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REVIEW ARTICLE

COVID-19 and ischemic stroke

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Abstract

Since the onset of the COVID-19 pandemic, a substantial proportion of COVID-19 patients had documented thrombotic complications and ischemic stroke. Several mechanisms related to immune-mediated thrombosis, the renin angiotensin system and the effect of SARS-CoV-2 in cardiac and brain tissue may contribute to the pathogenesis of ischemic stroke in patients with COVID-19. Simultaneously, significant strains on global healthcare delivery, including ischemic stroke management, have made treatment of stroke in the setting of COVID-19 particularly challenging. In this review, we summarize the current knowledge on epidemiology, clinical manifestation, and pathophysiology of ischemic stroke in patients with COVID-19 to bridge the gap from bench to bedside and clinical practice during the most challenging global health crisis of the last decades.

KEYWORDS
COVID-19, ischemic stroke, pathophysiology, SARS-CoV-2

INTRODUCTION

In the early phases of the COVID-19 pandemic, there has been a relatively high prevalence of thrombotic events, mainly among patients with severe COVID-19 but also among mildly symptomatic or asymptomatic patients [1,2]. This seems to be the case also for stroke, even though the overall number of stroke admissions has been reduced during the pandemic, possibly because patients experiencing stroke symptoms did not seek medical attention especially when symptoms were mild, due to the fear of contracting the

coronavirus [2,3]. In contrast to coronary and peripheral artery disease, which are primarily caused by atherosclerosis, ischemic stroke is a heterogenous syndrome comprising multiple pathophysiological mechanisms including vascular and cardiac pathologies, many of which seem to be influenced by SARS-CoV-2 infection. In this review, we discuss the potential pathophysiology of ischemic stroke in COVID-19 and summarize the accumulating evidence on ischemic stroke prevalence, characteristics, and treatment.

METHODS

Search strategy

We systematically searched PubMed and Scopus between first available date and August 14, 2020 for full-text articles published in the English language providing data on ischemic stroke in patients with COVID-19. We used the terms "SARS-CoV-2" or "covid-19" or "corona virus" and "stroke" or "cerebrovascular accident" or "cerebrovascular disease." To be eligible, the studies had to be published full-text English-language articles providing data on ischemic stroke incidence among COVID-19 patients and the impact of COVID-19 on ischemic stroke admissions and stroke treatment pathway. Eligible studies that were returned from the systematic literature search were assessed independently by all authors and evaluated again by two authors (D.S. and A.K.) based on prespecified criteria and presented in the Appendix S1. In addition, we searched the references of related letters, reviews, and editorials to identify other potentially eligible studies. Apart from the systematic search, we searched the literature for studies reporting on clinical characteristics and studies supporting the potential pathophysiological mechanisms of atherothrombosis and stroke in patients with COVID-19.

Ischemic stroke in patients with COVID-19

Through the systematic search of the literature we identified 26 studies that reported ischemic stroke incidence in COVID-19 patients with an average incidence of 1.5%, which varied from as low as 0.1% to 6.9% among hospitalized patients [1,4–28] (Table S1). The variation in reported incidence rates may be associated with the hospital setting (i.e., whether patients were admitted to intensive care units [ICUs] or normal COVID-19/stroke wards, reflecting the severity of COVID-19. In a recent meta-analysis, patients suffering from severe COVID-19 had a fivefold increase of the risk of stroke (odds ratio: 5.1, 95% confidence interval [CI]: 2.72–9.54) [29]. In a multicenter, observational study including 26,175 hospitalized COVID-19 patients, the overall stroke risk was 0.5%, whereas ischemic stroke was diagnosed in 79% of these patients [30]. These data may suggest a lower incidence of stroke in COVID-19 patients, although this may have been limited by the limited access to imaging and underdiagnosis of sedated and mechanically ventilated patients. Despite that several studies reported ischemic stroke incidence in patients with COVID-19, these results are limited only to hospitalized patients and do not reflect the actual prevalence of ischemic stroke among all patients with SARS-CoV-2 infection.

Compared to non–COVID-19 patients, patients with COVID-19 suffering a stroke were younger (median [interquartile range (IQR)] in years: 63 versus 70, $p = 0.001$) and male (given proportions), with more severe neurological deficits compared to historical controls (median National Institutes of Health Stroke Scale [NIHSS]: 19 versus 8, $p = 0.007$) [9]. In line with these results, an international retrospective analysis from 16 countries of 174 consecutive patients with COVID-19 and acute ischemic stroke reported increased stroke severity (NIHSS: 10 [IQR: 4–18] among 174 vs. 6 [IQR: 3–14] among 330), whereas 51% of patients with COVID-19 and acute ischemic stroke had severe disability at discharge (modified Rankin Scale score 4 vs. 2, $p < 0.001$), with increased mortality as compared to non–COVID-19 historical controls [31]. In a recent systematic review including patients with cerebrovascular events in the context of SARS-CoV-2 infection, COVID-19 patients with ischemic stroke had a median NIHSS score of 15 (95% CI: 13–18), presenting frequently with large vessel occlusion (LVO) (79.6%), mainly due to either cryptogenic or cardioembolic strokes (44.7% and 21.9%, respectively) [29]. The surprisingly high proportion of COVD-19 patients presenting with cryptogenic strokes may be attributed to the limited resources and time to complete a thorough investigation in such patients at high risk of dying in a healthcare system under high pressure. In addition, social distancing and stay-in-shelter recommendations may have led to a decrease in hospital referral of stroke patients with minor symptoms [32], increasing the overall proportion of patients with LVO.

Despite timely treatment with intravenous thrombolysis and favorable postthrombectomy reperfusion, patients with COVID-19 and acute ischemic stroke had poorer clinical and radiographic outcomes than non–COVID-19 patients, which may be largely driven by LVO and early reocclusion in the prothrombotic milieu of COVID-19 [33–35]. There are likely several factors contributing to increased stroke severity and mortality in these patients, including delayed presentation with higher initial NIHSS score, tendency for large vessel involvement, and multisystemic complications of COVID-19 itself [31].

Though intravenous thrombolysis remains the standard of care for patients who present within 4.5 h of symptom onset, in a small series of four patients, intravenous use of recombinant tissue plasminogen activator (tPA) was associated with catastrophic hemorrhage, suggesting patients with COVID-19 and stroke may be at increased risk of bleeding complications [34]. The overall risk of hemorrhagic conversion in the setting of thrombocytopenia and coagulopathy, frequently encountered in COVID-19 patients, is currently unknown and should be considered on a case-by-case basis.

Pathophysiology and possible mechanisms of ischemic stroke in COVID-19

Four possible pathophysiological axes seem to be related to thromboembolism and stroke in patients diagnosed with COVID-19: (i) immune-mediated thrombosis and hypercoagulopathy, (ii) the alternative renin-angiotensin system (RAS) pathway, (iii) cardio embolism and COVID-19–associated cardiopathy, and (iv) SARS-CoV-2–mediated damage of the neurovascular unit (Figure 1).

Immune-mediated thrombosis and hypercoagulopathy

SARS-CoV-2 is a cytopathic virus that causes injury and death of affected cells [36]. Its structural protein, spike (S) glycoprotein, processed by the transmembrane protease serine 2 (TMPRSS2), allows SARS-CoV-2 to bind angiotensin converting enzyme 2 (ACE2) and entry into the host's epithelial alveolar cells [37]. Dying epithelial cells then release replicated viruses that are recognized by Toll-like receptors and upregulate the pro-interleukin (IL)-1β expression of macrophages [38]. Viral and alveolar cell fragments, recognized as pathogen- and damage-associated molecular patterns (DAMPs) by the local macrophages, trigger the activation of inflammasome (Figure 1) [38]. Inflammasome and macrophage activation leads to a local pulse of proinflammatory acute-response cytokines (tumor necrosis factor [TNF] and IL-1β) and chemotactic cytokines (IL-8 and monocyte chemoattractant protein-1 [MCP-1]), facilitating a sustained increase of IL-6. IL-6 binds to either the membrane-bound or soluble IL-6 receptor and regulates the levels of IL-6, MCP-1, and granulocyte-macrophage colony-stimulating factor (GM-CSF), perpetuating the inflammatory processes and the cytokine release syndrome [39,40].

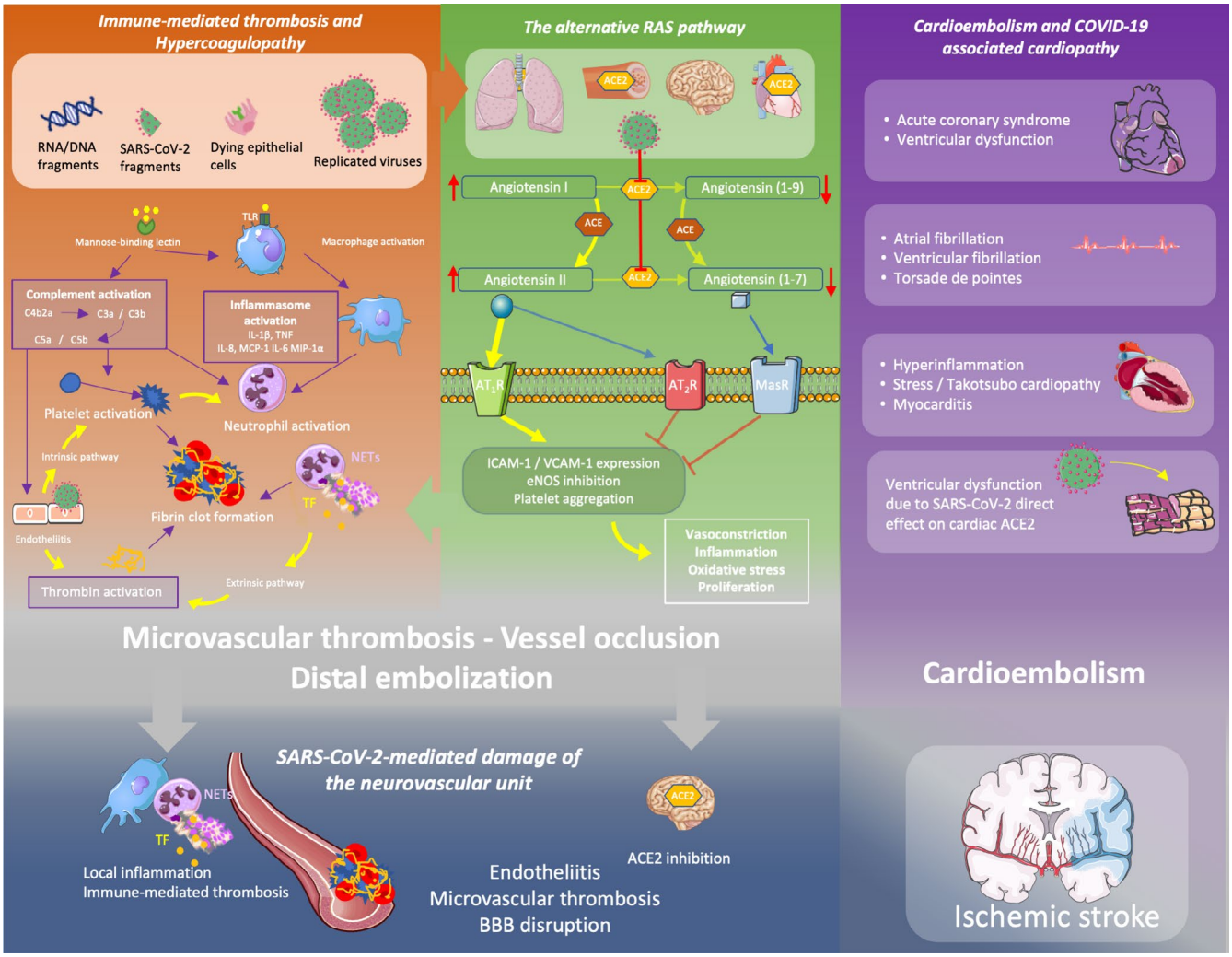

FIGURE 1 Potential mechanisms of ischemic stroke in patients with COVID-19. ACE2, angiotensin converting enzyme 2; AT_1R, angiotensin receptor type 1; AT_2R, angiotensin receptor type 2; BBB, blood–brain barrier; eNOS, endothelial nitric oxide synthase; ICAM-1, intercellular adhesion molecule 1; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; MasR, Mas receptor; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein 1α; NETs, neutrophil extracellular traps; RAS, renin angiotensin syndrome; TF, tissue factor; TLR, Toll-like receptor; TNF, tumor necrosis factor; VCAM-1, vascular cell adhesion molecule-1 [Colour figure can be viewed at wileyonlinelibrary.com]

Patients with COVID-19 who were admitted in the ICU had higher levels of GM-CSF, interferon gamma-induced protein 10, MCP-1, macrophage inflammatory protein 1a, and TNF-α, suggesting the presence of this excessive inflammatory process in critically ill patients [41]. Similarly, hospitalized COVID-19 patients presenting with neurologic disorders had increased levels of IL-6, C-reactive protein, and D-dimers [42]. Simultaneously, circulating viruses perpetuate the inflammatory response by binding to other cells expressing ACE2 [43], such as endothelial cells, where SARS-CoV-2 has the ability to enter and facilitate local inflammation and endotheliitis, which could possibly explain the presence of impaired microcirculatory function [44]. This effect was reported also in COVID-19 patients admitted to the ICU, where von Willebrand factor, P-selectine, and soluble thrombomodulin were significantly increased [45]. These data further support the hypothesis of substantial direct effect of SARS-CoV-2 in endothelial cell activation and microvascular thrombosis in patients with severe COVID-19. During this hyperinflammatory state, locally activated platelets were shown to induce the release of neutrophil extracellular traps (NETs) covered with tissue factor, which in turn activates the extrinsic coagulation cascade leading to thrombin formation [46]. Additionally, histopathological assessment of COVID-19 autopsy cases showed that microvascular thrombi were present in the lung, kidney, and heart, containing NETs-platelet aggregates, whereas a distinct neutrophil-platelet activation pattern reflects the disease severity and systemic hypercoagulability [47]. Recent histopathological data report the identification of terminal complement components deposits such as the C5b-9 (membrane attack complex), the C4d, and mannose binding lectin–associated serine protease 2, in the microvascular network, suggesting a sustained systemic activation of the complement pathways [48]. Moreover, obliterating endotheliitis was associated with the accumulation of macrophages overexpressing C5a receptor (C5aR1/CD88) around the arteries and in thrombi of patients with COVID-19, suggesting that complement activation is a major pathophysiological pathway of sustained and diffuse inflammation and coagulation in these patients, providing important knowledge for future treatment opportunities [49]. This cross-talk between innate immunity, platelets, and endothelial cells in the maladaptive host immune system leads to excessive activation of microvascular immune-mediated thrombosis and hypercoagulability [50]. Furthermore, several studies reported the presence of antiphospholipid antibodies or lupus anticoagulant in COVID-19 patients [51,52]. These antibodies have been shown to induce NETosis of healthy donor neutrophils, promoting inflammation and potentiating thrombosis when injected into mice [52]. Nevertheless, it remains unknown whether these antibodies play a role in thrombogenesis in COVID-19 patients [53]. Although, the presence of a diffuse microvascular coagulopathy in COVID-19 patients may lead to severe coagulopathy resembling disseminated intravascular coagulation (DIC) [54], several laboratory values, such as high fibrinogen, can differentiate this coagulopathy from classic DIC [55].

The alternative RAS pathway

The RAS is the primary peptide hormone system in charge of blood pressure and volume regulation in circulation. The classical RAS pathway involves renin, which stimulates the production of angiotensin I from angiotensinogen. ACE transforms angiotensin I and generates the biologically potent peptide, angiotensin II (AngII), stimulating AngII type 1 and type 2 receptors (AT_1R and AT_2R). Although AT_2R exerts vasodilatory and anti-inflammatory properties, the higher affinity of AngII to AT_1R leads to vasoconstriction and stimulation of aldosterone release from adrenal glands [56]. Apart from ACE, which is the basic component of the classic RAS pathway, ACE2 plays a pivotal role for the alternative RAS pathway. ACE2 cleaves AngII to angiotensin 1-7 (Ang[1-7]), promoting its vasodilating and anti-inflammatory effects through binding to the Mas and AT_2 receptor (Figure 1) [57]. ACE2 is present in lung alveolar epithelial cells, small intestinal epithelial cells, vascular endothelial cells, and smooth muscle cells, among others [43].

SARS-CoV-2 selectively binds with the S glycoprotein to ACE2, which serves as a functional host receptor [37], leading to a significant downregulation of the ACE2 expression in the affected cells and thus higher formation of Ang II by ACE [58,59]. AngII induces intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, and normally, its cleavage by ACE2 to Ang(1–7) inhibits the adhesion and migration of leukocytes in the tissues and may serve as an anti-inflammatory factor [60]. Additionally, ACE2 exerts significant antithrombotic effects by reducing platelet aggregation and nitric oxide release [61]. This effect, together with the direct effect of SARS-CoV-2 in the endothelial cells causing endotheliitis [44], the complement [48], platelets, and neutrophils activation [46] under the effect of a cytokine storm, may affect both the stability of already vulnerable atherosclerotic plaques and simultaneously predispose to a hypercoagulable state, contributing to arterial embolism seen in stroke patients with COVID-19.

Although the blood–brain barrier (BBB) prevents the entry of AngII and Ang(1–7) in the central nervous system [62], their effects are evident also in brain tissue. The alternative RAS system has been found to provide endogenous neuroprotection especially in the acute ischemic stroke phase. Animal model studies on ischemic stroke showed that Ang(1–7) exerts its vasodilation, anti-inflammatory, and antioxidant effects via the Mas receptor and AT_2R activation locally in the brain [63–65]. As a result, SARS-CoV-2–related inhibition of these neuroprotective effects of ACE2 may result in severe and disabling strokes as previously described in animal models [66].

Cardioembolism and COVID-19–associated cardiopathy

Even in the early phases of the pandemic, studies reported several mechanisms of cardiac involvement in patients affected by SARS-CoV-2 (Figure 1). Studies from China reported a high prevalence of increased troponin I, up to 17% among hospitalized COVID-19

patients [67], whereas cardiac injury was significantly associated with higher risk of cardiac arrhythmias and death [68].

Myocardial injury in patients with COVID-19 can be either attributed to myocardial infarction, direct SARS-CoV-2 injury, or indirect injury through stress and inflammatory response. In a case series of COVID-19 patients with ST-segment elevation, 56% presented with electrocardiographic abnormalities, and among those who underwent coronary angiography, 33% had no evidence of obstructive coronary disease [3]. Similarly, among patients diagnosed with ST-elevation myocardial infarction and COVID-19, 60.7% did not require culprit revascularization, and 39.3% did not have obstructive coronary artery disease [69]. Left ventricular (LV) dysfunction, especially in the setting of anterior wall myocardial infarction is considered an important cause of LV thrombi in the general population, significantly increasing the risk of stroke [70]. In the setting of hyperinflammation and hypercoagulability in COVID-19 patients, stasis and thrombus formation in the dysfunctional LV is an important possible cause of cardioembolism.

Apart from coronary events that may lead to cardiac dysfunction, systematic inflammatory response or direct invasion of the SARS-CoV-2 may result in significant myocardial dysfunction. Several studies reported myocardial dysfunction in the setting of nonspecific myocarditis or Takotsubo cardiomyopathy in patients with COVID-19 [71–73], which could be associated with ischemic stroke as reported recently [74,75]. Similarly, viral particles were reported in the interstitial macrophages of cardiac tissue of a patient with COVID-19 and cardiogenic shock [72], whereas among COVID-19 patients who underwent cardiac magnetic resonance imaging, 78% had cardiac involvement, and 60% had ongoing inflammation with lymphocytic infiltration [76].

Although the effect of SARS-CoV-2 on cardiac function may be attributed on systemic hyperinflammation and microvascular thrombosis seen in these patients leading to severe myocardial dysfunction, we cannot discount the potential interplay of ACE2 with cardiac dysfunction. Previous studies in animal models showed that ACE2-knockout mice developed severe LV dysfunction [77]. The essential tropism of SARS-CoV-2 to ACE2 and its downregulation, which is also expressed in the cardiac tissue [43], may provide another potential mechanism of cardiac dysfunction in these patients [78].

Systemic inflammation and myocardial dysfunction in the setting of increased cardiac output may lead to malignant ventricular arrhythmias or atrial fibrillation (AF), which in turn can be a potential cause of cardioembolism. COVID-19 patients with elevated troponin levels had a significantly higher rate of malignant ventricular arrhythmias [79], whereas evidence suggests that hyperinflammation, especially through IL-6 and TNF-α, may affect cardiomyocyte function leading to long-QT syndrome and torsades-de-pointes [80]. Sepsis and hyperinflammatory response may predispose in AF, which was prevalent in 19% to 21% of hospitalized COVID-19 patients [81]. This in-hospital stress-induced AF may significantly increase the risk of ischemic stroke or cardiovascular death in these patients [82].

SARS-CoV-2–mediated damage of the neurovascular unit

SARS-CoV-2 may have deleterious effects to the neurovascular unit (Figure 1). Systemic inflammation, endotheliitis, and microvascular thrombosis may affect the permeability of BBB, this affecting the central nervous system (CNS) directly, as seen in neurotropic respiratory viruses [83]. Although it was believed that there is a direct SARS-CoV-2 invasion to the brain through the olfactory cranial nerve leading to olfactory dysfunction [84], recent data based on animal and human models debunked this hypothesis, supporting that the olfactory dysfunction is a result of direct invasion of SARS-CoV-2 to olfactory epithelium and vascular pericytes while olfactory sensory and bulb neurons remain intact [85].

A neuropathological study of COVID-19 patients showed that 14% of the patients had new ischemic lesions, whereas SARS-COV-2 was detected in 53%, and 79% of these patients had significant cytotoxic T-lymphocytes infiltration and microglia activation, mainly in the brainstem [86]. This study had several limitations including the absence of critically ill control brains, not correlating the presence of SARS-CoV-2 and pathological findings to clinical presentation and the severity of other neuropath changes, whereas the low viral RNA identified may have been blood derived. On the other hand, another neuropathological study identified severe hypoxic changes with no cytoplasmic viral staining on immunohistochemical analysis and low levels of the SARS-CoV-2, findings that may be attributed to secondary brain ischemia and virus transfer into the brain from the disrupted BBB [87]. In addition, an experimental study using a rodent model and human autopsies, identified SARS-CoV-2 in brain tissue accompanied with neuronal death, which interestingly did not colocalize directly with virus infection [88]. Furthermore, SARS-CoV-2 was identified within microischemic regions, suggesting that CNS involvement in COVID-19 may be secondary to microvascular thrombosis and injury to the neurovascular unit, resulting in BBB disruption and viral translocation [88].

Apart from a possible direct effect of SARS-CoV-2 in the brain, which may have a causal relationship to local brain ischemia and inflammation, an indirect inflammatory effect in patients who are presented with ischemic stroke cannot be excluded. Brain tissue death, seen in ischemic and hemorrhagic stroke, results in excessive release of DAMPs, which in turn elicit localized and global inflammation, promoting BBB disruption [89]. During the hyperinflammatory state of COVID-19, the overproduction of proinflammatory acute-response proteins and adhesion molecules, together with the circulating activated leukocytes, may result in the augmentation of the local inflammatory process in the ischemic brain. This may be one possible explanation of the increased ischemic stroke severity seen in patients with COVID-19 [9,31].

Influence of COVID-19 on stroke treatment pathway

The COVID-19 pandemic exhibited a significant influence on the stroke chain of survival, with an impact on acute stroke treatment,

secondary prevention, and stroke rehabilitation. Through the systematic search of the literature we identified 20 studies reporting data on the impact of COVID-19 in ischemic stroke admissions [22,27,90–107] (Table S2) and 19 studies that reported the impact of COVID-19 in the stroke treatment pathway [22,92,93,98,101,102,104,105,107–117] (Table S3). Since the onset of the COVID-19 pandemic, many stroke centers around the globe have reported a sharp decrease in the number of stroke admissions compared to the pre–COVID-19 era. (Table S2). The exact reasons for these findings remain unclear. Most of these studies suggest that the stay at home or shelter in place orders were a major reason for this decline. Increased stroke severity during the COVID-19 pandemic [9] may suggest that patients with minor stroke or transient ischemic attack were staying at home due to lock-down orders and fear of exposure to COVID-19 in the hospital. Another possible explanation is decreased recognition of stroke, given reduced social contacts, and the overwhelming burden of COVID-19 on healthcare facilities with a high in- and outflow of patients. COVID-19 screening protocols, as well as delayed patient arrivals and the fact that hospitals exceeded their operational capacity during the pandemic, may have led to delays in providing time-sensitive acute stroke treatments, as reported in the majority of studies provided in Table S3.

Open questions and future perspectives: Potential prevention and treatments of ischemic stroke in COVID-19 patients

Although accumulating evidence revealed several pathophysiologic mechanisms of thromboembolism and hypercoagulopathy in COVID-19, future studies uncovering the mechanisms of thrombosis and stroke in the setting of COVID-19 and possible interventions are imperative. Based on the current knowledge of thrombosis pathophysiology in COVID-19 patients, the interplay of innate immunity with the coagulation cascade, and the importance of the RAS pathway, several antithrombotic and immunomodulatory drugs are being tested in clinical trials [118–121].

Medical personnel should maintain a high index of suspicion for stroke symptoms among COVID-19 patients to ensure timely revascularization treatment of acute ischemic stroke, especially of LVO, as timely reperfusion is of paramount importance to prevent further functional decline and death. Due to the accumulating evidence on the potential direct correlation of SARS-CoV-2 and cardiovascular events or stroke, treating physicians should be alerted for potential signs of COVID-19 infection, despite the fact that there are no specific signs or symptoms of the disease, and the majority of patients are asymptomatic. Although telemedicine on an outpatient level already has an increasing role in acute stroke assessment and treatment [122], its inevitable use during the COVID-19 pandemic may lead to improvements in stroke assessment in the outpatient and inpatient level, in the follow-up of patients with severe neurological deficits, or even the enrollment of stroke patients in research trials [123]. Although, this will never substitute for clinical examination and patient–physician physical interaction, telemedicine, especially in the COVID-19 pandemic era, will provide important future perspectives to reinvent stroke care worldwide.

Despite the increasing number of published studies correlating ischemic stroke with COVID-19, it is still unknown whether SARS-CoV-2 has a causal relationship to ischemic stroke. Current studies including COVID-19 patients with ischemic stroke do not provide long-term outcome data and are characterized by their retrospective designs, from different countries and with different resources, affecting the results both in prevalence and clinical outcome of patients with ischemic stroke and COVD-19. More reliable information on stroke prevalence may be provided by international prospective multicenter studies [124] to shed light on longitudinal functional disability in patients with COVID-19 and acute ischemic stroke.

The expanding knowledge on the interplay of innate immunity with atherothrombosis and stroke pathophysiology and treatment attracted more attention during the COVID-19 pandemic [125]. Preventive anticoagulation in hospitalized COVID-19 patients beyond the usual prophylaxis of venous thromboembolic disease is probably not effective [126], because it increases the bleeding risk disproportionally. Several previous experimental stroke models investigated the effect of innate immunity and immunomodulatory agents in stroke volume or the thrombus formation and lysis. In particular, blockage of the IL-1 receptor with a canakinumab-surrogate antibody improved outcomes in experimental stroke in a murine model [127], although an IL-1 receptor agonist did not show any benefit in functional outcome in ischemic stroke patients versus placebo [128].

The high reocclusion rate of LVO strokes and the decreased efficacy of intravenous tPA seen in patients with COVID-19 may be partially attributed to the hyperinflammation syndrome. Previous experimental studies suggested that NETs-rich thrombi originated from atherosclerotic plaques may be resistant to thrombolytic therapy, and that DNAase treatment may have more favorable results [129]. A recent study of the IL-6 antagonist tocilizumab in hospitalized patients with COVID-19 did not identify any difference in patients treated with tocilizumab either in clinical deterioration or in thrombotic events, although it was underpowered to investigate thrombotic events and was characterized by the small number of included patients [130]. Currently, several studies using immunomodulatory agents are recruiting patients with severe COVID-19 hyperinflammation syndrome, using either IL-1 blockade with anakinra or canakinumab [131,132] or by blocking several compounds of the complement pathway [133,134]. Moreover, SARS-CoV-2–specific drugs, such as comostat mesilate, a potent TMPRSS2 protease inhibitor interfering with SARS-CoV-2 cell entry, or TRV027, are under clinical investigation [119].

CONCLUSIONS

Several potential inflammatory and prothrombotic mechanisms may contribute in the risk of cardiovascular events and stroke

among patients with COVID-19. A growing body of evidence on pathophysiological mechanisms of COVID-19 and the launch of several safe and effective vaccines allows optimism for the future [135,136]. However, until broad global vaccinations and immunizations are achieved, the burden of the SARS-CoV-2 effect will be apparent in everyday clinical practice. In this context, stroke physicians will continue to encounter patients with COVID-19. The available related evidence is accumulating rapidly as depicted in this review and will enhance our ability to understand, prevent, and treat ischemic stroke patients in the era of COVID-19 more effectively.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Dimitrios Sagris: Conceptualization (equal), data curation (equal), formal analysis (lead), investigation (lead), methodology (lead), writing–original draft (lead), writing–review & editing (equal). **Aikaterini Papanikolaou:** Data curation (equal), formal analysis (equal), methodology (equal), writing–original draft (supporting). **Alexandra Kvernland:** Data curation (equal), methodology (supporting), writing–original draft (supporting), writing–review & editing (equal). **Eleni Korompoki:** Writing–original draft (supporting), writing–review & editing (equal). **Jennifer A. Frontera:** Writing–original draft (supporting), writing–review & editing (lead). **Andrea B. Troxel:** Writing–original draft (supporting), writing–review & editing (equal). **Maria Gavriatopoulou:** Writing–review & editing (equal). **Haralampos Milionis:** Writing–original draft (supporting), writing–review & editing (equal). **Gregory Y. H. Lip:** Writing–review & editing (lead). **Patrik Michel:** Writing–review & editing (lead). **Shadi Yaghi:** Conceptualization (lead), investigation (equal), writing–original draft (equal), writing–review & editing (lead). **George Ntaios:** Conceptualization (lead), investigation (lead), methodology (equal), writing–original draft (equal), writing–review & editing (lead).

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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