Review

The emerging association between COVID-19 and acute stroke

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Prior to COVID-19, only two human-tropic coronaviruses resulted in epidemics and cerebrovascular disease was rarely reported. Evidence now suggests that 1–6% of hospitalized COVID-19 patients develop stroke. According to some reports, stroke risk is more than sevenfold greater in patients with COVID-19 than influenza. Concerningly, outcomes of COVID-19-related stroke are often worse than in stroke patients without COVID-19 from the same cohorts. In this review, we highlight the emerging association between COVID-19 and stroke and discuss putative pathogenetic mechanisms. Etiology of stroke in COVID-19 patients is likely multifactorial, related to coagulopathy, inflammation, platelet activation, and alterations to the vascular endothelium. Significant work remains to be done to better understand the pathogenesis of COVID-19-related stroke and for designing optimal primary and secondary prevention strategies.

The global coronavirus disease 2019 (COVID-19) pandemic and stroke prevalence

On 11 March 2020, the World Health Organization declared COVID-19 a global pandemic. Previously, only two of the coronaviruses known to infect humans, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), resulted in epidemics [1–3]. Rare neurologic manifestations were reported with SARS and MERS, including small numbers of patients with ischemic and hemorrhagic stroke (see Glossary) [4–7].

The impact of the COVID-19 pandemic on healthcare systems around the world, and also on patients of other diseases, has been dramatic [8]. Resources have been diverted to care for patients with COVID-19, sometimes at the expense of other patients [9–11]. At the outset, the American Heart Association/American Stroke Association Stroke Council, and other leading stroke organizations around the world, offered guidance on how best to preserve evidence and guideline-based stroke despite overwhelming strain on the healthcare system [12–15]. However, global stroke admissions have declined in individual centers and across regions [16–19]. In a review of over 230,000 patients who received advanced stroke imaging with automated processing in more than 850 hospitals in the United States, the number of patients who underwent acute stroke imaging decreased by 39% during a 14-day period from 26 March 2020 through 8 April 2020 compared with a 29-day period from 1 February 2020 through 29 February 2020 [20]. Concerningly, this decrease was seen across all ages, sex, and stroke severity, as well as throughout the country. Meanwhile, the World Stroke Organization reported that nearly 90% of members surveyed from 100 countries worldwide had seen a decrease in stroke admissions, with median decrease in stroke admissions of 50–70% [21].

Reasons for the decline in observed stroke volumes are not entirely clear, but may be related to fewer patients seeking care, mortality due to COVID-19, or a true decrease in incidence perhaps resulting from changes in lifestyle during pandemic conditions. We suspect that fewer patients seeking care for mild stroke, as well as perhaps greater mortality in patients with traditional

Highlights

Growing comparisons of COVID-19 positive and COVID-19 negative stroke cohorts support an association between COVID-19 and stroke.

COVID-19-related stroke can be severe and has impacted young patients and minimally symptomatic individuals, as well as patients with traditional cerebrovascular risk factors and severe disease.

When compared with stroke patients without COVID-19, morbidity and mortality are much worse in patients with stroke and COVID-19.

Etiology of COVID-19-related stroke is frequently unknown and the pathogenesis may be related to coagulopathy, inflammation, endotheliopathy, and platelet activation.

Anticoagulation may benefit those hospitalized with severe COVID-19, including those diagnosed with stroke.
cerebrovascular risk factors, contribute significantly to the observed decline. A true decrease seems unlikely, we would argue, as stay at home orders, psychosocial stress, and poor utilization of routine medical care likely worsen traditional stroke risk factors. In fact, a recent study demonstrated that the decrease in stroke-related emergency medical service calls was associated with excess stroke deaths in 23 states and New York City [22]. In the following sections, we discuss studies suggesting an association between COVID-19 and an enhanced risk for stroke. We also outline a number of putative pathophysiological mechanisms that could underlie the observed association (Figure 1). Of note, in addition to the morbidity of COVID-19-related stroke cases and potential excess of stroke-related deaths during the pandemic, one must worry about future impact on those with mild stroke who possibly failed to seek adequate care and may face greater long-term risk of stroke and its complications.

Infection as a trigger of stroke
Respiratory viruses are potential triggers of stroke, as well as other infections such as urinary tract infections and sepsis [23–26]. Many viral infections, including varicella zoster, herpes simplex virus, human immunodeficiency virus, cytomegalovirus, and parvovirus B19, have also been implicated in the pathogenesis of stroke through arteriopathy, inflammation, and atherosclerosis [27].

As a highly prevalent respiratory virus, influenza provides an especially useful historical comparison with COVID-19 [28]. In the United States, for instance, in 2019 influenza infected over 30 million individuals and resulted in hospitalizations of over 400,000 patients. A case-crossover study of over 36,000 California patients hospitalized for ischemic stroke found that 1.5% had infection with influenza-like illness in the prior year. Odds were highest for infection within 15 days of stroke.

Figure 1. The pathogenesis of ischemic stroke in coronavirus disease 2019 (COVID-19), similar to other arterial thromboses seen in this disease, such as peripheral arterial thrombosis and myocardial infarction, is likely multifactorial, stemming from inflammation and coagulopathy. There is an emerging body of evidence demonstrating the association between COVID-19 and stroke and highlighting the difference in affected population, clinical presentation, and outcomes between COVID-19 positive and COVID-19 negative stroke patients. This figure highlights the major putative mechanisms. Severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) binds to ACE2 receptors in various tissues, entering the body and activating the immune system, leading to release of cytokines. This inflammation directly induces a hypercoagulable state. Direct effects on the endothelium also occur, which results in local inflammation and platelet activation, potentially causing plaque rupture. Finally, cardioembolic sources of stroke can be caused by the virus’s direct inflammatory effect on the muscle or injury due to increased oxygen demand.

Glossary

**Cryptogenic stroke**: ischemic stroke with unknown etiology even after all appropriate investigations into potential causes. In the young, cryptogenic stroke accounts for a large percentage of stroke cases.

**Hemorrhagic stroke**: disruption of blood flow to the brain caused by rupture of a blood vessel and accumulation of blood in the brain. Accounts for approximately 13% of all stroke cases.

**Ischemic stroke**: disruption of blood flow to the brain caused by blockage of one of the large blood vessels of the head or neck. Accounts for approximately one-third of all ischemic strokes, yet a disproportionate percentage of post-stroke dependence and death.

**TOAST classification**: system for classification of ischemic stroke etiology, originally developed for the Trial of Org 10172 in Acute Stroke Treatment (TOAST). By this classification system, subtypes of ischemic stroke include: large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined etiology, and stroke of undetermined etiology.
hospitalization for stroke and the greatest odds for ischemic stroke were in patients younger than 45 years [29]. A case-control study of patients admitted for stroke found an approximately 50% reduction in odds associated with influenza vaccination that year, further supporting the association between influenza and stroke [30]. Recently, New York City COVID-19 patients were compared with historical influenza controls, with stroke affecting 1.6% of patients with COVID-19 versus 0.2% with influenza and more than sevenfold greater adjusted odds of ischemic stroke in patients with COVID-19 compared with influenza [31]. However, the extent to which COVID-19 increases risk of stroke, and by what mechanisms, has not been fully elucidated (see Outstanding questions).

**Concerning early observations**

In a retrospective single-center report on patients in Wuhan early in the pandemic, approximately 5.0% of hospitalized patients were reported to have stroke with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, 90.9% of whom suffered ischemic stroke compared with 9.1% (n = 1) intracerebral hemorrhage [32]. In the first detailed report of neurologic manifestations in three centers in Wuhan, 5.7% of 88 patients with severe infection had stroke, four ischemic and one intracerebral hemorrhage, compared with only 0.8% of patients with nonsevere infection [33]. Notably, one-third of patients with stroke had not yet demonstrated typical COVID-19 symptoms on presentation.

Although there is no uniform case definition for COVID-19-related stroke, multiple comparisons of stroke patients with and without COVID-19 support the association between COVID-19 and cerebrovascular disease. A predominance of ischemic stroke has been reported, similar to that of the typical stroke epidemiology, but with a significant increase in a cryptogenic etiology when classified by TOAST classification [34,35]. Studies have described large vessel involvement, including in younger patients without traditional risk factors or typical manifestations of COVID-19 at stroke onset, with a disproportionate impact on male and non-white individuals [36–39]. Most concerning, outcomes among COVID-19 stroke patients seem much worse than in stroke patients without COVID-19 [40–42]. Now that more than 10 months have passed since official pandemic declaration, experience in caring for COVID-19 patients with stroke has grown around the world. With more than 100 million infections and 2.1 million deaths globally as of the end of January, the apparent association between COVID-19 and stroke is growing.

The incidence of COVID-19-related stroke reported in the literature has ranged from 1–6% among patients hospitalized with COVID-19 [31,33,40], with higher incidence in the setting of more severe infection [31,33,40,43–45]. In the sections that follow, we focus on some of the largest-scale studies to date, both at the New York City epicenter and from other locations in the United States and around the world.

**The New York City experience**

As the COVID-19 surge reached the United States in March 2020, New York City (in which the authors of this article are based) became one of its primary epicenters. Several concerning early clinical observations were made. Within our New York City health system, five cases of large-vessel stroke were reported in patients under 50 years of age in the 2 week period from 23 March 2020 to 7 April 2020 [36]. Compared with every 2-week period over the previous year, this was more than five times the number of patients under 50 years treated. Our group, and others, noted both occlusive and non-occlusive thrombi in the internal carotid artery in patients with and without underlying atherosclerotic risk factors [46,47]. Despite many reports that thrombotic events seemed to be associated with disease severity, multiple patients with large-vessel stroke had not displayed any symptoms of COVID-19 prior to presentation with stroke [33,36,44,47,48].
In our retrospective series, 1.9% (n = 105) of the 5469 COVID-19 patients admitted to our health system during March and April were diagnosed with stroke [49]. The majority of COVID-19 positive stroke patients suffered ischemic stroke (79.1%) followed by 15.2% intracerebral hemorrhage, 3.8% subarachnoid hemorrhage, and 1.9% transient ischemic attack. Ischemic stroke etiology was more than twice as likely to be cryptogenic in COVID-19 positive patients compared with COVID-19 negative (51.8% versus 22.3%), and small vessel and cardioembolic strokes occurred less frequently compared with historical controls. The majority of COVID-19 stroke patients had abnormalities in peak inflammatory markers, including D-dimer, erythrocyte sedimentation rate, C-reactive protein, fibrinogen, and interleukin-6. Additionally, ischemic stroke location was more commonly lobar in COVID-19 patients than COVID-19 negative. Most concerning, COVID-19 positive stroke patients had longer length of stay, were more likely to require intensive care unit care, had a greater rate of neurological worsening during admission, and were more than 2.5 times more likely to experience in-hospital death compared with COVID-19 negative stroke patients.

A smaller retrospective cohort study of 32 ischemic stroke patients in New York City from 15 March 2020 to 19 April 2020 compared COVID-19 stroke patients with concurrent and historical COVID-19 negative controls [40]. This study reported ischemic stroke in 0.9% of hospitalized patients. Cryptogenic stroke was also twice as likely in this smaller cohort of COVID-19 stroke patients (65.6% versus 30.4% COVID-19 negative, P = 0.003). Additionally, in-hospital death was even more common, occurring in 64.6% of COVID-19 stroke patients (versus 9.3% concurrent controls, P < 0.001).

Another retrospective series compared 86 COVID-19 stroke patients in New York City and Long Island between 14 March 2020 and 26 April 2020 with historical controls [41]. Stroke subtype was comparable with typical stroke epidemiology and multivascular territory strokes occurred in 45.8%. When compared with historical controls, COVID-19 positive patients were more commonly black or multiracial minority (58.1% versus 36.9%; P = 0.001), more likely to have an in-hospital stroke (47.7% versus 5.0%; P < 0.001), and less likely to have a cerebrovascular history (10.5% versus 23.1%; P = 0.008). Mortality was also high in this COVID-19 stroke cohort, occurring in 29.1% (versus 9.0% of controls, P < 0.001).

While the New York City experience is likely representative of manifestations of COVID-19 in a population with a high prevalence of disease, there are likely several factors that may be unique to the New York City experience. The data comes from the early surge in the United States, when experience in treating the disease was limited and hospitals in the region were overwhelmed. In March and April, only the sickest COVID-19 patients were admitted, patients with and without COVID-19 were often avoiding seeking healthcare unless absolutely necessary and availability of staff and testing likely impacted utilization of diagnostic testing. Furthermore, centers with high volumes of COVID-19 may have been quicker to implement treatment protocols, including around prophylactic and treatment dose anticoagulation.

The global experience
Outside of New York City, similar associations between COVID-19 and severe stroke have been described. A retrospective study of 111 COVID-19 patients admitted to a neurological hospital unit in Italy during the surge from 21 February 2020 to 5 April 2020 reported cerebrovascular disease in 76.8% of those COVID-19 positive compared with 58.1% of those COVID-19 negative [42]. There was no significant difference in type of cerebrovascular event between the COVID-19 positive and negative stroke cohorts. Patients with COVID-19 had higher platelets, erythrocyte sedimentation rate, lactate dehydrogenase, alanine aminotransferase, aspartate aminotransferase,
prothrombin, and fibrinogen than COVID-19 negative patients, and lower lymphocyte count. Similar to the New York City experience, in-hospital mortality among COVID-19 stroke patients was also high (34.9% versus 5.9% of COVID-19 negative, \( P < 0.001 \)).

Much can be learned from pooled, multicenter data. In a multinational observational study of patients with COVID-19 and stroke patients from 31 hospitals in the Society of Vascular and Interventional Neurology registry, 1.13% (\( n = 172 \)) of 14 483 COVID-19 patients were diagnosed with stroke [50]. The majority (\( n = 156 \)) experienced ischemic stroke. Interestingly, incidence ranged from 0.19% to >5% and was less common at centers that treated more COVID-19 patients. Similar to other series, cryptogenic stroke was more than twice as common than in historical controls and cardioembolism accounted for just over one-quarter of events. Additionally, slightly more than 38% of ischemic and 58% of hemorrhagic stroke patients suffered in-hospital mortality.

Another multinational study of 174 consecutive patients with COVID-19 and ischemic stroke from 28 centers in 16 countries in the Global COVID-19 Stroke Registry demonstrated similarly severe stroke in patients with COVID-19 [51]. Using propensity matching to patients in the Lausanne Registry, patients with COVID-19 were found to have higher National Institutes of Health Stroke Scale score as well as greater risk of severe disability and death.

One of the largest meta-analyses to date has demonstrated similar findings. Of 67 845 patients from 18 cohort studies with COVID-19, 1.1% were hospitalized with ischemic stroke and 0.2% hemorrhagic stroke [52]. When compared with COVID-19 negative controls, odds of ischemic stroke were more than 3.5 times greater and cryptogenic stroke almost four times greater. Concerningly, odds of in-hospital mortality were more than five times greater among COVID-19 stroke patients compared with COVID-19 negative controls.

Large-vessel occlusion stroke patients

Epidemiologic studies suggest that \textbf{large-vessel occlusion stroke} typically accounts for about 38% of ischemic stroke [53]. However, emergent large-vessel occlusion (ELVO) stroke is more severe and disabling, accounting for approximately 60% of post-stroke functional dependence or death [53]. At one hospital outside of Philadelphia, identified cases of mild stroke declined during the lockdown period of the pandemic. However, patients with ELVO continued to present, likely because of the severity of their neurologic deficits, resulting in a greater percentage of ELVO stroke [16]. Many COVID-19 associated stroke series have reported mean ages of thrombectomy patients younger than 60 years, which is younger than concurrent controls and the typical age of thrombectomy patients [54]. Even if acute stroke affects only a minority of COVID-19 patients, it is concerning that the most disabling form of stroke is being seen in younger patients given the prevalence of COVID-19 globally.

In our experience, caring for ELVO patients during 3 weeks beginning on 21 March 2020, 45 patients with ELVO presented to our health system hospitals and 53% were COVID-19 positive [38]. Concerningly, mean age was 59 ± 13 years in COVID-19 positive ELVO patients compared with 74 ± 17 years in COVID-19 negative ELVO patients. Additionally, when comparing COVID-19 positive ELVO patients with COVID-19 negative ones, a larger fraction of the patients were male (79% versus 43%) and non-white (38% versus 8%). Notably, 42% of the COVID-19 positive ELVO patients presented without expected COVID-19 symptoms. Additionally, atrial fibrillation and congestive heart failure, which may traditionally predispose to cardioembolic ELVO stroke, were less common. At a time when overall stroke volumes were reduced, when compared with the preceding consecutive 3-week periods, Poisson
Other studies have reported similar findings in ELVO patients. Among 37 ELVO patients during a 6-week surge in Paris from 1 March 2020 to 15 April 2020, of the ten that were COVID-19 positive, median age was 59.5 years and 80% were male [39]. Two patients were younger than 50 years of age and two were asymptomatic at the time of stroke onset; 60% suffered in-hospital mortality. A much larger retrospective series of 3165 patients who underwent thrombectomy in 45 states in the United States from April through July 2020 in the Vizient Clinical Data Base included 104 patients with COVID-19 [37]. Compared with 3061 concurrent COVID-19 negative controls, COVID-19 patients were younger, with 24% of them at the age range 18–50 years and 36.5% aged 51–64 years (versus 12.7% and 25.1%; \( P < 0.001 \)), more likely male (68.3% versus 51.3%; \( P = 0.001 \)), and more commonly Black (26.0% versus 16.9%; \( P < 0.001 \)) or Hispanic (19.2% versus 5.6%; \( P < 0.001 \)). Although diabetes was more common in COVID-19 patients (47.1% versus 33.9%; \( P = 0.005 \)), COVID-19 stroke patients were less likely to have a history of smoking (<1% versus 16.0%; \( P = 0.011 \)) or atrial fibrillation (28.9% versus 42.5%; \( P = 0.006 \)). Outcomes were also poor in COVID-19 patients treated with thrombectomy. Not only was length of stay longer, but COVID-19 patients treated with endovascular thrombectomy (EVT) were more than twice as likely to die in hospital (29.8% versus 12.4%; \( P < 0.001 \)) than COVID-19 negative patients treated with EVT. Importantly, when COVID-19 stroke patients not treated with EVT were compared with those treated with EVT in a sensitivity analysis, there was no significant difference in in-hospital death (30.6% versus 29.8%; \( P = 0.868 \)). We feel strongly that poor outcomes in COVID-19 positive ELVO patients treated with EVT compared with COVID-19 negative ELVO patients reflects the severity of COVID-19 and its medical complications as opposed to a lack of benefit from EVT. Stroke guideline societies, including the American Heart Association/American Stroke Association, Heart and Stroke Foundation of Canada, and international consensus panels, have emphasized continuing to strive for evidence-based stroke care and established guidelines for patient selection for acute stroke therapy [12–15].

Implications of presentation without typical COVID-19 symptoms

The implications of stroke patients presenting without typical COVID-19 symptoms cannot be overstated, as traditional screening protocols will not protect providers. At all times, stroke teams must ensure that members are adequately protected against potential exposure. Individual needs will vary, but adequate personal protective equipment is essential, team processes and staffing need to be streamlined, thrombectomy infection control and procedural protocol may need to be altered, and telestroke technology should be considered to minimize exposure risk. Every acute stroke patient should be assumed to be infected with COVID-19 and tested at presentation. When possible, expedited testing should be prioritized to ensure adequate infection precautions can be taken during thrombectomy and when admitted to stroke and intensive care units. For centers concerned about delays to treatment, early data suggests that pandemic conditions have resulted in 45% lower odds of treatment with thrombolysis in the Target:Stroke goal of 60 minutes but no significant delay in door-to-groin puncture for thrombectomy [55].

One cannot be certain when COVID-19 infection is incidental. Even in stroke patients with confirmed COVID-19 infection, a full stroke workup should be undertaken to assess for potentially modifiable traditional risk factors for stroke. If resources are limited due to the pandemic, every effort should be made to ensure that additional testing to complete the full evidence-based stroke workup is undertaken after discharge, including transesophageal echocardiography and prolonged cardiac arrhythmia monitoring, when indicated and safe. It is reasonable to consider
routine COVID-19 antibody testing as part of the stroke workup given the potential for one’s risk for thrombotic events to remain elevated for an unclear duration after the acute infection, but, again, one cannot assume that recent COVID-19 infection is causative. It is essential to ensure long-term outpatient follow up to continue to assess recovery and ongoing stroke risk factor profile. As we better understand the pathophysiology of COVID-19-related stroke, clarity may be gained on how risk of stroke in patients with recent COVID-19 infection changes over time and how best to modify secondary prevention strategies accordingly.

Controversy about the association between COVID-19 and stroke

Although emerging evidence increasingly supports the association between infection with SARS-CoV-2 and stroke, including ELVO, some have questioned this association [56,57]. A cross-sectional study of discharges from a suburban New York State healthcare system from January to April 2020 reported that patients diagnosed with COVID-19 had one-fourth the odds of stroke compared with other patients [57]. It seems to us that there are significant shortcomings to this analysis, which may have led to biased calculation of stroke odds. Importantly, inclusion of patients who presented to the hospital in January and February, before the peak of the pandemic, has likely affected the composition of the study’s patients and complicates comparison with studies conducted within pandemic peak periods. Furthermore, the United States Centers for Disease Control and Prevention (CDC) criteria for who could be tested for COVID-19 was very restrictive until 5 March 2020, raising questions about the nature of the COVID-19 negative cohort. It seems likely, we would argue, that most of the stroke patients diagnosed with COVID-19 in the study were from the latter period of study, during lockdown, when some patients with stroke were avoiding hospital visits [20]. Relatedly, the authors’ analysis only includes patients presenting with symptoms of acute stroke, which may be masked by the symptoms of COVID-19 in the positive cohort.

On a different vein, some who have questioned the association between COVID-19 and stroke have been critical of the rigor of observational studies and also raised the question whether COVID-19 sepsis may increase risk of stroke more than other types of sepsis or infectious triggers. While we agree that observational studies should be interpreted with caution, it is worth noting that the support for the association continues to grow with more global experience and large meta-analyses [56]. At the same time, we acknowledge limitations to our reported New York City experience. The high prevalence of COVID-19 in New York City when these studies were performed (reaching a peak of 67.6% positivity in individuals tested on 31 March 2020) (https://www1.nyc.gov/site/doh/covid/covid-19-data.page) raises the possibility that COVID-19 infection in the young stroke patients described previously may have been incidental. In elderly patients, the presence of many traditional risk factors for stroke, including diabetes, hypertension, dyslipidemia, and atrial fibrillation [37–39], even at differential rates between COVID-19 positive and negative cohorts, makes elucidating the exact role of COVID-19 in stroke pathogenesis difficult. Further study of large cohorts is necessary to understand the extent to which COVID-19 infection precipitates stroke as well as the underlying pathogenesis.

Proposed pathogenesis

Coagulopathy

Multiple pathogenic mechanisms for COVID-19-related stroke have been proposed. Coagulopathy was noted early in the Wuhan experience and found to be a poor prognostic sign [58]. Hospitalized patients have been found to have elevated D-dimer, and even more so in those with severe disease, and there is increasing data to suggest that D-dimer at admission can predict severity and mortality [58–60]. Other markers of coagulopathy have been reported but do not appear to have the same prognostic significance, including mild prolongations in prothrombin time and
thrombocytopenia [1,59,61,62]. The International Society of Thrombosis and Haemostasis (ISTH) published interim guidance on management of COVID-19 coagulopathy in March 2020 [61]. In this guidance, they advised checking D-dimer, prothrombin time, and platelet count in patients presenting with COVID-19 to aid in risk stratification and prothrombin time, D-dimer, platelets, and fibrinogen in monitoring prognosis.

Endotheliitis and inflammation
Inflammation of endothelial cells secondary to direct invasion by SARS-CoV-2 may result in thrombus formation. SARS-CoV-2 invades cells through binding of the ACE2 receptor [63], which is expressed widely throughout the body, including on endothelial cells [64]. Indeed, several case reports have emerged of COVID-19 patients with evidence of viral invasion of endothelial cells in the heart, bowel, kidney, liver [65], and brain [66]. Endotheliitis may then precipitate further damage and inflammation, leading to coagulation pathway activation.

Beyond the endothelium, COVID-19 is also associated with widespread systemic inflammation and more so in severe cases. A study from China of 522 COVID-19 patients found elevations in the proinflammatory cytokines interleukin-6 and tumor necrosis factor-α but not in interferon-γ [67]. In contrast, another study of 41 patients with COVID-19 found elevations in interleukin-1β, tumor necrosis factor-α, and interferon-γ [1]. Furthermore, a study comparing patients who died of COVID-19 with patients who were discharged after COVID-19 infection found that patients who died had higher C-reactive protein and interleukin-6 compared with those that were discharged [68]. Several of these cytokines, including interleukin-6 and C-reactive protein, have been associated with elevated stroke risk [69] and, in general, a proinflammatory state is associated with activation of coagulation pathways through tissue factor expression [70].

Platelet activation
Previous work has demonstrated the importance of platelet activation in viral illnesses, including influenza [71]. Platelets not only result in formation of thrombus, but they also play a role in the inflammatory response by influence neighboring cells such as leukocytes [72,73]. Researchers from Brazil demonstrated increased platelet activation and formation of platelet–monocyte aggregates, as well as an association between monocyte tissue factor expression and platelet–monocyte interaction, in patients with severe COVID-19 [73]. Furthermore, RNA sequencing has shown altered gene-expression in platelets of those infected with COVID-19 and higher aggregates of platelets with inflammatory neutrophils, monocytes, and T cells [74].

Cardioembolism
More traditional causes of stroke must still be considered in the COVID-19 population. It is well known that a substantial faction of patients hospitalized with COVID-19 experience cardiac manifestations. Among 416 consecutive patients with COVID-19 in Wuhan, 19.7% suffered cardiac injury, as defined by elevation in cardiac biomarkers, and cardiac injury was associated with in-hospital mortality [75]. Cardiac injury can predispose to arrhythmia, heart failure, and intracardiac thrombus as sources of cardioembolism. Given the high rate of deep venous thrombosis in COVID-19, a paradoxical cardioembolic source is possible [76,77]. Additionally, cardioembolism in the setting of sepsis could be considered.

Implications of pathophysiology on treatment
A better understanding of the underlying pathophysiology of COVID-19 thrombotic complications is of the utmost importance for optimizing primary and secondary prevention. It is likely that multiple mechanisms are at play in COVID-19-related stroke and perhaps in a differential manner depending on stroke subtype. While hypercoagulability and cardioembolism would likely best
Trends in Neurosciences

respond to anticoagulation-based treatment (Box 1), enhanced platelet activation would likely best respond to platelet aggregation inhibitors. The optimal antithrombotic strategy for primary and secondary prevention of stroke has not yet been established and could conceivably require both anticoagulation and platelet aggregation inhibitor based strategies. This underscores the importance of the need for multicenter randomized clinical trials.

**Anticoagulation for secondary stroke prevention**

Some centers, including ours, have utilized anticoagulation for secondary stroke prevention [85]. Not only are patients with stroke and COVID-19 at high risk for systemic thrombotic complications, but the suspected pathogenesis and patterns of ischemic stroke described in the literature, including large vessel, multivascular, or lobar, point to large clot burden and may support anticoagulation for secondary prevention in select patients. The benefit of anticoagulation in these patients likely decreases with time, assuming the thrombotic risk wanes with time, and in the absence of an established indication for long-term anticoagulation such as atrial fibrillation, the bleeding risk presumably increases with time. In contrast, however, it is likely that patients with small-vessel events benefit more from platelet aggregation inhibitors as in traditional small-vessel stroke. However, every stroke etiologic workup and treatment decision must be individualized, even in pandemic conditions, and the potential benefits of antithrombotic therapy must be weighed in light of suspected underlying mechanism and against the risk for hemorrhagic conversion and systemic bleeding.

**Concluding remarks and future perspectives**

Given the number of people infected with COVID-19 worldwide, high mortality seen with COVID-19-related stroke and resulting disability of younger people and those without traditional risk factors, the potential societal implications of COVID-19-related stroke are immense. Public health campaigns

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**Box 1. Anticoagulation and COVID-19**

The ISTH and American Society of Hematology both recommend prophylactic dose low molecular weight heparin consideration for all patients without contraindication hospitalized for COVID-19 and stroke patients should be no exception unless there is a strong contraindication [78]. Of note, the two aforementioned organizations did not recommend prophylactic full dose anticoagulation. The potential benefit of heparin’s anti-inflammatory properties have been noted [61,79]. With a sepsis-induced coagulopathy score (which includes prothrombin time, platelets, and sequential organ failure assessment) of four or higher, or D-dimer more than six times greater, the upper limit of normal, 28-day mortality was lower in patients treated with prophylactic heparin than patients treated without (40.0% versus 64.2%; \( P = 0.029\), 32.8% versus 52.4%; \( P = 0.017\), respectively) [61,80].

There have been efforts to better understand the role of antithrombotic therapy prior to diagnosis of COVID-19. In a propensity-matched study of hospitalized and ambulatory patients with confirmed COVID-19 in our health system from 1 March 2020 and 1 April 2020, comparing those who were on anticoagulation prior to infection with those who were not on anticoagulation or antiplatelet therapy, as well as those on antiplatelet therapy with those not on antiplatelet therapy or anticoagulation, there was no difference in survival or time to mechanical ventilation [81].

Some centers have adopted anticoagulation guidance with intermediate- and treatment- dose anticoagulation. In our health system, in an observational study of 4389 patients with COVID-19, therapeutic (\( n = 900\)) and prophylactic anticoagulation (\( n = 1959\)) were both associated with lower adjusted hazard of in-hospital mortality (aHR 0.53, 95% CI 0.45–0.62 and aHR 0.80, 95% CI 0.45–0.57, respectively) and intubation (aHR 0.69, 95% CI 0.51–0.94 and aHR 0.72, 95% CI 0.56–0.90, respectively). Overall major bleeding rate was low at 2% [82].

There are ongoing international clinical trials assessing full-dose anticoagulation in hospitalized COVID-19 patients, including the randomized, embedded, multi-factorial adaptive platform trial for community-acquired pneumonia (REMAP-CAP), therapeutic anticoagulation, accelerating COVID-19 therapeutic interventions and vaccines-4 (ACTIV-4), and antithrombics inpatient, and the antithrombotic therapy to ameliorate complications of COVID-19 (ATTACC) [83]. It is important to note that in December 2020, the oversight boards for most if not all of these trials recommended no longer enrolling COVID-19 patients requiring intensive care unit care because of a lack of benefit, while continuing to enroll patients not requiring intensive care unit care [84].

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**Outstanding questions**

What is the risk of stroke in patients with COVID-19? Risk appears to differ based on age, vascular risk factor profile, and severity of disease, but large scale epidemiologic studies are lacking. It is also unclear whether risk has changed with the ongoing growing experience in treating the disease.

How does the risk and pathogenesis of stroke compare with other thrombotic events in COVID-19? It is unclear whether the pathogenesis is the same for arterial and venous thrombotic events and the same in all types of stroke.

How can animal models help elucidate the underlying pathogenesis of COVID-19 and stroke?

When is risk of stroke greatest in patients with COVID-19? The spectrum of COVID-19 manifestations at clinical presentation varies, with stroke being the presenting symptom in some individuals. What precautions should be taken in the highest risk periods and how can the public be most effectively educated on risk of stroke in individuals with COVID-19?

For how long are patients with COVID-19 at risk for stroke? Although it is conceivable that at some point one’s risk of stroke returns to baseline, the long-term implications of infection on stroke risk factor profile are not known. To what extent does variable pathogenesis impact future risk of stroke?

How does risk of stroke differ between patients with mild and severe disease? Can viral activity accurately predict future risk of stroke?

What is the optimal treatment for primary and secondary prevention of stroke in patients with COVID-19? There is increasing data to suggest that severely ill patients do worse with systemic anticoagulation, but the best strategy in those hospitalized with milder illness and thrombotic events such as stroke is not known. It is possible that a combination of anti-thrombotic therapies best targets the underlying pathogenesis.

Do patients without typical manifestations of COVID-19 at the time of their stroke...
must continue to emphasize the importance of seeking care for stroke, even during pandemic conditions, and hospitals must continue to prioritize evidence-based acute treatment of stroke patients with thrombolysis and thrombectomy. The need for high-quality epidemiologic study and randomized trials cannot be understated, as well as the need for a more uniform case definition [86]. With a more uniform case definition, as well as larger numbers of patients and centers enrolled in clinical trials and research collaboration, hopefully we can better understand the most significant risk factors and optimal primary and secondary prevention strategies for COVID-19-related stroke.

Declaration of interests
The authors declare no competing interests in relation to this work.

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