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REVIEW

Epidemiology, pathogenesis, and management of coronavirus disease 2019-associated stroke

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Abstract **The coronavirus disease 2019 (COVID-19) epidemic has triggered a huge impact on healthcare, socioeconomics, and other aspects of the world over the past three years. An increasing number of studies have identified a complex relationship between COVID-19 and stroke, although active measures are being implemented to prevent disease transmission. Severe COVID-19 may be associated with an increased risk of stroke and increase the rates of disability and mortality, posing a serious challenge to acute stroke diagnosis, treatment, and care. This review aims to provide an update on the influence of COVID-19 itself or vaccines on stroke, including arterial stroke (ischemic stroke and hemorrhagic stroke) and venous stroke (cerebral venous thrombosis). Additionally, the neurovascular mechanisms involved in SARS-CoV-2 infection and the clinical characteristics of stroke in the COVID-19 setting are presented. Evidence on vaccinations, potential therapeutic approaches, and effective strategies for stroke management has been highlighted.**

Keywords SARS-CoV-2; ischemic stroke; stroke; hemorrhagic stroke; cerebral venous thrombosis; vaccination

Introduction

The World Health Organization declared coronavirus disease 2019 (COVID-19) a global pandemic on March 11, 2020, which was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Only two human-tropic coronaviruses have resulted in epidemics, and cerebrovascular diseases have rarely been reported [1–3]. An increasing number of investigations have revealed an association between SARS-CoV-2 infection and the cerebrovascular system over the past 2 years. Approximately 76.8% of patients admitted to neurological wards after COVID-19 showed stroke-like symptoms, of which nearly half were diagnosed with stroke [4]. COVID-19 is 7.6 times more likely to cause stroke than influenza [5], and the occurrence of stroke in patients with COVID-19 complicates treatment, notwithstanding the elongated interval between stroke onset and hospital admission and the notable reduction in admissions during the COVID-19 pandemic [6–8]. Moreover, patients with COVID-19 and stroke have a higher risk of intensive care unit (ICU) hospitalization, disease progression, and poor clinical outcomes [9–11]. Additionally, vaccines are associated with immune thrombotic thrombocytopenia [12].

This review aims to present a comprehensive update on the impact of COVID-19 and vaccines on stroke, specifically highlighting the distinct characteristics of arterial and venous strokes. Given the ongoing global presence of COVID-19 and the severity of stroke as both a comorbidity and a complication, it is crucial to understanding underlying neurovascular mechanisms, clinical manifestations, potential therapeutic approaches, and effective management strategies for stroke (Fig. 1).

Search methodology and selection criteria

A comprehensive search strategy was employed to identify the relevant literature pertaining to the

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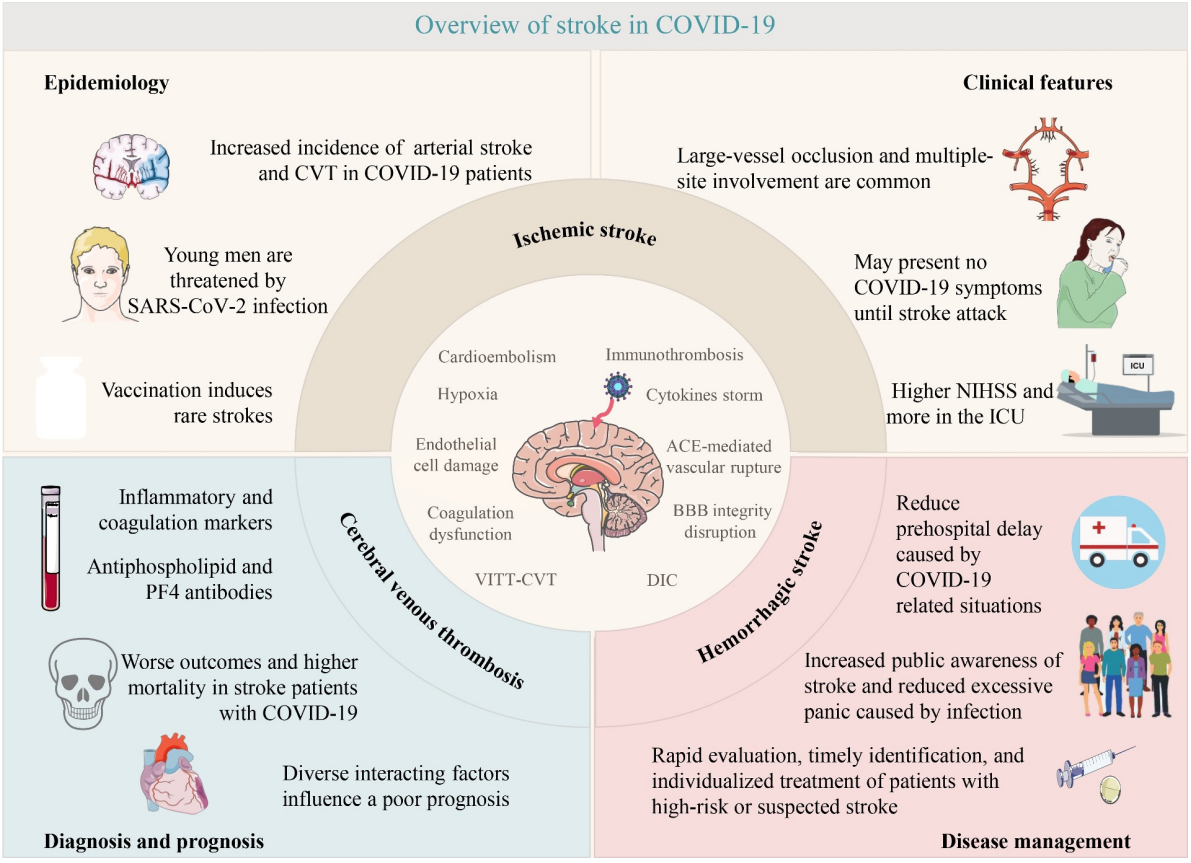

Fig. 1 Overview of stroke in patients with COVID-19. CVT, cerebral venous thrombosis; NIHSS, National Institutes of Health Stroke Scale; ICU, Intensive Care Unit; PF4, platelet factor 4.

intersection of COVID-19 and stroke. PubMed, MEDLINE, and Scopus databases were meticulously searched from their inception to April 30, 2023. The search was restricted to articles published in English and involving human subjects, aligning with the scope of this investigation. A combination of pertinent terms were utilized, such as "COVID-19," "novel coronavirus," "SARS-CoV-2," or "coronavirus" in conjunction with terms, including "stroke," "cerebrovascular disease," "cerebrovascular accident," "brain infarction," "ischemic stroke," "intracranial hemorrhage," "intracerebral hemorrhage," "hemorrhagic stroke," "cerebral venous thrombosis," and "cerebral venous sinus thrombosis," and tailored to each database's search capabilities. This strategy facilitated a comprehensive retrieval of relevant studies. We scrutinized the reference lists of the identified studies to uncover additional pertinent articles. Furthermore, we engaged with experts to mitigate the risk of overlooking significant preprints and unpublished research findings.

To ascertain methodological soundness and reliability of the included major cohort studies, we used the Newcastle-Ottawa Scale (NOS) for quality assessment. The outcomes of this assessment are succinctly presented in Table S1 for reference.

Epidemiology of stroke during the COVID-19 pandemic

The epidemiology of stroke demonstrated changes in individuals infected with COVID-19 compared with the general population, which has a 3% prevalence of stroke. Ho *et al.* [13] demonstrated an incidence rate ratio (IRR) of 4.22 (95% confidence interval (CI) 2.50–7.12) for ischemic stroke in nonhospitalized patients with COVID-19 during the initial week following infection. Interestingly, the IRR considerably decreased to 0.51 (95% CI 0.19–1.37) during the subsequent two or three weeks of observation. By comparing stroke risk between nonhospitalized patients with COVID-19 and those without COVID-19, the study indicated an elevated stroke risk within the first week post-SARA-CoV-2 infection. However, this risk diminished over time after infection, aligning with the findings from other investigations reporting stroke ratios in a range of 1%–2% from the second week to six months after infection [14,15]. Notably, this risk can escalate to 6% in the ICU setting [16]. Thirty-one (1.6%) of 1916 COVID-19 patients had acute ischemic stroke (AIS) in another retrospective cohort study in two New York City hospitals, and the median time from the onset of

COVID-19 symptoms to stroke diagnosis was 16 days (IQR 5–28 days) [5].

Ischemic stroke has a higher prevalence than hemorrhagic stroke in patients with COVID-19, having an overall prevalence of 1.11% (95% CI 1.03%–1.22%) in a cohort of 58 104 patients with COVID-19. This rate was higher than that in another group of 67 155 patients with COVID-19 (0.46%; 95% CI 0.40%–0.53%). Within the subset of patients with COVID-19 who experienced stroke, ischemic stroke was more prominent than hemorrhagic stroke (71.58% and 28.42%, respectively) [17]. Notably, the incidence of hemorrhagic stroke displayed variability across different stroke types in patients with COVID-19 in another systematic review [18–21]. This variation can be attributed to differences in study quality and assessment criteria.

The number of reports on cerebral venous thrombosis (CVT) in the context of COVID-19 is increasing in the literature. This increase is notable because the anticipated rate of CVT is only 2–5 per million per year in the general population and constitutes 0.5%–1% of all stroke types. However, different cohorts have reported varying instances of CVT according to distinct inclusion criteria [22–24]. Whereas CVT was diagnosed in only 0.001% of patients with SARS-CoV-2 in Singapore [25], multicenter cohorts of hospitalized patients with COVID-19 showed an increase from 0.02% to 1% [26–29]. Moreover, Tommaso *et al.* [30] reported in a meta-analysis that the estimated frequency of CVT among patients hospitalized for COVID-19 was 0.08% (95% CI 0.01–0.5, P = 0.007), and CVT accounted for 4.2% of the cerebrovascular complications in patients with COVID-19 (cohort of 406 patients, 95% CI 1.47–11.39, P = 0.02). Another study of 171 stroke centers from 49 countries reported that the incidence of CVT hospitalization volume as COVID-19 progressed was higher than in patients without COVID-19 [31]. A large study of electronic health record data found increased rates of CVT in patients after SARS-CoV-2 infection (42.8 per million people, 95% CI 28.5–64.2), whether compared with a matched cohort receiving mRNA vaccine or suffering from influenza virus infection [32].

Risk factors for stroke in patients with COVID-19

Patients with COVID-19 and ischemic stroke have stroke-associated risk factors, such as atrial fibrillation, coronary artery disease, diabetes mellitus, hyperlipidemia, hypertension, and obesity [4,21,33–35]. For example, approximately two-thirds of a cohort of 300 severely ill patients with COVID-19 were either obese or overweight [36]. Another multicenter retrospective study in China reported that 63.0% of patients who went into stroke after SARS-CoV-2 infection had a combination of other chronic diseases, including hypertension, diabetes, and cardiovascular disease [37]. Additionally, a previous history of cerebrovascular disease may be associated with an increased risk of stroke and mortality in patients with COVID-19 [38]. Moreover, severe infectious diseases have been associated with stroke in patients with COVID-19 (OR = 5.10, 95% CI 2.72–9.54) [21]. Moreover, severe COVID-19 was more likely to be associated with combined stroke than mild COVID-19 (OR = 1.95, 95% CI 1.11–3.42, P = 0.020) [39]. Men seem to be more likely to suffer an ischemic stroke when infected with SARS-CoV-2 than women [40] because women are affected less frequently (150/395 vs. 773/1670; OR = 0.71 (95% CI 0.51–0.99)) [21].

Risk factors for CVT have been inconsistently reported and can be classified as hereditary thrombophilia factors (e.g., protein C, protein S, and antithrombin III deficiency) [41,42], acquired thrombophilia factors (antiphospholipid syndrome, nephrotic syndrome, and hyperhomocysteinemia) [43,44], or sex-specific factors (oral contraceptives and pregnancy) [45,46]. However, the abovementioned known risk factors for CVT independent of COVID-19 were reported in 30.6% of 35 patients [30].

Pathogenesis of COVID-19-associated stroke

The mechanisms that induce COVID-19-associated stroke have not been fully elucidated because the virus is still being studied. The accumulation of excess quantities of angiotensin II (Ang II), endothelial cell damage, dysregulated activation of the coagulation cascade, and overproduction of proinflammatory cytokines contribute to the prothrombotic state (Fig. 2) [47].

Pathogenesis of COVID-19-related arterial stroke

Although the precise dominance of a particular mechanism underlying COVID-19-associated stroke remains a subject of ongoing discourse, the convergence of intricate factors orchestrates the manifestation of hemorrhagic and ischemic strokes in COVID-19-inflicted individuals. Notably, ischemic stroke in patients afflicted by COVID-19 is often attributed to prevalent factors, such as hypercoagulability, endothelial cell impairment, immunothrombosis, cardio embolism, and hypoxia. The genesis of hemorrhagic stroke in the context of COVID-19 is thought to involve multifarious elements encompassing angiotensin-converting enzyme 2 (ACE2)-modulated vascular rupture, immune responses, cytokine storm, and perturbations in the endothelial integrity of the blood-brain barrier (BBB) [48,49].

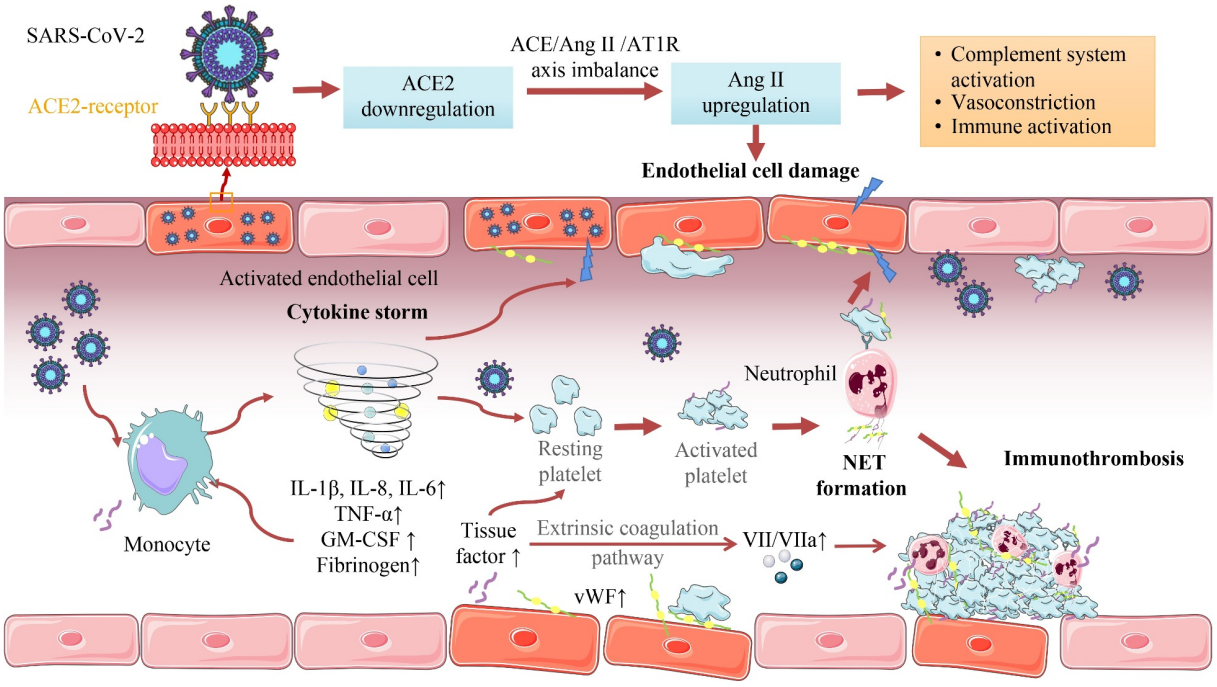

Fig. 2 Main mechanisms of COVID-19-associated stroke. The ACE2 receptor on the endothelial cells interacts with the spike protein of SARS-CoV-2. This interaction reduces productive ACE2 and increases Ang II levels. Pathogen-associated antigens activate monocytes, releasing a proinflammatory cytokine storm, which increases TF expression and fibrinogen production and promotes platelet hyperactivation. TF activates the extrinsic coagulation pathway and promotes the expression of coagulation factor VII/VIIa. The impaired endothelium also exposes vWF, which exacerbates platelet aggregation. NET formation generates a thrombotic-inflammatory response and facilitates thrombosis. The interaction among cytokine storm, endothelial cell damage, ACE/Ang II /AT1R, and coagulation dysfunction ultimately leads to thrombosis and hemorrhage. ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II; TF, tissue factor; vWF, von Willebrand factor; NETs, neutrophil extracellular traps.

Cytokine storm and immunothrombosis

SARS-CoV-2 enters cells after SARS-CoV-2 infection, undergoes viral replication, and is released into the bloodstream. Pathogen-associated antigens contribute to the production of proinflammatory tumor necrosis factor (TNF) and chemotactic cytokines by activated monocytes, and promote an increase in interleukin (IL)-6, which in turn induces granulocyte-macrophage colony-stimulating factor. Persistent viremia accompanied by a positive feedback loop can produce high levels of proinflammatory cytokines, which may eventually cause a “cytokine storm” [50] characterized by an excessive release of C-reactive protein and proinflammatory cytokines, such as TNF-α, IL-α, IL-8, and IL-6 [51,52]. TNF-α and IL-6 can lead to hypercoagulation by disrupting endothelial cell ligand proteins [53]. Additionally, IL-6 may cause microvascular injury by triggering acute endothelial cell activation [54] and activating an acute phase response, thereby increasing fibrinogen production by hepatocytes, increasing tissue factor (TF) expression, and promoting platelet hyperactivation and aggregation [55–57]. Furthermore, TNF-α and antiphospholipid antibodies are elevated because COVID-19 upregulates the expression of TF in endothelial cells, platelets, neutrophils, and macrophages; this effect is an important factor influencing the cascade activation of the coagulation system [58,59]. TF promotes the expression of coagulation factors VII/VIIa in the TF-involved extrinsic coagulation pathway, leading to increased thrombin production, which further activates the conversion of fibrinogen to fibrin and the production of fibrin-based clots [60]. Interaction between inflammatory response and coagulation factors ultimately leads to severe coagulation dysfunction and thrombosis [51,61].

COVID-19-associated stroke may occur through different mechanisms, such as an innate immune and immunoinflammatory-mediated hypercoagulability rather than atherosclerosis [4,62]. The concept of “immunothrombosis” has been proposed, whereby platelets, TF, endothelial cells, and innate immune effector systems (macrophages, neutrophils, and complement systems) interact with one another and form neutrophil extracellular traps (NETs) during infection, thereby activating the external coagulation cascade via interaction with platelets [63–65], generating a thrombotic–inflammatory response that induces further endothelial damage and leads to increased thrombin production. In turn, activated platelets enhance NET

formation and amplify thrombosis [66,67]. This apparent neutrophil–platelet activation pattern represents the severity of COVID-19 and the systemic hypercoagulable state [68].

Endothelial cell damage

Endothelial dysfunction is closely associated with coagulation abnormalities and arterial and venous thrombosis and cannot be separated from the interaction among thrombotic inflammation, cytokine storm, and ACE2 downregulation. SARS-CoV-2 occupies the ACE2 receptor as a portal into host cells [69], affecting normal balance in the renin–angiotensin system (RAS), leading to the excessive activation of the ACE–Ang II–angiotensin type 1 receptor axis, and resulting in the reduction of productive ACE and increase in Ang II levels [70]. Ang II increases capillary permeability, induces the transcription and expression of TF in endothelial cells, and activates thrombogenic factors [58]. Additionally, it triggers the release of certain complement system components from endothelial cells [71]. ACE-mediated vascular rupture cannot be ignored in COVID-related hemorrhagic stroke, especially that ACE2 receptors are expressed in the endothelial cells of the brain and arterial smooth muscle cells. The direct damage of intracranial arteries may be caused by the affinity of SARS-CoV-2 to ACE2 receptors and leads to the dissection or rupture of the vessel wall. This damage is associated with the development of hemorrhagic stroke [21]. The dysregulation of the RAS system leads to the enhanced availability of angiotensin II, which also induces vasoconstriction, immune activation, and vasogenic edema. Plasma Ang II levels are significantly higher in patients with COVID-19 pneumonia than in healthy controls, and plasma Ang II level in patients with COVID-19 is correlated with viral load and lung injury [72]. Furthermore, in the cerebral thrombi of patients with COVID-19, the ACE2 receptor interacts with the spike protein of SARS-CoV-2 and is predominantly expressed in monocytes or macrophages at higher levels than that in controls [73]. An impaired endothelium releases factor VIII and exposes von Willebrand factor (vWF), which exacerbates platelet aggregation. Unusually large vWF (ULvWF) activates platelet adhesion to endothelial cells and promotes thrombosis [74]. The pre-thrombotic alterations of the multiple factors described above further confirmed the critical role of the endothelium in venous and arterial thrombosis in patients with COVID-19.

Endothelial dysfunction may contribute to ischemic or hemorrhagic stroke caused by SARS-CoV-2 involving direct and indirect endothelial toxicity [75–77]. The first mechanism is caused by viral invasion of endothelial cells, leading to viral replication and subsequent apoptosis, vasculitis, and local inflammation in various organs, including the lungs, heart, and kidneys, which may also affect the brain [78]. However, the precise contribution of this mechanism to the development of ischemic stroke in patients with COVID-19 remains unclear. The second mechanism is mediated by systemic factors, such as the excessive production of prothrombotic factors and inflammatory cytokines, activation of the coagulation cascade, and complement-mediated microvascular thrombosis [79, 80]. In particular, the cytokine storm accompanying an immune response can induce the degradation of the critical components of blood vessels, including matrix metalloproteinases, tight junction (TJ) proteins, and extracellular matrix (ECM), increasing the permeability of the BBB, rupturing of blood vessels, and thereby contributing to the development of hemorrhagic stroke [17,81].

Brain tissue biopsies from patients with COVID-19 and hemorrhagic stroke show signs of thrombotic microangiopathy and endothelial injury without evidence of vasculitis or necrotizing encephalitis [82]. Moreover, the disruption of BBB integrity may explain hemorrhagic transformation in ischemic stroke and hemorrhagic posterior reversible encephalopathy syndrome reported in some patients with COVID-19 [83].

Dysregulated function of the coagulation

One of the features of patients with severe COVID-19 is a coagulation disorder accompanied by elevated D-dimer, fibrinogen, and thrombocytopenia, which is similar to sepsis-induced coagulopathy (SIC). These components are all associated with infection-induced systemic inflammatory responses with endothelial dysfunction and microthrombosis, which may increase the risk of thrombosis and stroke [52,84]. This effect explains why young patients lack common vascular risk factors. For example, the microthrombosis of small penetrating arteries and dissection of large arteries have been associated with stroke during SARS-CoV-2 infection [85]. In addition, fibrinogen-depleting coagulopathy secondary to metabolic acidosis, and DIC increase the risk of hemorrhagic stroke [85]. However, reduction in platelet levels in COVID-19 is much lower than that in SIC and DIC [86]. Most patients with DIC exhibit severely reduced plasma concentrations of natural anticoagulants. By contrast, COVID-19-associated coagulation abnormalities often do not have true consumption coagulation dysfunction [87,88]; therefore, severe thrombocytopenia and intravascular hemolysis are not the key features of COVID-19 [89].

The contribution of antiphospholipid (APL) to ischemic stroke in patients with COVID-19 is controversial, although the presence of APL antibodies is associated with a prothrombotic state. Zhang *et al.* [90] described coagulation dysfunction and multiregional infarcts, as

well as anticardiolipin and anti-β_2 microglobulin antibodies in three patients with COVID-19, while a substantial study reported that more than half of the patients with COVID-19 had lupus anticoagulant positivity [91].

Cardioembolism

SARS-CoV-2 may indirectly contribute to ischemic stroke by affecting the cardiovascular system [21], and various manifestations have been introduced through which SARS-CoV-2 increases the risk of thrombosis and stroke by damaging cardiomyocytes, including viral myocarditis, systemic inflammatory response related to the cytokine storm, destabilizing coronary plaques, and exacerbating hypoxia [85,92]. All these factors may cause arrhythmias, heart failure, and subsequent intracardiac thrombus formation, and when combined with a hypercoagulable state, increase the likelihood of cardiogenic stroke [93]. Moreover, 21.9%–40% of ischemic strokes associated with COVID-19 are cardiogenic embolisms [21,34,94], explaining why young people with COVID-19 develop large artery occlusion with high levels of D-dimer, pulmonary embolism, or venous thrombosis in the absence of any vascular risk factor and present with rare large artery atherosclerosis and plaque rupture [95, 96].

Hypoxia

Hypoxia is common in patients with COVID-19 and may contribute to cerebrovascular events [97]. Brain histopathology in patients who died from COVID-19 showed hypoxic changes [98], and failure to match oxygen supply and demand may result in infarction in patients with preexisting intracranial stenosis [99]. Additionally, cerebral perfusion deficits secondary to RAS downregulation can increase the risk of large-vessel and SVD infarctions, as demonstrated by the typical border–zone distribution [100,101]. Hypoxemia increases the expression of hypoxia-inducible factor, which directly activates platelets and coagulation factors, increases TF expression, and inhibits anticoagulant protein S production [102]. Moreover, hypoxia can promote further inflammation by inducing the excessive secretion of proinflammatory mediators, such as TNF-α and IL-1 [71,103], aggravating coagulation disorders and ischemia.

Pathogenesis of COVID-19-related venous stroke

A potentially strong association between venous stroke and COVID-19 has been demonstrated, and several possible mechanisms that initiate a prethrombotic state have been proposed, including endothelial damage, excessive inhibition of fibrinolysis, platelet dysfunction, increased blood viscosity, and sepsis-related coagulopathy [30,65,104]. In addition, venous thrombosis can be caused by systemic inflammation or cytokine storms, direct immune-mediated post-infection mechanisms, or virus-induced vasculitis [76,78].

Clinical features of stroke during the COVID-19 pandemic

Clinical symptoms

COVID-19-related cerebrovascular events occur on an average of two weeks after infection; however, many patients do not present any COVID-19 symptoms until a stroke attack, and the time delay between the first COVID-19 symptoms and stroke onset is 8 days [21,105]. Stroke severity is high in the setting of COVID-19, as evidenced by high National Institutes of Health Stroke Scale (NIHSS) scores [82] and considerably higher rate of admission to ICU than hospital admission (2.7% vs. 1.3%) [4,10]. The clinical presentation of stroke in the context of COVID-19 exhibits distinct characteristics owing to the involvement of arteries or cerebral veins.

COVID-19-related ischemic stroke

The three most common ischemic stroke symptoms reported in COVID-19-related case reports are unilateral limb weakness, altered mental status, and dysarthria. Altered mental status was more prominent in patients with COVID-19 combined with AIS than in patients without COVID-19 (51.4% vs. 15%–23%) [105, 106].

The age distribution of patients with ischemic stroke is altered by the effect of COVID-19 (Table 1). Approximately, 36% of patients with COVID-19 and AIS are < 55 years old, much higher than the pre-pandemic rate (12.9%–20.7%) [62]. Additionally, Majidi *et al.* [107] reported that the incidence of large-vessel occlusion (LVO) in patients showed a clear age cutoff due to COVID-19 infection. In patients aged ⩽50 years, an incidence of 10% in patients without COVID-19 is consistent with the pre-pandemic period; and an incidence of 25%, with those with co-infection.

Wang *et al*. [108] found that young COVID-19 patients with LVO have a high thrombus load, propensity for multiple occlusions, and thrombus fragmentation when undergoing mechanical thrombolysis, whereas older patients with COVID-19 and ischemic stroke are more likely to have preexisting cardiovascular comorbidities and severe infections [109–113]. Thus, patients with ischemic stroke in combination with SARS-CoV-2 pneumonia tend to be young, are prone to severe anterior circulation LVO with large infarct core volumes, and have high risk of multiple-vessel occlusion and adverse outcomes. Notably, Alberto *et al*. [1] summarized the

Table 1 Discrepancies among different stroke populations

Aspect	Stroke with COVID-19	Stroke without COVID-19	References
Demographics	More young patients (⩽50 years)	Older (average age > 50 years)	[21, 62, 114]
	Male predisposition	Higher incidence in older men	
Risk factors	Fewer vascular risk factors	Nonmodifiable risk factors: age, sex, genetics	[21, 40, 114, 172, 209, 210]
	Combined risks could increase disease severity	Modifiable factors: hypertension, hyperlipidemia, etc.	
	More severe infectious disease	Common risks in young: extracranial arterial dissections, inflammatory arteriopathies, cardiomyopathy, antiphospholipid syndrome	
Stroke subtype and imaging characteristics	Larger vessel occlusion, cryptogenic stroke, followed by cardioembolic stroke	More small vessel disease	[21, 26, 29, 62, 107, 109, 113, 150, 209, 211]
		Men: more likely to suffer lacunar infarction	
	Less small artery stroke	Women: more likely to suffer cardioembolic stroke	
	Multiple arterial territory involvement	Children under 15 years old : congenital heart disease, nonatherosclerotic vasculopathies, infection, and hematologic defects, such as sickle cell disease, etc.	
	No significant difference between different populations due to limited data	Patients between 15–35 years old: dissection, cardio embolism, nonatherosclerotic vasculopathies, and prothrombotic states, etc.	
Clinical symptoms and severity during hospital	Common neurological manifestation: fatigue, fever	Adults: the sudden onset of a focal clinical deficit: hemiparesis, hemianesthesia, aphasia, homonymous hemianopsia, and hemispatial inattention, etc.	[209, 212, 213]
	Higher NIHSS score and in-hospital mortality, longer hospital stays	Children: atypical presentations	
	Often requiring intubation, ICU admissions		
Clinical prognosis	Worse prognosis, higher 90-day mortality	Younger patients: lower short-term mortality rates, long-term follow-up revealed a surplus of mortality	[82, 94, 172, 209, 214]
	Mortality correlation with age, especially >25 years old	Older patients: excess long-term mortality	

NIHSS, National Institutes of Health Stroke Scale; ICU, Intensive Care Unit.

distinctive clinical characteristics of young-onset cases of stroke (< 50 years) during the COVID-19 epidemic: rare or no prior risk factors and comorbidities [2], stroke often occurs before the onset of COVID-19 symptoms [3], large-vessel occlusion is common, and [4] COVID-19 seems to play a major role in stroke occurrence in previously healthy populations [16]. NIHSS scores and severity of clinical presentations are substantially high after ischemic infarction in young individuals lacking vascular risk factors [114,115]. We speculate that these conditions are related to intensified immune response and cytokine storm produced by young people in response to COVID-19. Thus, clarifying the mechanisms involved may be the key to improved prognosis.

In a single-center retrospective analysis of COVID-19 patients with AIS in Spain [82], stroke with undetermined etiology was the most common (52.9%), followed by a cardioembolism (CE). The incidence of large vessel occlusion increased to 40.9%–79.6% of ischemic stroke in patients with COVID-19 [21,62,115–118], compared with 24%–38% in the population without COVID-19 [119,120]. The occurrence of posterior circulation stroke was more frequent than expected in some studies (35.3%) [94]. Cryptogenic stroke, which accounts for 19.6%–28% of the cases in the general population [121], is more prevalent in COVID-19 than it is in ischemic stroke cases (42.6%–66%) [94,122–126]. Similarly, a meta-analysis based on 10 studies from different countries showed that cryptogenic stroke was significantly more prevalent in patients with ischemic stroke associated with SARS-CoV-2 pneumonia, with a combined prevalence of 35% (95% CI 12%–59%; $P < 0.01$) [40]. However, John *et al*. [114] concluded that the difference was not significant (31.82% vs. 42.11%, $P = 0.183$), although the number of cases of cryptogenic stroke was higher. Differences in population inclusion and patients' infectious conditions may account for these differences; however, these studies showed that the SARS-CoV-2 epidemic significantly complicates the subtype distribution of ischemic stroke. In addition, the incidence of lacunar cerebral infarction due to small vessel occlusion was only 2% (95% CI 0%–5%; $P = 0.44$), much lower than the 20%–30% reported in most previous studies mentioned before the outbreak of SARS-CoV-2 pneumonia [40,127,128], and the reasons behind this finding warrant further exploration.

COVID-19-related hemorrhagic stroke

The relationship between COVID-19 and hemorrhagic stroke remains controversial, and a relatively low incidence of COVID-19-associated primary intracranial hemorrhage or subarachnoid hemorrhage has been observed; most hemorrhages are likely caused by the hemorrhagic transformation of ischemic stroke [129]. Difference in the acceptance of patients with hemorrhagic stroke between centers affected by the COVID-19 pandemic may have influenced the results of the study. For example, a large medical center in China reported that patients with hemorrhagic stroke admitted during the COVID-19 pandemic were markedly fewer than in the pre-pandemic period, and the severity of hemorrhagic stroke in hospitalized patients was lower than that in the pre-pandemic period [130]. By contrast, another study in the United Arab Emirates showed that more patients with hemorrhagic stroke were admitted to the hospital than before the pandemic; however, no significant differences were found in age, sex, presence of vascular risk factors, severity, and prognoses in patients with hemorrhagic stroke who were not infected with SARS-CoV-2 during the same period and before the pandemic [114].

Several studies have further explored the pattern of presentation of COVID-19-related hemorrhagic stroke, suggesting that 11%–41% of patients present with neurological symptoms [131]. Interestingly, in 216 patients with hemorrhagic stroke, who were included in 11 studies, hospitalization for respiratory symptoms was more common than that for neurological symptoms (20.83% vs. 6.94%), and the rest had no definite neurological or respiratory symptom episodes (156/216, 72.22%) [17]. The initial symptoms and course of the disease seem to be important to predicting the severity of systemic disease, as patients with a respiratory onset suggest more severe COVID-19 with abnormal vital signs, markedly elevated markers of inflammation and coagulopathy, and altered mental status and may require mechanical ventilation and ICU care [17,132].

Kvernland *et al*. [133] showed that the median age of patients with COVID-19-related hemorrhagic stroke was 60 years in their cohort, and males were predominant (78.9%). The patients had higher NIHSS scores than historical and contemporary controls without SARS-CoV-2 infection; however, patients with COVID-19-associated hemorrhagic stroke were less likely to have deep cerebral hemorrhage, consistent with the low incidence of hypertension at the time of diagnosis and low systolic blood pressure. However, Romero *et al*. [131] hypothesized that the primary mechanism of hemorrhagic stroke in patients with COVID-19 presenting with neurological symptoms may be related to a hypertensive crisis because multifocal bleeding in their cohort was significantly associated with pulmonary symptoms and the presence of a typical location of hypertensive hemorrhage.

COVID-19-related venous stroke

Patients with COVID-19-associated CVT seem to be older than previously reported classical patients with CVT without SARS-CoV-2 infection (49.26 vs. 37.77 years) [134–136] possibly because older patients seem to be more susceptible to SARS-CoV-2 infection. Thus, the average age of patients with CVT had been expected to increase during the COVID-19 epidemic. The clinical presentation of COVID-19-related CVT is highly heterogeneous, similar to that of classical CVT, and new-onset, severe, and persistent headaches are the most common symptoms, followed by focal neurological deficits, seizures, and impaired consciousness. The sex difference is likely to be less significant, as one multicenter study reported that 25% of CVT cases in the context of COVID-19 were predominantly in individuals under 25 years of age with male predominance [24,29].

The results of several meta-analyses have shown that patients with COVID-19-associated CVT commonly occur in the transverse sinus (65%–75%), sigmoid sinus (47%–50%), and superior sagittal sinus (44%). Additionally, multiple venous involvements are more common than single-vessel thrombosis (67% vs. 33%) [30], whereas in another study, only 27.8% of the patients had multiple sinus or venous involvement, which was significantly lower than previously reported in patients with non-SARS-CoV-2 infection [62]. The above difference is believed to be a result of the high severity of the disease in patients with multiple CVT, which obscures correct diagnosis. Furthermore, the involvement of the deep venous sinus system (33.3%) is common in patients with COVID-19 and may be related to the much higher mortality rate in COVID-19 patients (45.5%) as compared with that in a non-COVID-19 population (15%) [137].

Laboratory indicators

Inflammatory and coagulation tests based on SARS-CoV-2 infection status showed significant differences in acute-phase protein and coagulation profiles between patients with COVID-19 and stroke and controls [26,138]. Significant increases in D-dimer (≥1000 μg/L) and lactate dehydrogenase (LDH) levels were observed in patients with ischemic stroke in conjunction with vascular occlusion [94,109,139]. Systemic inflammation and hypercoagulability are present even in the absence of a significant cardiogenic embolism or arterial disease [140], exhibiting high levels of baseline inflammatory markers

(leukocytes and C-reactive protein) and coagulation markers (D-dimer and fibrinogen) [105,141]. Elevated D-dimer levels are prevalent in patients with COVID-19 and coexisting ischemic and hemorrhagic strokes and are correlated with higher all-cause mortality [94]. In addition, abnormal activated thrombogenic time and elevated D-dimer levels increase the risk of CVT in patients with COVID-19 [30,142]. Elevated serum ferritin and fibrinogen levels are associated with a high risk of hemorrhagic stroke [133,143], and a significant number of patients with AIS tested positive for antiphospholipid antibodies [116].

Imaging characteristics

One of the radiological features of COVID-19 accompanying ischemic stroke is large-artery occlusion (including the internal carotid artery, M1 and M2 segments of the middle cerebral artery, and basilar artery) and involvement of multiple arterial regions [21,105,116,144]. It may also involve the affected vessels that are rare in general stroke, such as occlusion of the pericallosal artery [145] or the presence of multiple focal stenoses in the V4 segment of the vertebral artery [82]. Diffuse microhemorrhages were observed in COVID-19 patients experiencing hemorrhagic stroke revealed using MRI, which were mainly dispersed in the paracortical white matter, corpus callosum, and brainstem [146,147]. Subarachnoid hemorrhage, parieto-occipital leukoencephalopathy, microbleeds, and single or multiple focal hematomas have been reported as characteristic radiological manifestations of hemorrhagic stroke in patients with COVID-19 [82]. Vessel wall magnetic resonance imaging detected signs of intracranial vessel wall inflammation in the majority (75%) of patients with cryptogenic AIS, showing diagnostic value [148].

The involvement of multiple venous vessels (67%) and the deep venous system (37%) in patients with COVID-19 combined with CVT was more frequent compared with the usual reporting rates of deep venous system involvement (11%) [30,149]. One-quarter of patients with stroke have imaging evidence of systemic thrombosis, including emboli at multiple sites in the brain, spleen, and lungs [150].

Vaccination-induced stroke

Adenovirus-based SARS-CoV-2 vaccination is associated with the rare occurrence of vaccine-induced immune thrombotic thrombocytopenia (VITT) [151–154], which includes reports of both ischemic and hemorrhagic strokes after COVID-19 vaccination [155,156]. The reported incidence of VITT-associated CVT is conservatively estimated at approximately 0.87 cases per million (0.000 087%) [157,158]. These occurrences have predominantly been documented in females under the age of 50 years, necessitating comparison with heparin-induced thrombotic thrombocytopenia (HITT) [159].

The exact pathophysiological mechanisms underlying VITT-induced stroke remain unclear. mRNA or adenovirus vector vaccine, followed by an expression of SARS-CoV-2 spike protein, can bind to ACE2 receptors, then undergoes endocytosis, causes direct endothelial cell injury, and the accompanying autoimmune responses, namely, complement activation and increased cytokine expression, further disrupt the BBB and result in a thrombotic or hypercoagulable state [160]. Another putative mechanism implicates the COVID-19 vaccine in the generation of platelet-activating antibodies targeting platelet factor 4 (PF4). The subsequent binding of the antibody–PF4 complex to macrophages, monocytes, natural killer cells, and dendritic cells via FC γ receptors triggers cellular activation and the release of PF4, thereby fostering a prothrombotic state [161].

Comparatively, the incidence of CVT following SARS-CoV-2 infection is markedly reduced after an mRNA-based SARS-CoV-2 vaccination [162]. Thus, acknowledging that VITT is a rare side effect of COVID-19 vaccination is essential, and CVT is the prevalent and severe manifestation of this syndrome [152,163,164]. Primarily observed in individuals aged < 60 years, particularly women, VITT-associated CVT is defined by the presence of acute thrombosis within 28 days of vaccination, thrombocytopenia ($< 150 \times 10^9$/L), and a positive result for anti-PF4 antibodies [159,165]. Typically occurring within 2–4 days post-vaccination, this phenomenon tends to affect individuals with few predisposing risk factors for venous thrombosis but with a high incidence of severe outcomes, including fatality. The prevailing symptoms associated with stroke stemming from VITT include intensifying headaches, frequently coinciding with seizures, visual impairments, focal neurological indications, and elevated intracranial pressure. These clinical presentations may be accompanied by markers indicative of disseminated intravascular coagulation (DIC), inclusive of cerebral hemorrhages and extracranial thrombotic occurrences, such as pulmonary thromboembolism and visceral venous thrombosis [166]. Furthermore, this distinctive pattern of multifocal thrombus formation, which encompasses both arterial and venous clotting instances, could be particularly concentrated within cerebral and abdominal regions [167].

VITT-associated CVT is characterized by decreased platelet counts ($< 150 \times 10^9$/L), elevated levels of D-dimer (> 2000 μg/L), diminished fibrinogen levels, and detectable PF4 antibodies discernible through enzyme-linked immunosorbent assay, collectively signifying systemic coagulation activation [168,169].

Prognosis of COVID-19-associated stroke

The prognosis of coexisting COVID-19 and arterial stroke appears to be much worse than that of each condition alone, particularly in patients with the onset of neurological symptoms [109,138,170]. Mortality rate in patients with COVID-19 who experienced hemorrhagic stroke was 44.72%–48.6% [17,171], and the rate was slightly lower in those who experienced ischemic stroke (22.8%–36.23%) [10,17]. A retrospective study confirmed COVID-19 as an independent risk factor for stroke and mortality in hospitalized patients with a predominance of ischemic stroke (83.7%) and nonfocal neurological manifestations (67.4%), usually involving a multivessel distribution (45.8%) with associated bleeding (20.8%) [172]. In another systematic review involving 44 studies that reported hospital discharge outcomes for patients with stroke and COVID-19, of the 1655 patients for whom mortality information was available, 31.5% (521) died during hospitalization. In-hospital mortality was higher in patients with stroke combined with COVID-19 (144/432 vs. 191/1643; OR = 5.21, 95% CI 3.43–7.90), although a similar proportion of patients received acute stroke treatment (intravenous thrombolysis and embolization) [21].

The prognostic impacts of COVID-19 and CVT were compounded, the current estimated mortality rate for COVID-19 was 5.7% [173], and the known mortality rate for CVT is 15% [174]. A cohort that included nonventilated patients reported an in-hospital mortality in patients with COVID-19 who experienced CVT, of whom 14/35 patients died (40%) [30]. Another study on patients with COVID-19 and diagnosed CVT reported an unusually high mortality rate of 45.5%, which was lower than that of the patients with mild COVID-19 (40.0%) [170]. Katsanos *et al*. [4] found that patients with COVID-19 had an approximately fivefold increase in in-hospital mortality risk compared with those without infection. Deep cerebral vein thrombosis seems to be associated with increased incidence of mortality in patients with COVID-19, and 50% have been reported [170].

Some predictors of poor prognosis are consistent with known non-COVID-19 stroke, such as old age, high NIHSS score on admission, and baseline glucose and creatinine levels for COVID-19-related cerebrovascular disease, whereas other factors seem to be more specific to this particular population of COVID-19, such as a preponderance of cardiogenic embolism, cryptogenic stroke, and large- or multibranch vessel occlusions. In addition, the severity of COVID-19, thrombocytopenia, lymphopenia, and elevated D-dimer and LDH levels are suspected to be associated with poor clinical prognosis [175–177].

Disease management of COVID-19-associated stroke

Substantial attention should be paid to the possible bidirectional relationship between stroke and SARS-CoV-2 infection in clinical care and adequate vigilance for timely and effective interventions for COVID-19-induced stroke given that the current COVID-19 epidemic continues and millions of people worldwide are still at risk.

Strategies to mitigate time lags in pre-hospital and emergency procedures

The concept of "time is brain" is widely acknowledged in stroke management, underscoring the critical role of minimizing pre-hospital delays stemming from COVID-19-related circumstances and thereby potentially enhancing the clinical trajectory and prognostic outcomes of stroke patients [178]. A retrospective cohort study encompassing 1194 cases of AIS conducted at a prominent academic hospital in Shanghai unveiled that stroke patients experienced prolonged durations in the emergency department before hospitalization for two years at the beginning of the COVID-19 outbreak [179]. Furthermore, notable delays in intervals from hospital arrival to subsequent stages, including the time to hospital admission, initial imaging confirmation, and eventual revascularization, were evidently due to the pressure imposed by COVID-19 consultations, adaptations in medical systems, and adherence to COVID-19 prevention protocols. These delays were particularly pronounced in comprehensive stroke centers during the pandemic [180]. Multiple countries, including China, the United States, France, and Singapore, have conducted studies encompassing a broad array of local hospitals. The findings corroborated the global impact of the pandemic on stroke care, extending beyond temporal and quantitative domains, encompassing the very quality of care provided. Significant reductions were observed in hospital admissions, thrombolysis procedures, and recanalization rates in stroke patients during the COVID-19 outbreak [108, 179,181–188].

In addressing the challenge posed by COVID-19 on stroke care, strengthening online education and raising public awareness about stroke is critical. Many hospitalized stroke patients present with more severe vascular occlusions and critical conditions than before the pandemic, and the mild-to-moderate presentation of stroke is often overlooked. Additionally, encountering young people with COVID-19 and stroke without previous risk factors is increasingly common, emphasizing the need for prompt access to hospitals.

The Expert Committee of the Stroke Prevention and

Treatment Project of the National Health Commission of China has released several consensus versions to guide the prompt management of stroke during the COVID-19 pandemic [189,190]. These guidelines include pre-hospital emergency procedures for stroke patients, where medical personnel should inquire about stroke symptoms and the time of onset, while simultaneously screening for SARS-CoV-2-related symptoms and epidemiological history within 14 days of onset. Suspected stroke patients with SARS-CoV-2 infection should be transferred to designated hospitals with stroke treatment capabilities for SARS-CoV-2 pneumonia. In addition, the use of pre-hospital and emergency online communication channels, such as mobile internet, mobile applications (such as the First Aid Green Channel APP), and workgroups, is recommended to complete the communication of patients' conditions before arrival at the hospital. This step facilitates the hospital's timely preparation of treatment and protective measures based on patients' specific conditions and reduces delays. China has developed innovative technologies and its telemedicine strategies, which enable doctors to diagnose and treat patients with suspected COVID-19-associated stroke remotely, while minimizing the risk of infection transmission within the hospital [191]. Telemedicine adoption in stroke patients across western China during the COVID-19 pandemic has been associated with improved thrombolysis rates, reduced admission delays, and enhanced neurological outcomes [192]. Some medical facilities have established official "Stroke Map" WeChat platforms, which can aid in the rapid and accurate identification of stroke cases [193]. In areas restricted due to the epidemic or medical institutions with insufficient stroke treatment, China centralizes the allocation and extraction of personnel from unrestricted areas or areas with sufficient medical resources to treat stroke patients promptly. Moreover, the use of mobile stroke units equipped with mobile CT, testing equipment, monitoring instruments, and remote mobile consultation systems is vigorously promoted. These units integrate stroke physical examination, CT diagnosis, thrombolysis, and monitoring and play an essential role in the timely diagnosis and treatment of stroke patients during the COVID-19 pandemic. The mobile stroke unit based on 5G mobile edge computing technology and artificial intelligence can shorten the time from patient contact to thrombolysis treatment to 17–28 min, thereby enhancing the management of stroke patients in the context of COVID-19.

Recommendations for in-hospital examination and clinical process

Rapid evaluation, timely identification, and screening of patients at high risk or with a suspected stroke at admission or emergency are still essential. Laboratory examinations and a low threshold for imaging studies are needed in patients with COVID-19 and those with neurological symptoms. Establishing buffer wards in hospitals and performing SARS-CoV-2 nucleic acid testing and serum SARS-CoV-2-specific antibody testing, where feasible, are essential to the mitigation of the risk of nosocomial infections. When patients present with suspected or confirmed SARS-CoV-2 infection, head CT and chest CT should be conducted [189,190]. Additionally, biomarkers, such as D-dimer and fibrinogen, should be evaluated to provide further evidence of COVID-19-related thrombotic status until the hospital COVID-19 screening results are negative. Given that the signs of ischemic stroke are particularly vague in critically ill patients who are often intubated and heavily sedated, which may obscure their clinical features [94], screening for the presence of COVID-19 should also be performed in patients with CVT and neurological complications without significant respiratory symptoms or known prethrombotic risk factors. CVT in the setting of SARS-CoV-2 infection is primarily diagnosed in patients with mild-to-moderate COVID-19. However, venography should be performed to rule out CVT if patients with SARS-CoV-2 infection have an atypical infarct or bleeding patterns or have unexplained elevated intracranial pressure. Furthermore, CVT within 28 days of COVID-19 vaccination needs to be monitored because of potential immunological thrombocytopenia [165].

Therapeutic management of ischemic or hemorrhagic stroke in patients with COVID-19 should be based on safety and performed with the same standard of care as that performed in non-COVID-19 patients, and infection prevention and control measures are required. Several studies have substantiated the safety of employing thrombolysis and endovascular thrombectomy (EVT) as interventions for AIS in the context of COVID-19 [194,195]. Other potential treatments exist for patients with stroke and COVID-19, such as anticoagulants, anti-inflammatory drugs, and antiplatelet agents, which must be selected on an individual patient basis [193,196,197]. For example, one study found that a multinational stroke study group with moderate COVID-19 who received an intermediate dose of anticoagulation showed improved survival, suggesting that disease severity is one of the references for assessing whether to initiate thrombo-prophylaxis and dose in hospitalized patients [198]. Furthermore, acknowledging that patients afflicted with COVID-19 may manifest liver dysfunction concomitant with coagulopathy, evidenced by alterations in prothrombin time, INR, activated partial thromboplastin time, or diminished platelet count, is imperative. Thus, the benefits and risks must be evaluated before the intravenous administration of rt-PA to individuals who have COVID-19 and associated organ problems [199].

With respect to eligible AIS patients afflicted by COVID-19, the timely administration of EVT is of paramount importance, given the substantial benefits associated with this intervention, which progressively diminish over time until treatment [200]. The quantification of stroke load or size and assessment of hemorrhagic transformation are important factors. In mild nondisabling stroke, the cautious administration of thrombolysis is recommended after the potential risks and benefits are considered [190]. For patients suspected of having aortic occlusion, a multidisciplinary team of stroke, infection, and respiratory physicians may perform multimodal imaging in the emergency room with strict control over surgical indications. Central to the paradigm of acute stroke management, stroke units should persist as the linchpin, delivering specialized multidisciplinary care that greatly enhances patient outcomes. Hospitals with appropriate resources should perform interventional procedures in a dedicated catheterization room or if available, a negative pressure catheterization room. Following the procedure, patients should be admitted to a designated isolation ward [189,190].

Given the high mortality rate of CVT in SARS-CoV-2 infection, the early initiation of anticoagulation therapy may play a role in patients with suspected CVT or a propensity for thrombosis. Some guidelines recommend early prophylactic low-molecular-weight heparin therapy in SARS-CoV-2-positive patients with clinical indications (e.g., pulmonary embolism). Whether this measure is sufficient to reduce the CVT risk should be explored in future prospective studies [201,202]. The treatment recommendations for CVT caused by VITT were established in March 2021 and were based on the autoimmune pathogenesis of VITT [203]. As mortality is low in patients receiving immunomodulatory therapy, immunomodulation seems to be essential to the reduction of mortality in VITT-CVT [151].

Prospects for future treatments and research in COVID-19-related stroke

As the COVID-19 pandemic continues to affect millions of people worldwide, COVID-19-related stroke is complex and evolving, and thus future therapeutic and research areas may become a focus of interest in several key fields that address related challenges. First, to better understand the pathophysiology of COVID-19-related stroke, the mechanisms by which COVID-19 affects the brain and increases the risk of stroke should be investigated. The inflammatory response in the body plays a critical role in COVID-19-related stroke [204,205], and thus immunomodulatory therapies that target the immune system by blocking activated inflammatory signaling pathways and reducing immunothrombosis may be effective in preventing or treating COVID-19-related stroke [206,207]. Second, advancements in diagnostic tools and imaging technologies can aid in the early and accurate diagnosis of COVID-19-related strokes, which are crucial for prompt treatment and outcomes. The use of mobile stroke units equipped with advanced imaging technologies and telemedicine capabilities can help in the timely diagnosis and treatment of COVID-19-related stroke, especially in areas with limited access to stroke centers. Furthermore, the integration of artificial intelligence and machine learning algorithms in mobile stroke units can facilitate the analysis of medical images, assist in the identification of COVID-19-related strokes, and aid in the decision-making process for treatment. Third, an additional pivotal consideration necessitates comprehensive rehabilitation as an indispensable facet that warrants attention, particularly in stroke patients afflicted with COVID-19 during the pandemic. The administration of rehabilitation interventions not only contributes to the physical recuperation of these patients but also addresses cognitive and emotional dimensions, thereby augmenting the overall quality of life of individuals who went into stroke. Future research may focus on developing and testing rehabilitation programs, such as virtual and augmented reality, which are specifically tailored to the needs of these patients [208]. Finally, addressing the management of stroke during the COVID-19 pandemic may require a thorough understanding of potential differences in COVID-19-associated stroke caused by different subtypes of SARS-CoV-2. Although most studies have focused on the broad impact of COVID-19 on stroke risk and outcomes, specific variations based on viral subtypes have been inadequately explored. Comprehensive research is essential to elucidating potential discrepancies in COVID-19-associated stroke across various SARS-CoV-2 subtypes and acquiring deep insights into the underlying mechanisms contributing to these variations.

Conclusions

Arterial stroke and CVT are complications associated with COVID-19, and controlling COVID-19 has become a priority for the medical community worldwide over the past 3 years. Several contributing factors, including SARS-CoV-2-activated endothelial dysfunction, immune inflammation, and coagulation dysfunction, may cause stroke and threaten young people and those without traditional risk factors, suggesting that the management and publicity of stroke should not be overlooked. We still need to continue to optimize high-quality stroke care and treatment strategies in the context of clinical reality and societal needs, as the current epidemic storm caused by COVID-19 is not yet over, and the challenge of long COVID-19 syndrome has already begun, combining the interplay between SARS-CoV-2 infection and stroke.

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Compliance with ethics guidelines

Conflicts of Interest Lu Liu, Chenxia Zhou, Huimin Jiang, Huimin Wei, Yifan Zhou, Chen Zhou, and Xunming Ji declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

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