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Cerebrovascular Disorders (D Jamieson, Section Editor)

Cerebrovascular Manifestations of SARS-CoV-2: A Comprehensive Review

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Abstract

Purpose of review The risks of cerebrovascular manifestations due to SARS-CoV-2 infection are significantly increased within the first 6 months of the infection. Our work aims to give an update on current clinical aspects of diagnosis and treatment of cerebrovascular manifestations during acute and long-term SARS-CoV-2 infection.

Recent findings The incidence of acute ischemic stroke and haemorrhagic stroke during acute SARS-CoV-2 patients is estimated at 0.9 to 4.6% and 0.5–0.9%, respectively, and were associated with increased mortality. The majority presented with hemiparesis, dysarthria, sensory deficits, and a NIHSS score within 5–15. In addition, beyond the first 30 days of infection people with COVID-19 exhibited increased risk of stroke. During acute

phase, age, hypertension, diabetes, and medical history of vascular disease were increased in patients with COVID-19 with new onset of cerebrovascular manifestations, while during long-COVID-19, the risk of cerebrovascular manifestations were found increased regardless of these factors. The management of patients with large-vessel ischemic stroke fulfilling the intravenous thrombolysis criteria are successfully treated according to the guidelines, while hyperosmolar therapy is typically administered in 4- to 6-h intervals. In addition, prophylaxis of anticoagulation therapy is associated with a better prognosis and low mortality during acute and post hospital discharge of patients with COVID-19.
Summary In this work, we provide a comprehensive review of the current literature on acute and post-acute COVID-19 cerebrovascular sequelae, symptomatology, and its pathophysiology mechanisms. Moreover, we discuss therapeutic strategies for these patients during acute and long-term care and point populations at risk. Our findings suggest that older patients with risk factors such as hypertension, diabetes, and medical history of vascular disease are more likely to develop cerebrovascular complications.

Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has becoming a global pandemic health problem [1–3] accounting more than 753,823,259 reported cases and more than 6.8 million deaths worldwide as of February 2, 2023 [4]. SARS-CoV-2 is a member of the genus *Betacoronavirus* which is a positive-sense single-stranded RNA (ssRNA) genome of 27–32 kb in size enveloped in crown-like morphology viral particles of 100–160 nm diameter presenting a great capacity for fast mutations and recombination [5••, 6]. The Middle East respiratory syndrome (MERS) virus caused by MERS-CoV, another *Betacoronavirus*, highly pathogenic coronavirus, appears more distantly related with only 79.6% genomic sequence identity with that of SARS-CoV-2 [7]. The SARS-CoV-2 target cells through the binding of spike (S) protein with angiotensin-converting enzyme 2 (ACE2) [8•], a membrane-bound aminopeptidase which plays a vital role in heart function, hypertension, and diabetes [9, 10]. Among the structural proteins, the S protein has pivotal roles in virus attachment and entry and disease pathogenesis [11]. Binding of spike protein with ACE2 is followed by cleavage of the first one by the transmembrane protease serine 2 (TMPRSS2) which facilitates the entry of the virus by fusion of the viral membrane with the membrane of the host cell [12•]. These proteins are mostly expressed by respiratory tract epithelial cells making the lungs the main gateway for the virus [13], enterocytes of the small intestine kidney, vascular endothelial cells, and the heart cells leading to cardiovascular complications and partially explain the extrapulmonary manifestation of SARS-CoV-2 infection [9, 14]. Patients frequently present with symptoms of a respiratory infection such as fever, dry cough, dyspnoea, headache, fatigue, and bilateral ground-glass opacities on chest computerized tomography (CT) scans [15, 16]. Common laboratory abnormalities found in patients with COVID-19 include lymphopenia [2] and elevation in lactate dehydrogenase and inflammatory markers such as C-reactive protein, D-dimer, ferritin, and interleukin-6 (IL-6) which levels may correlate with disease severity and a procoagulant profile [17]. IL-6 levels may correlate with disease severity and a procoagulant profile [18].
Complications of SARS-CoV-2 infection include viral pneumonia, acute respiratory distress syndrome (ARDS), a life-threatening form of respiratory failure [19], septic shock, anaemia, and acute cardiac injury [1, 16]. In addition, SARS-CoV-2 infection can trigger a cytokine storm resulting in multiorgan failure [20] and coagulation abnormalities leading to thromboembolic events [21]. The central nervous system vasculature can also be affected by complications arising from the effects of SARS-CoV-2 [22]. It is estimated that the risk of cerebrovascular events such as acute ischemic stroke and intracranial haemorrhage was found to be significantly increased within the first 6 months after

SARS-CoV-2 infection [23]. Moreover, survivors of COVID-19 may be left with chronic post-viral complications similar to the previous severe acute respiratory syndrome (SARS) and MERS pandemics [24]. According to the Royal College of General Practitioners, SARS-CoV-2 infection is divided into 3 timeframe points; the acute-COVID-19 in which patients present with up to 4 weeks of symptoms of SARS-CoV-2 infection and long-COVID-19 include patients with symptoms persisting more than 4 weeks [25, 26].

In this work, we provide a comprehensive review of the current literature on acute and long-COVID-19 cerebrovascular manifestations, symptomatology, and its pathophysiology mechanisms. Moreover, we discuss therapeutic strategies for these patients during acute and long-term care and point populations at high risk.

Underlying pathophysiology mechanisms of SARS-CoV-2

The majority of patients with COVID-19 who experience acute ischemic stroke or haemorrhagic stroke have underlying traditional vascular risk factors such as hypertension (56 to 95%) or diabetes mellitus (34 to 60%) [27, 28, 29••]. The main mechanism is thought to originate from infection of brain vascular pericytes via the Spike protein, which connects on the ACE2 receptor, leading to oxidative damage and immunoreactivity [30], while renin-angiotensin-aldosterone axis (RAAS) dysfunction due to decreased ACE2 expression may promote increased blood pressure in patients with a history of hypertension, a known risk factor of intracerebral haemorrhage (ICH) [31]. Potential contributions from hypercoagulable states or endothelial dysfunction may explain why cryptogenic stroke aetiology appears more likely in COVID-19-related ischemic stroke [32]. The hypercoagulability may further add to the risk of developing cerebral venous thrombosis (CVT) or ischemic stroke [33, 34]. Endothelial dysfunction may be coupled with coagulopathy to produce the phenotype of COVID-19-associated AIS. A study in 2098 patients suggested that elevated D-dimer levels are predictive of increased stroke risk and severe disease progression. This finding was validated in a hospital cohort, in which cryptogenic stroke cases were significantly more likely to have elevated D-dimer levels compared with cardioembolic and atherosclerotic/lacunar stroke subtypes (50.8% versus 32.7% versus 4.5%, $p = 0.0064$) [35]. A study of inflammation markers in 60 COVID-19 AIS cases concludes that elevated D-dimers, lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), and CRP were strong predictors of AIS occurrence ($p < 0.001$) [36]. Increased content of neutrophils and a higher neutrophil-to-lymphocyte ratio in thrombi from large vessel occlusion (LVO) in patients with COVID-19 efficiently differentiated them from non-COVID-19-related thrombi [37]. Cardiac dysfunction related to SARS-CoV-2 infection including myocarditis, stress cardiomyopathy, myocardial ischemia or infarction, and new arrhythmia could also increase the risk for cardioembolic stroke [38, 39]. A meta-analysis estimated an 11% prevalence of atrial fibrillation in hospitalized patients with COVID-19 and up to 10% of patients with new-onset atrial fibrillation [40, 41].

Another proposed mechanism for ICH concerns degenerative changes in cerebral vessels, caused either by comorbidities like diabetes mellitus (DM) or by SARS-CoV-2-induced inflammatory coagulopathy [31]. In addition,

anticoagulation therapy increases the risk of ICH development. In the study by Kvernland et al., patients with COVID-19 who developed haemorrhagic stroke were more likely to be on anticoagulation therapy compared to controls, 90.9% vs. 11.8%, respectively ($p < 0.001$). Of all patients with COVID-19 and haemorrhagic stroke, only three had isolated non-aneurysmal subarachnoid haemorrhage with no associated intraparenchymal haemorrhage. Interestingly though, hypertension was the most common aetiology for contemporary controls; therefore, the haemorrhagic stroke was mostly attributed due to coagulopathy [42]. Anticoagulation use associated with increased risk of ICH in patients with COVID-19 was also reported by Melmed et al. [43]. In a different study, since cerebral microhaemorrhages are increasingly being recognized as a complication of COVID-19 [44], Dixon et al. investigated the potential pathophysiology through assessing the pattern of microhaemorrhage and clinical characteristics of patients with COVID-19 [45]. Dixon et al. concluded that the pattern of cerebral microhaemorrhage is similar to the pattern reported in patients without COVID-19 who are critical ill and other causes of severe hypoxia rising questions regarding whether microhaemorrhage occurs from endothelial dysfunction due the direct effect of SARS-CoV-2 infection or from the secondary effects of critical illness and hypoxia [45].

Clinical cerebrovascular manifestation of SARS-CoV-2

In a recent neuropathological study, infected primates consistently presented with brain microhaemorrhages, and SARS-CoV-2 could be detected in the cerebral vasculature, but not the parenchyma [22, 44]. Additionally, perivascular inflammation and microangiopathy were encountered in the majority of brain autopsies from patients with COVID-19 [46–49]. Studies in hospitalized [50] and recovered [51] patients exhibited lower cerebral blood flow velocity values than healthy controls. The decrease correlated with disease severity and serum levels of inflammatory markers C-reactive protein (CRP), procalcitonin, and interleukin 6 (IL-6) [51]. These findings emphasize the importance of high clinical suspicion for stroke in this group.

Ischemic stroke

Acute ischemic stroke concomitant with SARS-CoV-2 infection has been extensively described in the literature [28, 52•, 53–60, 61•, 62] ranging from 0.9 to 4.6% (Table 1). A representative CT scan image of patients with COVID-19 diagnosed with ischemic stroke in the distribution of the right posterior cerebral in the presence of vascular risk factors is shown in Fig. 1. In a single-centre, retrospective, observational study of 219 patients with COVID-19, 10 patients (4.6%) developed AIS. Patients with COVID-19 and with new onset of cerebrovascular disease were significantly older (75.7 ± 10.8 vs 52.1 ± 15.3) years and more likely to have cardiovascular risk factors, including hypertension and diabetes. In addition, they were more likely to present with severe COVID-19 (81.8% vs 39.9%) and to have increased inflammatory response

Table 1. Cerebrovascular manifestation of COVID-19 and clinical characteristics

Reference	Patients	*Ischemic stroke (%)*	*Intracerebral haemorrhage (%)*	Clinical Characteristics
Li et al. [52•]	219	4.6	0.5	Older age, hypertension, diabetes mellitus, medical history of vascular disease
Yaghi et al. [28]	3556	0.9		Diabetes mellitus
Wang et al. [53]	36,358	0.34		Older age, smoking, hypertension, hyperlipidemia, diabetes mellitus, heart disease, chronic kidney disease
Merkler et al. [54]	2132	1.5		
Rothstein et al. [55]	844	2.4	0.9	95% hypertension, 60% a history of diabetes mellitus
Cantador et al. [56]	1419	0.4		
Lodigiani et al. [57]	388	2.3		
Jain et al. [58]	3218	0.8	0.3	
Shahjouei et al. [62]	17799	0.7	0.1	
Katsanos et al. [61•]	Meta-analysis study (67,845 patients)	1.1	0.2	Diabetes mellitus
Kvernland et al. [42]	Retrospective cohort study (4071 patients)		0.5	Coagulopathy
Leasure et al. [77]	Retrospective, cross-sectional analysis (21,483 patients)		0.2	Older age, male sex, hypertension, hyperlipidemia, diabetes mellitus
Bekelis et al. [59]	Multicenter cross-sectional study (24,808 patients)	0.9		
Luo et al. [60]	Meta-analysis study (26,691 patients)	2		Hypertension, hyperlipidemia, diabetes mellitus

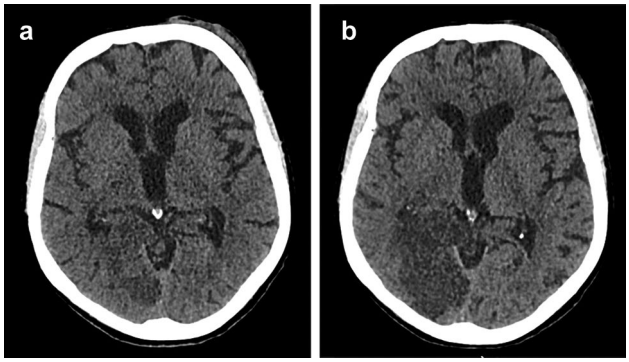

Fig. 1 Representative figure of a CT scan of an 80-year-old COVID-19-positive patient with a history of hypertension and diabetes, presented at the ER reporting headache and fall after vertigo and loss of balance. A left hemiparesis was evident. **a** Ischemic stroke in the distribution of the right posterior cerebral artery (hypodense imaging and blurring of gray-white matter) at the day of presentation. **b** Three days later. COVID-19, coronavirus disease 2019; CT, computed tomography.

and hypercoagulable state [52•]. A meta-analysis of 18 cohort studies, with a total of 67,845 participants, estimated a pooled prevalence of 1.1% (95% CI = 0.8% to 1.3%) [61•]. Infection from SARS-CoV-2 increased the odds ratio (OR) for ischemic (OR = 3.58, 95% CI = 1.43–8.92) or cryptogenic stroke (OR = 3.98, 95% CI = 1.62–9.77) [61•]. A slightly different pooled estimate was calculated from a meta-analysis of 26,691 COVID-19 cases, namely, a prevalence of 2% (95% CI = 1 to 2; $p < 0.01$) [60]. Intriguingly, some later studies indicated a different prevalence. In a retrospective study of 36,358 hospitalized patients from Wuhan, only 124 (0.34%) were diagnosed with AIS, which was correlated with severity of infection [53]. Furthermore, a multicentre study from New York identified 22 AIS incidents from 2513 COVID-19 cases (0.9%), with an OR of 0.35 (95% CI = 0.23–0.55) compared to a non-COVID-19 cohort [59]. However, these patients had a ninefold increase in mortality [59]. These discrepancies have prompted opinions that attribute the increased risk of AIS not on the virus but rather on sepsis, cardiovascular factors, and their interplay with COVID-19 [63–65]. COVID-19-associated AIS can also affect young patients (< 55 years old) at higher rates, even without any known risk factors [66], and children [67]. Generally, outcomes in AIS COVID-19 patients are worse in comparison with non-COVID-19 cases. In a comparative study, COVID-19 AIS patients ($n = 62$) were discharged with a higher mean modified Rankin scale score (mRs; 3.58 vs 1.86; $p = 0.001$) and mean NIHSS score (9.5 vs 2.31; $p = 0.001$) [68].

Symptomatology varies significantly between patients. The Global COVID-19 Stroke Registry among 174 AIS patients identified predominantly motor symptoms (67.8%), dysarthria (46%), and sensory deficits (42%) [69]. Furthermore, when matched with 336 patients without COVID-19, patients with COVD-19 infection and AIS presented with a higher National Institutes of Health Stroke Scale (NIHSS) score (10 versus 6, $p = 0.03$; OR = 1.69, 95% CI = 1.08–2.65) [69]. Among 323 participants in the Multinational COVID-19 Stroke Study, the majority presented with hemiparesis (72.4%) and a NIHSS score within 5–15 (43.8%) [70]. Using neuroimaging as the diagnostic modality of choice, categorization of AIS events has been possible.

COVID-19 AIS patients (156) were classified using the Trial Org 10172 in Acute Stroke Treatment (TOAST) criteria into cryptogenic stroke (35.6%), cardio-embolism (CE; 22.4%), large vessel occlusion (LVO; 9.6%), small vessel occlusion (SVO; 2.5%), and miscellaneous causes (7%). Cryptogenic strokes were associated with increased mortality [71]. Additional evidence resulted from a meta-analysis of 10 different epidemiological studies, which derived a pooled prevalence of 35% (95% CI = 12–59%; $p < 0.01$) for cryptogenic stroke, while only 2% for SVO [60]. Some studies have proposed even greater incidence of cryptogenic stroke close to 50%, which may be attributed to cerebral endothelitis [72, 73]. In other cohorts, an increased incidence of LVO has been noted, varying from 40% [28, 74] to 60% [75, 76].

Haemorrhagic stroke

Haemorrhagic stroke encompasses both intracerebral haemorrhage (ICH) occurring within the brain parenchyma and haemorrhages occurring between the brain and the meninges, most importantly subarachnoid haemorrhage (SAH). Li et al., in a single-centre, retrospective, observational study, reported that 1 out of 219 patients with COVID-19 (0.5%) developed intracerebral haemorrhage [52•]. A retrospective cohort study of 4071 patients with COVID-19 by Kvernland et al. calculated a prevalence of 0.5% for haemorrhagic stroke. Out of them, only 3 presented with SAH [42]. Another report identified 48 (0.2%) patients with ICH [77], while a study focused on SAH reported, 86 patients with non-traumatic SAH among 85,645 patients with COVID-19 (Table 1) [78]. Patients with COVID-19 and SAH had higher mortality rates compared to control group (patients with SAH) (31.4% vs. 12.2%, $p < 0.0001$) [78].

Diagnostic workup of ICH is non-specific. From a cohort of 33 patients with haemorrhagic stroke, 17 (51.5%) presented with encephalopathy, 7 (21.2%) with focal neurological deficits, 4 (12.1%) with absent brainstem reflexes, while in 2 (6.1%) as an incidental finding [79]. These patients have been found to have elevated blood levels of inflammatory markers (D-dimers, CRP, IL-6, ferritin, LDH) in different case series [77, 80]. Imaging typically involves non-contrast CT. Patients with ICH and COVID-19 have been observed via CT to have a higher bleeding speed, more haemorrhagic foci, and extension in a larger area than with a typical ICH, independent of vascular risk factors [81].

Cerebral venous or sinus thrombosis

Cerebral venous or sinus thrombosis (CVST) cases may be exacerbated by COVID-19. Using data from the Society of Vascular and Interventional Neurology registry, an estimated 207.1 per million COVID-19 cases presented with CVST (99%CI = 23.3 to 757.7 per million), in contrast with pre-pandemic rates of 2.4 per million (99% CI = 2.1–2.6 per million) [82]. The meta-analysis by Katsanos et al. estimated a pooled rate of 0.03, in accordance with the previous results [61•]. Although this condition is known to be elicited by

pro-thrombotic states [83], no studies exist in the literature investigating the precise mechanism implicating COVID-19 with CVST.

A multicentre study across 31 hospitals managed to identify 8 patients with COVID-19 and CVST, as well as 33 described in the literature. The overall cohort (75%) had no identifiable risk factors, and the majority presented with non-specific symptoms like headache, gastrointestinal irritations, and low-grade fever [84]. Neurologic symptoms, such as loss of consciousness, focal deficits, and seizure tended to present later, as did to radiologic signs of CSVT [84]. Another observational study of 20 patients recorded similar symptomatology, but also identified several eliciting factors in patients' history, such as smoking, polycythaemia, deep venous thrombosis, and oral contraceptive use. Interestingly, many different laboratory serum markers associated with coagulation were elevated: D-dimers (87.5%), ESR (69%), homocysteine (50%), and lupus anticoagulant (10%) [85].

Neuroimaging can assist in distinguishing CSVT from AIS. Commonly encountered CT and MRI findings in COVID-19 patients with CSVT include haemorrhagic venous infarctions, microhaemorrhages and oedema, as well as hyperdensity of the affected vessels. Lesions were mostly localized in the parieto-occipital area. Confirmation of diagnosis can be made via MR venography [86, 87].

Reversible cerebral vasoconstriction syndrome

Albeit rare, reversible cerebral vasoconstriction syndrome (RCVS) has been noted to occur in patients with COVID-19 [88, 89]. RCVS represents a group of conditions with reversible multifocal narrowing of the cerebral arteries, as noted on vascular imaging studies, with clinical manifestations that typically include thunderclap headache and may include neurologic deficits related to brain oedema, venous infarcts, or seizures [90–92]. RCVS has been hypothesized to be elicited by downregulation of the ACE2-receptors, activating the sympathetic nervous system, and the RAAS, eventually promoting dysregulation of arterial tone and vasoconstriction [89]. A multicentre case series identified 10 patients with COVID-19 that developed RCVS. Out of them, 3 reported no predisposing conditions, 7 reported use of vasoconstrictive medication, and 2 had a history of migraine. Regarding symptomatology, 5 presented with thunderclap headache, the characteristic symptom of RCSV, and 3 with focal neurologic deficits [88]. Signs of ischemic or haemorrhagic stroke were evident in MRI, and RCVS was confirmed via CTA, MRA, or catheter angiography [88] by demonstrating the characteristic pattern of multifocal segmental vasoconstriction of medium and large cerebral vessels [93]. RCVS has also been described in two paediatric patients [94].

Posterior reversible encephalopathy syndrome

Posterior reversible encephalopathy syndrome (PRES) is another rare clinico-radiological syndrome characterized by a headache, seizures, altered mental status, and visual loss. It is characterized by white matter vasogenic oedema predominantly affecting the posterior occipital and parietal lobes of the brain,

although characteristic imaging changes can be found throughout the central nervous system [95]. Only few cases PRES have been documented in the COVID-19 literature. In the largest case series until now, 6 patients were described with the characteristic clinical and radiologic signs of PRES. More specifically, the patients with PRES present with hypertensive episodes or blood pressure alterations, impaired consciousness, seizures, and visual disturbances. All patients recovered partially or fully without PRES-specific interventions [96]. MRI imaging via T2-FLAIR revealed bilateral parieto-occipital white matter oedema with bright signal intensity, which has been noted to frequently convert to haemorrhagic PRES in COVID-19 patients [87].

Long-term cerebrovascular manifestations of COVID-19

Many COVID-19 survivors suffer from long-COVID-19 syndrome, with the number dramatically increasing as more are infected [97]. Long-COVID-19 is characterized by a highly variable severity ranging from nearly asymptomatic, mild (e.g., slight fatigue) to severe disability (e.g. ongoing dyspnoea, neuropsychiatric symptoms, such as chronic fatigue, to arterial, venous, and microvascular thrombotic complications) spanning multiple organ systems and affecting the quality of life [98]. Most studies have found that the severity of the disease can lead to worse or prolonged symptoms; therefore, it is important and to include multidisciplinary collaboration for the management of patients with long-COVID-19 [99]. The estimated annual incidence rate of AIS in South Asian males aged 50 years or younger was reported significantly higher in those with asymptomatic COVID-19 infection compared to those to historical data. The AIS was reported to occur post-SARS-CoV-2 infection with a median time from a positive serological test result to stroke being 55 days (range 0–130 days) [100]. Survivors from COVID-19 among non-vaccinated population were associated with increased risks of cerebrovascular diseases, such as stroke, hazard ratio (HR) = 1.618 (95% CI 1.545 to 1.694), and transient ischemic attack (TIA) (HR) = 1.503 (95% CI 1.353 to 1.670) [101•]. Yan Xie et al., using national healthcare databases from the US Department of Veterans Affairs of 153,760 US veterans who survived the first 30 days of COVID-19 and two control a cohort of total of 11,497,058 non-COVID-19-infected VHA, provided the evidence that beyond the first 30 days of infection people with COVID-19 exhibited an increased risk of stroke (HR) = 1.52 (95% CI 1.43 to 1.62) (Table 1); burden 4.03 (95% CI 3.32 to 4.79) per 1000 persons at 12 months; and transient ischemic attacks (TIA) (HR = 1.49 (95% CI 1.37 to 1.62); burden 1.84 (95% Cs 1.38 to 2.34) [102•]. The risks were evident regardless of age, race, sex, and other vascular risk factors, including obesity, hypertension, diabetes, chronic kidney disease, and hyperlipidaemia. The exact mechanisms underlying cerebrovascular events remained undetermined, but the high incidence of high-risk cardioembolic conditions (e.g., atrial fibrillation, heart failure, acute coronary syndrome, myocarditis) suggests that strokes may be secondary to cardiac disease, while

other COVID-19-related mechanisms (e.g., hypercoagulopathy, endotheliitis) likely contribute to the final events. Elevated levels of plasma factor VII and plasminogen activator inhibitor-1 have been shown to persist after SARS-CoV-2 infection [103]. Moreover, it is reported that long-term effects of SARS-CoV infection have been found to also affect lipid and glucose metabolism in recovered SARS patients [104]. In addition, Bikdeli and coworkers reported AIS as a secondary wave of complications of COVID-19 and postulated that the prothrombotic state associated with acute COVID-19 may persist long term [21, 105].

Management of patients with cerebrovascular sequelae during acute-COVID-19 and post hospital discharge

Since the risk of thromboembolism is high in COVID-19 patients, especially in moderate and severe illness, a prophylactic dose of LMWH is recommended for all hospitalized COVID-19 patients [106, 107]. The American Society of Hematology (ASH) guidelines recommended prophylactic dose anticoagulation over intermediate and therapeutic intensity regimens due to small absolute risk difference, with no preference for any specific agent [108]. A case series of 17 patients receiving therapeutic doses of various anticoagulation medications pointed out the probability of resistance due to COVID-19 coagulopathy [109]. In a study comparing thrombotic outcomes between 108 patients receiving prophylactic dose and 71 receiving therapeutic dose heparin, the latter presented no AIS, while in the former group 6 patients (5.6%) eventually developed AIS. The difference was statistically significant [110]. Nevertheless, LMWH has been found to significantly increase the rate of symptomatic intracranial haemorrhage [111].

Anti-platelet therapy, specifically aspirin, did not prove effective in mitigating ischemic stroke risk in a control-matched study of 248 COVID-19 patients, but a small effect in preventing thrombotic events was noticed [112]. Hydroxychloroquine, which received Emergency Use Authorization from the US Food and Drug Administration for treatment of COVID-19, may potentially exert antithrombotic properties, especially against antiphospholipid antibodies [113], while, fingolimod, an immunomodulating medication is being tried for COVID-19, may reduce reperfusion injury and improve outcomes in patients suffering from AIS [114]. Thrombolysis is considered the mainstay of treatment for AIS (Fig. 2). The CASCADE multicentre study assessed the safety and efficacy of intravenous tissue plasminogen activator (IV-tPA) in 101 patients with AIS and COVID-19, which was not associated with increased risk of disability, haemorrhagic transformation or death [115]. A smaller, comparative study reached the same conclusion [116]. Patients with AIS due to LVO could benefit by mechanical thrombectomy (MT). A multicentre study collected data on 93 COVID-19 LVO patients who eventually underwent MT, and noted a 29% 30-day mortality, which was concurrent with higher inflammatory serum biomarker levels (aspartate, LDH) [117]. Poor

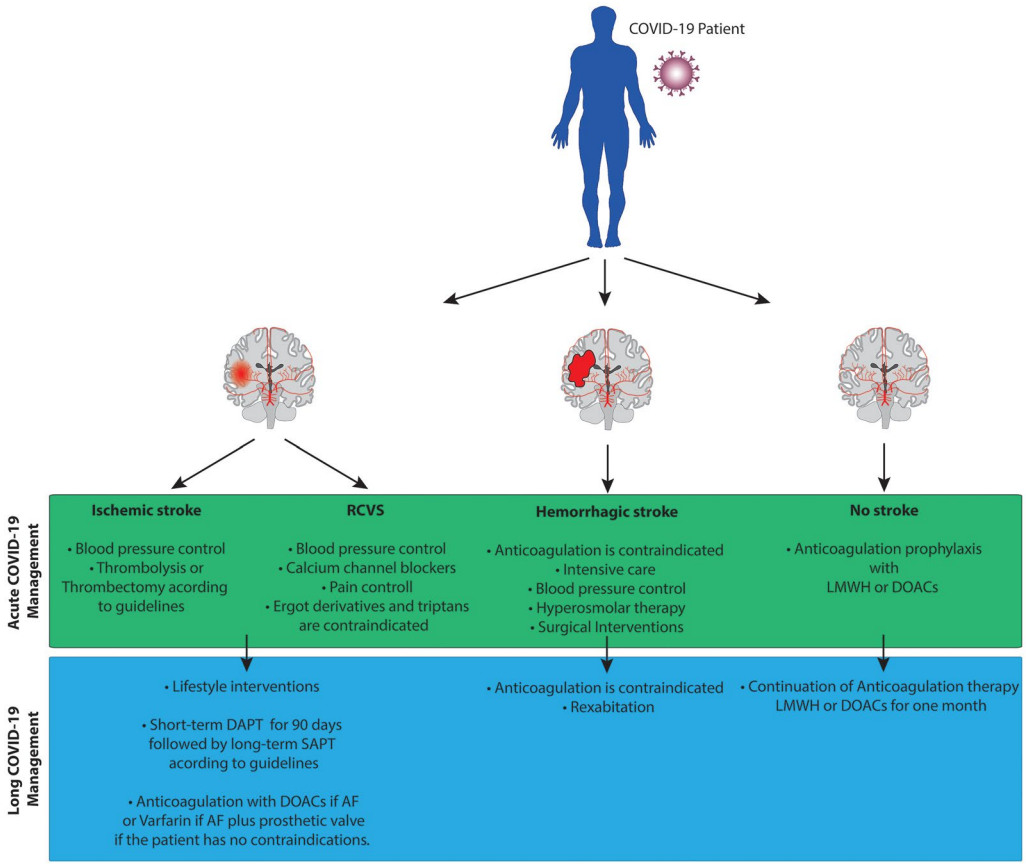

Fig. 2 Summary of therapeutic approaches during acute and long-COVID-19, graphical representation. Despite SARS-CoV-2 infection, thrombolysis is considered the mainstay of treatment for AIS according to guidelines, while patients with AIS due to LVO could benefit by mechanical thrombectomy. Patients with ischemic stroke or TIA should receive short-term DAPT for 90 days followed by long-term SAPT. Anticoagulation with DOACs is indicated if AF is present. Current recommendations for RCVS include withdrawal of precipitating agents, symptomatic and empiric treatment with IA calcium channel blockers (CCBs), and pain control using opioid analgesics. Ergot derivatives and triptans are contraindicated. The majority of patients with hemorrhagic stroke (90%) requires intensive treatment. Close monitoring, blood pressure control, and hyperosmolar therapy is indicated. Surgical interventions are recommended to certain patients according to guidelines. Anticoagulation in patients with hemorrhagic stroke is contradicted during both, hospitalization and post hospital discharge. A prophylactic dose of with LMWH or DOACs for 1 month is recommended to all hospitalized patients with COVID-19 to reduce the stroke incidence. RCVS, reversible cerebral vasoconstriction syndrome; TIA, transient ischemic attack; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet; LMWH, low-molecular-weight heparin; DOACs, direct oral anticoagulants; AF, atrial fibrillation.

prognosis, with a median NIHSS = 13 at discharge, and high rates of mortality (30.6% by discharge) were also consistently detected in another cohort of 111 LVO patients [118]. Treatment in the multicentre study by Abdalkader et al. and the observational study by Hameed et al. most commonly consisted of systemic anticoagulation administration of low-molecular-weight heparin (LMWH) or unfractionated heparin, for CVST. In both studies, 60–70% of patients were discharged home with minimal residual symptoms (mRS ≤ 2), while 10–40% of patients died [84, 85]. Thrombectomy, IV-tPA,

ventriculoperitoneal shunt, decompressive craniectomy, aspirin, and steroid infusions have also been described in the literature but have not been widely adopted [84]. According to guidelines, hyperosmolar therapy (Fig. 2) is typically administered in 4- to 6-h intervals. However, the duration of transient effects from hyperosmolar therapy in the setting of ICH is unclear [119, 120].

Decompressive hemicraniectomy has been described in a small case series of 3 patients with malignant cerebral oedema, 2 of which improved significantly [121]. Most patients haemorrhagic stroke eventually require intensive care – 90%, according to the COVID-19 Cardiovascular Disease Registry, vs 30% with non-COVID-19 ICH (Fig. 2). Accordingly, higher rates of mechanical ventilation (77% versus 19%) and extracorporeal membranous oxygenation (4% versus 0.6%) were recorded [77]. Mortality rates for larger cohorts in the literature range from 45 to 70%, in contrast with 20% in non-COVID-19 instances [31, 43, 77].

Concerning RCVS therapy, current recommendations include withdrawal of precipitating agents, symptomatic and empiric treatment with intra-arterial calcium channel blockers (CCBs), which may relieve arterial narrowing [93]. In the previously mentioned case series, treatment consisted of discontinuation of vasoconstrictive agents, and two patients were administered CCBs [88]. The pain of RCVS-associated headache should be controlled using opioid analgesics in addition to nonsteroidal anti-inflammatory drugs (NSAIDs). Ergot derivatives (e.g., dihydroergotamine and ergotamine) and triptans are contraindicated since they present a vasoconstrictive activity that may aggravate symptoms and outcome of RCVS (Fig. 2) [122].

After hospital discharge from acute illness, for COVID-19 patients with stroke and TIA, secondary stroke prevention [123] should be applied according to 2021 guidelines [124••]. Hypertension, smoking, physical activity, diet, psychosocial factors, abdominal obesity, alcohol, cardiac causes, and apolipoproteins account for 91.5% of the population-attributable risk for ischemic stroke, similar across world regions, sexes, and age [125]; therefore, lifestyle interventions are important to reduce the risk. Patients with stroke/TIA not attributable to other stroke causes related to specific antithrombotic recommendations (e.g., atrial fibrillation, intracranial stenosis) should receive antithrombotic therapy for the prevention of recurrent stroke. Starting short-term dual antiplatelet (DAPT) therapy followed by long-term single antiplatelet (SAPT) therapy is preferred compared with single antiplatelet therapy; however, beyond 90 days after stroke, DAPT is associated with increased risk of bleeding and no benefit in long-term reduction of recurrent stroke risk (Fig. 2) [126, 127•]. Low dose of aspirin is shown to reduce death and repeat stroke event while clopidogrel marginally superior to aspirin is slightly correlated with increased incidence of intracranial haemorrhage [128, 129]. Recommendations for the short-term (21–90 days) use of DAPT with aspirin and clopidogrel demonstrated a reduction in recurrent ischemic stroke [130]. Aspirin dosing 75–100 mg for patients weighing < 70 kg and higher doses for those > 70 kg is more effective for the prevention of vascular events [131]. Ticagrelor (180 mg loading dose, then 90 mg twice daily) plus aspirin (300 to 325 mg loading does, then 75–100 mg daily) for 30 days was shown to be slightly superior to aspirin alone in preventing recurrent stroke but was

also associated with significantly increased risk of severe bleeding [132]. In addition, COVID-19 patients are at high risk for atrial arrhythmia. As it is reported during acute-COVID-19, the prevalence for atrial arrhythmia was 9.2% (95% CI:6.5–12.7%) [133], while patients infected by SARS-CoV-2 present an increased fibrillation, with a hazard ratio (HR) = 1.71 (95% CI = 1.64 to 1.79); (burden) = 10.74 (95% CI = 9.61 to 11.91) [101•, 102•] as long-COVID cardiovascular complication. Therefore, extended prophylaxis of anticoagulation therapy should be considered with LMWH [134] or direct oral anticoagulants (DOACs) for all hospitalized patients with SARS-CoV-2 [135, 136, 137••] as they can reduce the risk of cerebrovascular manifestation as secondary events of atrial fibrillation and patients with increased incidence of thrombus formation, at the cost of increase in bleeding events, including major bleeding [138, 139]. For patients whose the cause of ischemic attack is atrial fibrillation/flutter, long-term with anticoagulation therapy (DOACs) as first choice or Varfarin in case of prosthetic valve is present should be covered for secondary stroke prevention [140].

Conclusions

Cerebrovascular complications are not rare during SARS-CoV-2 infection. The majority of COVID-19 patients who experience AIS or haemorrhagic stroke during the acute phase have underlying vascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia, and underlying vascular disease. In addition, studies suggest that SARS-CoV-2 infection is also an independent risk factor for development of stroke [61•]. Moreover, there is an increased risk for post-COVID-19 cerebrovascular complications regardless of age, sex, race, and cardiovascular morbidities such as hypertension, diabetes, hyperlipidaemia, and chronic kidney disease. In addition, the non-vaccinated population of COVID-19 survivors have an increased risk of cerebrovascular diseases, such as stroke and transient ischemic attack.

An extended prophylaxis of anticoagulation therapy should be considered with LMWH [134] or direct oral anticoagulants (DOACs) [135, 136, 137••] as they can reduce the risk of cerebrovascular manifestations during acute and post hospital discharge (Fig. 2). Emphasis should be given to high risk populations such as patients with advanced age (> 65 years) and underlying comorbidities prior to COVID-19 such as pre-existing respiratory disease, obesity, diabetes, hypertension, chronic vascular disease [27, 28, 29••]. Patients who have experienced AIS or TIA should be treated according to 2021 guidelines for secondary stroke prevention. Caution should be taken for patients more than 75 years old and those with chronic kidney disease due to increased incidence of bleeding and increase the risk of haemorrhagic stroke development. Nevertheless, each therapeutic decision should be personalized and the risk of systemic bleeding or haemorrhagic stroke should not be ignored.

Compliance with Ethical Standards

Conflict of Interest

Nikolaos Karvelas declares that he has no conflict of interest. Eleni Stefanou declares that she has no conflict of interest. Samuel Bennett declares that he has no conflict of interest. Christo Kole declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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