms endothelial dysfunction as a distinct risk factor for the long-term COVID-19 syndrome.

Case reports and initial investigations suggest that vascular responsiveness and microvascular function may not fully recover weeks to months after acute COVID-19 infection, highlighting persistent endothelial involvement [74, 172].

In a study, advanced age and subclinical left ventricular systolic dysfunction, assessed by LV global longitudinal strain (LVGLS), were identified as independent factors associated with impaired endothelial quality index (EQI) [78]. Subsequent investigations found subtle myocardial deformation characterized by decreased LVGLS in COVID-19 survivors, despite the absence of obvious myocardial damage. This observation suggests a potential link to inflammation affecting myocardial cells, oxygen deprivation, and impairment of the microvasculature due to endothelial dysfunction following COVID-19

infection [62, 173–179]. Changes in LVGLS may offer insights into the persistent occurrence of chest discomfort in individuals with prolonged COVID-19.

The association between cardiovascular disease (CVD) and COVID-19 is notable in patients experiencing long COVID. This condition frequently presents multimorbidity, prominently including CVD, highlighting the essential need for comprehensive, integrated care approaches. The cardiovascular risks linked to long COVID can place significant strains on healthcare resources. Therefore, successful management of long COVID hinges on addressing fundamental gaps in foundational research, clinical evidence, and patient care [180]. This understanding is pivotal for formulating effective strategies to manage and alleviate the enduring health consequences of the virus on cardiovascular health.

Shortly after the discovery of SARS-CoV-2, medical professionals observed that the infection not only causes acute respiratory issues but also leads to dermatological, cardiovascular, hepatic, and renal complications [181–183]. These complications, compounded by pre-existing health conditions, exhibit synergistic effects [184]. The likelihood of acute ischemic stroke is heightened during COVID-19, particularly among severely affected patients and those with pre-existing cardiovascular conditions [34, 185]. Pathophysiological mechanisms linking SARS-CoV-2 infection to ischemic stroke involve increased propensity for blood clotting, excessive cytokine release, pre-existing endothelial damage, and enhanced blood–brain barrier permeability [186–189]. Consequently, healthcare providers have adopted anticoagulant therapies to manage COVID-19-related coagulopathies, especially in the acute phase [190]. However, information on the long-term risk of ischemic stroke as a consequence of COVID-19 (known as post-acute COVID-19 sequelae or PACS) remains limited and conflicting [190, 191].

Meta-regression analysis indicated that stroke risk is directly influenced by age, female gender, hypertension, and obesity, while inversely associated with follow-up duration [192]. These findings are consistent with previous research showing elevated stroke risk during the acute phase of SARS-CoV-2 infection among elderly individuals, males, and those with hypertension [31, 39, 193]. It is important to note that conventional survival analysis may overestimate incidence rates in the presence of competing risks, especially if mortality rates are elevated due to factors unrelated to the disease under study [25].

The exact mechanisms underlying stroke occurrence in recovered COVID-19 patients remain elusive. Persistent inflammation and cytokine storms may activate platelets and initiate the coagulation cascade, potentially leading to cerebrovascular complications [60, 194, 195]. Factors such as hypoxia or hypotension observed in long-COVID syndrome could impair cerebral autoregulation, contributing to ischemic cerebrovascular events. Endothelial inflammation induced by SARS-CoV-2 could destabilize pre-existing atherosclerotic plaques, triggering ischemic cerebrovascular damage [196, 197]. Some individuals may experience symptomatic or asymptomatic episodes of atrial fibrillation, which have been identified as potential consequences of SARS-CoV-2 infection [198–200].

Recent studies have highlighted various acute and persistent cardiovascular issues that may manifest shortly after contracting COVID-19, including pulmonary embolism, deep vein thrombosis, myocardial dysfunction, elevated arterial pressure, arrhythmias, and diabetes [182, 198, 199, 201, 202]. However, it remains uncertain whether these cardiovascular complications directly stem from COVID-19 or exacerbate underlying medical conditions.

8 Concluding remarks

COVID-19 extends its impact well beyond respiratory complications, significantly increasing susceptibility to cardiovascular issues such as stroke [11]. This broader impact emphasizes the critical need to consider neurological implications and overall health in the comprehensive management of COVID-19 cases.

The development of strokes in COVID-19 patients arises from a multifaceted interplay involving healthcare access, standards, individual behaviors, and biological factors. Comprehensive understanding of these determinants is crucial for formulating effective stroke prevention strategies and targeted interventions specific to COVID-19 patients. This is particularly pertinent due to the virus's propensity to increase stroke risk through various pathophysiological mechanisms (Fig. 1) [203].

During the acute phase of COVID-19, especially among severely ill hospitalized patients, there is a crucial window when stroke occurrences are influenced by specific factors such as hypertension, atrial fibrillation, diabetes, prior stroke history, age, and biological sex [32]. Future research efforts should focus on elucidating these complex predisposing factors to refine management strategies for cardiovascular complications, including stroke, associated with COVID-19.

The intricate relationship between SARS-CoV-2 and the vascular system encompasses various pathogenic mechanisms contributing to COVID-19-associated strokes, including endothelial dysfunction, cytokine storms, increased coagulability,

and direct effects on blood vessels [103, 204]. Understanding these complexities across molecular, cellular, and clinical domains is essential for both immediate clinical management and the mitigation of long-term complications such as persistent endothelial dysfunction.

Future research should aim to elucidate the mechanistic links between COVID-19 and the onset of stroke. Key areas of investigation should include identifying endothelial injury and hypercoagulable states at both micro and macro levels and assessing inflammatory markers along with the development of prothrombotic autoantibodies. Incorporating vessel wall imaging can enhance our understanding of vasculopathy and help quantify stroke patterns in COVID-19 patients. However, imaging in critically ill patients presents challenges due to infection risks and strict isolation protocols, which may result in data misrepresentation.

While COVID-19 vaccines have demonstrated efficacy in reducing severe outcomes, ongoing research is necessary to clarify their impact on stroke risk, particularly across different vaccine platforms [205]. High-risk individuals should consider vaccine options based on individual health needs [143], emphasizing the importance of continued investigation into vaccination's role in preventing COVID-19-related strokes.

Beyond the acute phase, the persistence of COVID-19 as long COVID-19 underscores its profound impact on cardiovascular health, including an increased risk of stroke among vulnerable populations [206–208]. Addressing these challenges mandates sustained research efforts to comprehensively understand the virus's long-term cardiovascular implications and to establish comprehensive strategies for managing stroke risk in COVID-19 patients. The post-acute sequelae of COVID-19 pose a challenging landscape for clinicians, highlighting the necessity for ongoing research to unravel the intricacies of the virus's enduring effects on cardiovascular health, including stroke.

Many studies examining the relationship between COVID-19 and stroke may be subject to inherent biases, such as retrospective designs, varying methodologies, and limited sample sizes. Future research efforts should prioritize well-controlled studies that integrate multiple parameters and measures to provide more robust evidence on the significance of stroke in COVID-19 patients. Addressing these limitations is crucial for advancing our understanding of stroke pathophysiology in the context of COVID-19 and for informing effective clinical management strategies.

This review underscores the importance of investigating both conventional and novel mechanisms underlying stroke in COVID-19 patients. By leveraging the isolation of SARS-CoV-2 for laboratory research alongside continuous access to clinical data, researchers can explore diverse cellular and molecular pathways contributing to stroke development. This integrative approach may yield insights into potential biomarkers and therapeutic targets, ultimately enhancing strategies for stroke detection, prevention, and treatment in individuals affected by COVID-19.

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Declarations

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