Curr Treat Options Neurol (2022) 24: 155–171
DOI 10.1007/s11940-022-00713-8

Cerebrovascular Disorders (D Jamieson, Section Editor)

Stroke Treatment in the Era of COVID-19: a Review

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Published online: 25 April 2022

This article is part of the Topical Collection on *Cerebrovascular Disorders*

Keywords COVID-19 · Stroke · Ischemic stroke · Cerebrovascular disease · Intracerebral hemorrhage · Thrombosis

Abstract

Purpose of Review To describe a comprehensive review of the epidemiology, pathophysiology, and treatment of stroke in the era of COVID-19.

Recent Findings COVID-19 is associated with myriad neurological disorders, including cerebrovascular disease. While ischemic stroke is the most common, COVID-19 is associated with an increased risk of intracranial hemorrhage, arterial dissection, posterior reversible encephalopathy syndrome, and cerebral venous sinus thrombosis. In this review, we discuss the epidemiology, pathophysiology, and treatment of stroke due to COVID-19. In addition, we describe how COVID-19 has changed the landscape of stroke systems of care and the effect this has had on patients with cerebrovascular disease.

Summary While COVID-19 is associated with a heightened risk of stroke, the pandemic has led to advances in stroke systems of care that may reduce the long-term burden of stroke.

Introduction

As of July 2021, the COVID-19 pandemic caused by SARS-CoV2 has infected 196 million people and has led to over 4,200,000 deaths worldwide. A growing body of evidence had found an association between COVID-19 and a variety of neurological disorders, including cerebrovascular disease. The shift of hospitals' resources and health care staff towards the COVID-19 pandemic has led to alterations in regular medical care, particularly for stroke [1]. In this article, we review the epidemiology, pathophysiology, and treatment of stroke in the era of COVID-19. In addition, we describe how COVID-19 has changed systems of stroke care and the effect this has had on patients with cerebrovascular disease.

Stroke Incidence Among Patients With COVID-19

COVID-19 is associated with a variety of cerebrovascular complications. Multiple studies have found that patients with COVID-19 are at higher risk of stroke [2–4]. While ischemic stroke is the most common cerebrovascular manifestation, COVID-19 is also associated with intracranial hemorrhage, cervical artery dissection, posterior reversible encephalopathy syndrome (PRES), and cerebral venous thrombosis [5, 6].

In one large meta-analyses of over 60,00 patients hospitalized with COVID-19, a cerebrovascular event occurred in 1.3% of cases, the most common of which was ischemic stroke. As compared to non-infected contemporary or historic controls, patients with COVID-19 had a 3.6-fold increased risk of ischemic stroke, [7•] and similar findings have been found in other meta-analyses [8]. The risk of stroke appears to be correlated with the severity of COVID. The risk of stroke is approximately 1% among patients with mild COVID-19 symptoms, [9•] and may be as high as 5.7% among patients hospitalized in the intensive care unit with COVID-19 [9•, 10].

While respiratory illnesses in general have previously been found to be associated with a heightened risk of stroke, [11] COVID-19 appears to be associated with an even higher risk of stroke. As compared to patients with influenza, patients with COVID-19 faced a 7-fold higher risk of stroke [12•]. The particularly high risk of stroke among patients with COVID-19 may be related to the high levels of inflammation, hypercoagulability, or medical severity and systemic complications that result from COVID and place patients at heightened risk for stroke [13, 14].

One of the potential drivers for the heightened risk of stroke seen among patients with COVID-19 may be the propensity for clot formation and subsequent embolism to the brain. In support of this, studies have found an increased risk of large vessel occlusions (LVOs) among patients with COVID [13, 15, 16]. LVOs, defined as blockages of the proximal intracranial arteries in the anterior or posterior circulation, account for approximately 10 to 30% of acute ischemic strokes in the general population [17–19]. Patients with COVID-19 appear to be at heightened risk of having a LVO [17, 20–22]. In addition, patients with COVID-19 who have LVOs are younger than patients without COVID-19 with LVOs [28]. The difference may be that younger patients with COVID-19 have heightened levels of inflammation and hypercoagulability whereas patients without COVID-19 who have LVOs often have

risk factors associating with aging like atrial fibrillation or system atherosclerosis [23].

Little data exist regarding the impact of pregnancy and the risk of stroke in patients with COVID-19. Case reports have shown variable outcomes in pregnant patients with COVID-19 and strokes [24]. A single case report described cerebral vasculitis (or more likely reversible cerebral vasoconstriction syndrome) in a pregnant patient with COVID-19 who was found to have subarachnoid hemorrhage with complete resolution of symptoms [25].

Mechanism and Pathophysiology of Ischemic Stroke in COVID-19

The mechanism of stroke in patients with COVID-19 is likely multifactorial (Fig. 1). COVID-19 predisposes to a multitude of systemic complications including atrial fibrillation, myocardial infarction, myocarditis, and infective endocarditis, which are all well-associated with stroke [26, 27]. In addition, COVID-19 increases the propensity for direct viral-induced endothelium damage and inflammation, [28] and hypercoagulability from cytokine storm [4], both of which predispose to thrombus formation and stroke [29, 30]. The hypercoagulable state increases both the risk of venous thromboembolism leading to deep venous thrombosis (DVT) and pulmonary embolism (PE) which can travel to the brain and cause stroke through paradoxical embolism, [31•] and potentially also increases the risk of in situ arterial thrombosis [32, 33]. In a study of 3,334 hospitalized patients with COVID-19, thrombosis occurred in 16%, of which 6.2% were venous (DVT/PE) and 11.1% were arterial [34•]. In addition, an Italian study found that despite the use of prophylactic anticoagulation, the rate of venous and arterial thromboses in patients hospitalized with COVID-19 was as high as 8% [5].

The pathogenesis of hypercoagulability in COVID-19 patients involves all three components of the Virchow's triad, including endothelial injury, hypercoagulable state, and stasis [35]. Endothelial injury is evident both from the direct invasion of endothelial cells by SARS-CoV-2 and from increased cytokines release, such as interleukin IL-6, and various acute-phase reactants in COVID-19 that lead to endothelial injury [28, 36]. Stasis is due to immobilization in all hospitalized patients, especially those who are critically ill [35] . Finally, a hypercoagulable state is seen due to several coagulation abnormalities from elevated circulating prothrombotic factors such as von Willebrand factor (vWF), D-dimer, fibrinogen, and factor VIII [35, 37].

The increased inflammation and the release of pro-inflammatory cytokines including the tissue factor (TF) leads to coagulation activation and thrombin generation, causing both arterial and venous thromboembolism, [34•, 38] leading to DVT and PE and paradoxical embolism stroke [5, 31•]. Moreover, COVID-19 patients with elevated levels of D-dimer are at increased risk of venous and arterial events and poor prognosis [34•]. A recent study has shown that D-dimer was the only biomarker independently associated with prevalent stroke, with an 8-fold increase in COVID-19 patients [39].

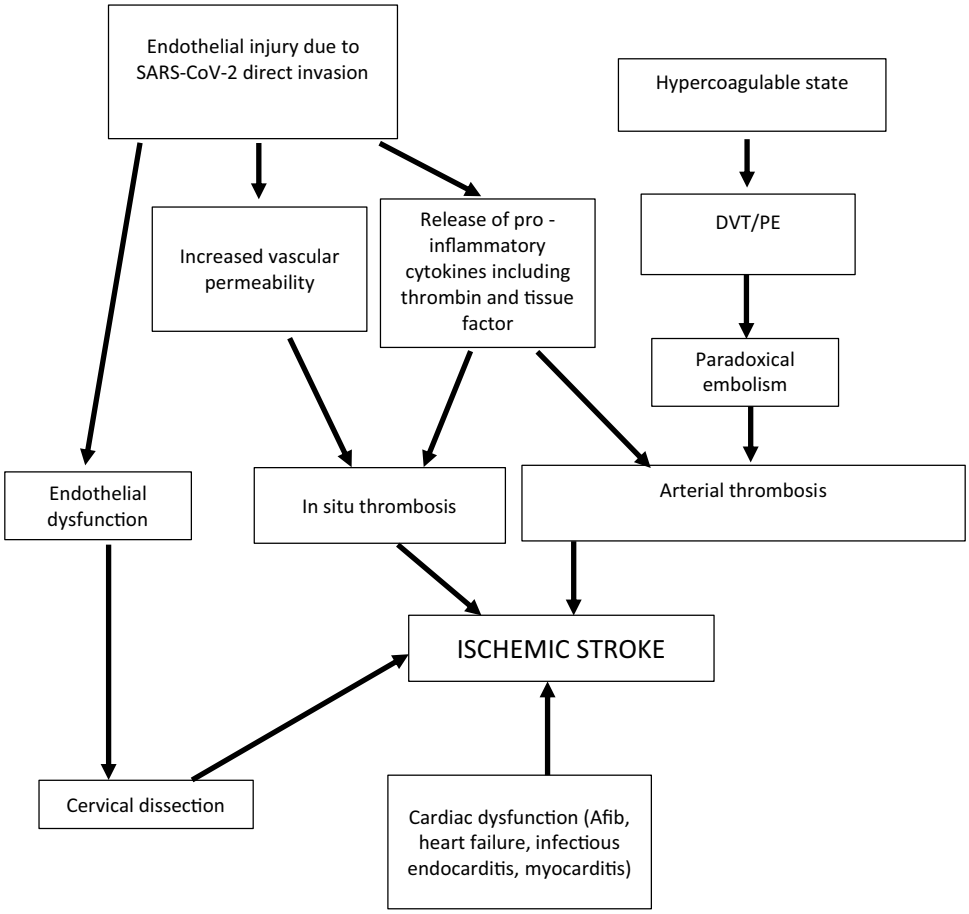

Fig. 1 Mechanism of ischemic stroke among patients with COVID-19. Proposed mechanisms of ischemic stroke due to COVID-19.

Notably, there appears to be a heightened proportion of cryptogenic stroke among patients with stroke due to COVID-19 [40]. In a meta-analysis of 60,000 patients hospitalized with COVID-19, as compared to non-infected contemporary or historic controls, patients with COVID-19 had a 4-fold increased risk of cryptogenic ischemic stroke (Fig. 2) [7•]. These findings have been replicated in other studies [41]. Although a proportion of these patients may have cryptogenic stroke due to incomplete workups or multiple stroke etiologies, many of these strokes appear to embolic stroke of undetermined source (ESUS) and are thought to occur due to a state of hypercoagulability without any obvious high-risk source of cardiac embolism [42]. COVID-19 is also associated with atrial and ventricular cardiopathy, arrhythmias, and endothelial activation which may predispose to stroke without satisfying the criteria for cardioembolism [43–45]. These cryptogenic strokes are not benign, and in fact portend a poor prognosis. A large population study found that cryptogenic stroke was an independent predictor of mortality, suggesting that COVID-19-associated cryptogenic stroke may represent a state of

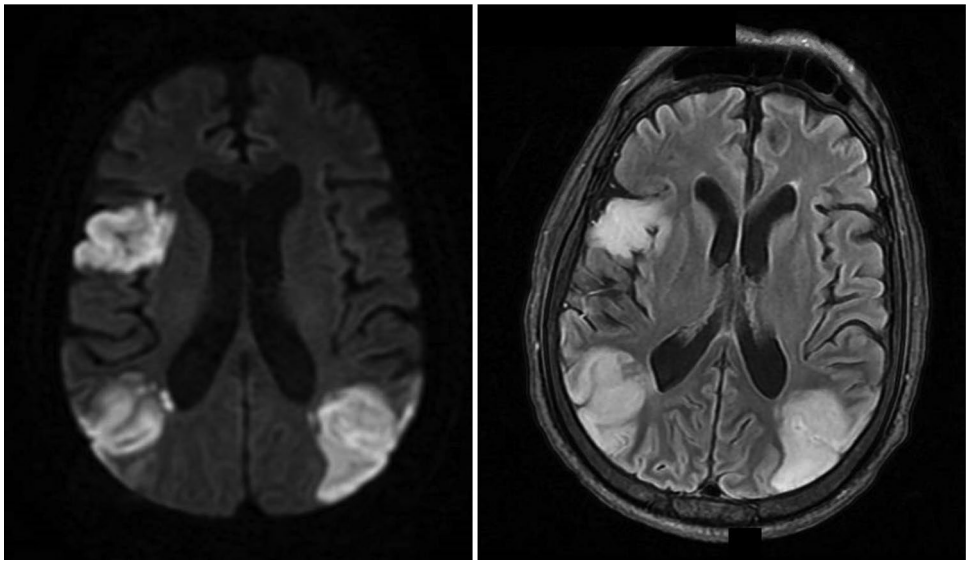

Fig. 2 Ischemic strokes in a patient with COVID-19. MRI brain in a patient with COVID-19. DWI (left) and FLAIR (right) imaging of bilateral posterior cerebral artery strokes and a right middle cerebral artery stroke. A 64-year-old man was admitted with shortness of breath and fever. He was found to have COVID-19 infection. He was intubated on day 2 after admission and he was started on remdesivir and 0.5 mg/kg of enoxaparin daily for thromboembolic prophylaxis. He was continued on propofol and fentanyl for sedation and on day 5 to 7 after admission he was paralyzed and proned twice daily for worsening respiratory function. On day 12 after admission, sedation was decreased on he was noted to have left-sided weakness. A brain MRI revealed a right middle cerebral artery stroke and bilateral posterior cerebral artery strokes. He was also found to have segmental pulmonary emboli and he was started on a heparin drip.

systemic hypercoagulability or endothelial activation that is associated with higher mortality [46].

Mechanism and Pathophysiology of Non-ischemic Stroke in COVID-19

COVID-19 is similarly associated with a heightened risk of non-ischemic cerebrovascular disorders. Prior studies have showed not only an increased risk of ischemic strokes, but also associations between COVID-19 and cervical artery dissection, intraparenchymal hemorrhage (IPH), cerebral venous sinus thrombosis (CVST), and posterior reversible encephalopathy syndrome (PRES) (Fig. 3).

COVID-19-related IPH is less common than ischemic strokes, but several studies have pointed to an association between COVID-19 and IPH [47–50]. IPH have been reported in about 0.5% of COVID-19 patients [51]. The proposed mechanisms of IPH in COVID-19 are related to both direct and indirect endothelial toxicity, the former via direct viral endothelial cell invasion and the latter through inflammation that leads to of thrombotic events which ultimately disrupt tight junction protein complexes,

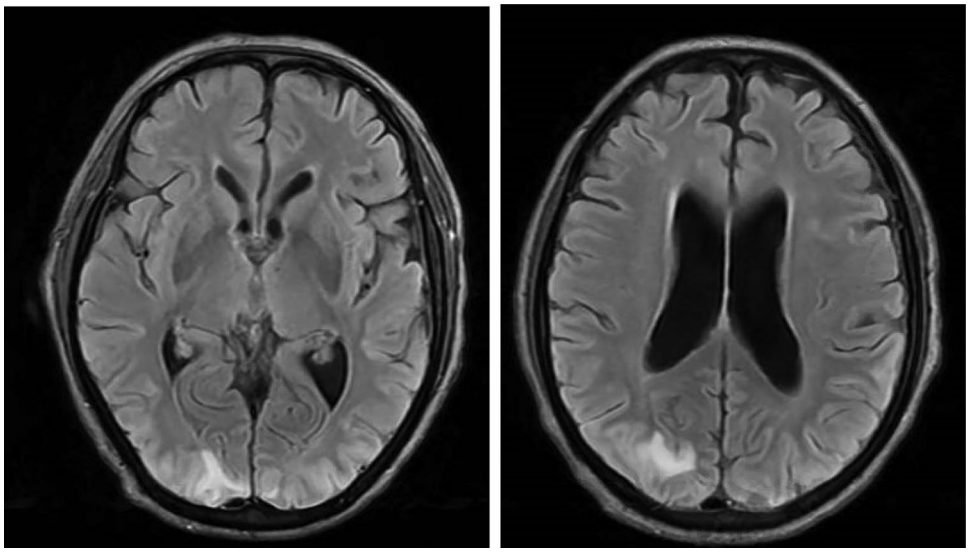

Fig. 3 Posterior reversible encephalopathy syndrome (PRES) in a patient with COVID-19. FLAIR imaging of posterior reversible encephalopathy syndrome (PRES) in a 74-year-old man intubated for COVID-19-associated acute respiratory distress syndrome and renal failure. A 74-year-old man was admitted for dyspnea and was found to be COVID-19 positive. On day 5 after admission, he developed acute kidney injury that required hemodialysis. He became intermittently hypertensive with systolic blood pressures (SBP) between 160 and 190. On day 9 after admission, he developed a generalized tonic–clonic seizure. Brain MRI was obtained and revealed evidence of PRES.

leading to blood-brain barrier compromise and IPH [48, 49]. In addition, the heightened risk of IPH among patients with COVID-19 may be related to the increased use of anticoagulation. Kvernland et al. showed that 89.5% of patients with COVID-19 and non-traumatic intracerebral hemorrhage or spontaneous non-aneurysmal subarachnoid hemorrhage were on therapeutic anticoagulation at the time of their hemorrhagic stroke [52].

Posterior reversible encephalopathy syndrome (PRES) has also been identified as a complication of COVID-19 and/or its treatment [53–55]. PRES may be due to direct invasion of endothelial cells by Sars-CoV-2 through surface angiotensin-converting enzyme 2 (ACE2) receptors, leading to endothelial dysfunction and to increased vascular permeability. It has been hypothesized that shifting the vascular equilibrium towards a more pro-inflammatory, pro-coagulant, and proliferative state may lead to inflammation with edema [56]. PRES may also be a consequence of medical illness and/or medical therapy utilized among hospitalized COVID-19 patients [57]. Renal failure, an independent predictor of PRES, is not uncommon among critically ill COVID-19 patients [58]. Immunomodulatory medications commonly given to COVID-19 patients, such as tocilizumab, are also associated with increased risk for PRES [59].

Cervical artery dissection is known to be associated with respiratory illnesses either through direct viral invasion, a heightened state of inflammation, or microtrauma due to coughing [11]. Few case series of dissections have also been reported in patients with COVID-19, [60] and the proposed mechanisms for arterial dissection seem related to the endothelial dysfunction

resulting from cytokine storm or direct SARS-CoV-2 invasion of the vascular endothelial cells through the surface ACE2 receptors [61, 62]. The propensity for cervical artery dissection among patients with respiratory illnesses has recently been borne out, [11] and it is uncertain whether COVID-19 predisposes to a higher risk of dissection than other respiratory illnesses.

Finally, cerebral venous thrombosis (CVT) has been reported in about 0.5% of patients hospitalized with COVID-19 [51]. CVT has been described to affect especially the transverse and sigmoid sinus, with involvement of the deep venous sinus system in about one-third of the cases [63–66]. Among hospitalized patients with COVID-19, CVT is associated with elevated D-dimer and C-reactive protein (C-RP) levels. The proposed mechanism is related to the pro-coagulant state induced by the virus [65, 67].

Prognosis in Patients With COVID-19 and Stroke

Patients with COVID-19 appear to have more severe strokes than patients without COVID-19 [68]. A recent systematic review found that patients with COVID-19 and stroke had higher National Institutes of Health Stroke Scale (NIHSS) scores than non-infected counterparts [68, 69]. Moreover, patients with COVID-19 and stroke were younger than non-COVID-19 patients with stroke, and patients with COVID-19 and stroke had more unfavorable neurological outcomes as compared to patients with stroke without COVID [70]. Thus, COVID-19-associated stroke affects younger patients, and is associated with higher stroke severity and worse neurological outcomes. Potential explanations of this higher stroke severity may be related to the higher risk of LVOs among COVID-19 patients, [17, 22, 71] or related to the underlying medical severity of patients with COVID-19 who have stroke. Another explanation for worse neurological outcomes may be related to the decreased use of acute stroke therapies such as tPA and mechanical thrombectomy (MT) [72, 73]. In fact, patients with COVID-19 may be less likely to receive tPA and MT, [73] especially in cases of severe infection. This may be due to several factors, including delay in stroke symptom identification due to the use of medially induced coma or paralytics. In addition, patients with severe COVID-19 may be on therapeutic anticoagulation for systemic clots or may have severe medical comorbidities that may exclude them from receiving MT and tPA [52, 72–75].

Outcomes for patients with COVID-19 and stroke appear to be worse than patients without COVID-19 and stroke. Initial reports from China described a higher risk of poor outcomes associated with a history of stroke among COVID-19 patients, with increased rates of in-hospital mortality [76]. Studies from the USA showed that up to 63.6% of COVID-19-infected patients died during their hospitalization after suffering a stroke [41]. A recent study from Qureshi et al. that analyzed over 27,000 patients, showed a 2-fold increase in the risk of discharge to destination other than home or of death with occurrence of acute ischemic stroke in patients with COVID-19 [74].

The worse outcomes in patients with COVID-19 and stroke may be related to the underlying severity of medical illness, the heightened state of inflammation or hypercoagulability, or delays in the delivery of acute stroke therapies like thrombolysis or mechanical thrombectomy. A recent meta-analysis of 2955 patients who presented with stroke symptoms during the COVID-19 pandemic found that during the initial peak COVID-19 period (March 1, 2020, to July 31, 2020), patients with stroke had lower odds of receiving thrombolysis within 60 min of arrival (OR 0.61) as compared to patient who presented with stroke symptoms in the pre-COVID-19 period [77]. Despite the increased door-to-needle time, the study found no significant delay in door-to-groin time for patients who underwent MT [77]. However, a study conducted in 28 centers from North America, South America, and Europe found that during the pandemic stroke patients were more likely to undergo intubation prior to thrombectomy, leading to prolonged door-to-reperfusion time, higher in-hospital mortality, and lower likelihood of functional independence at discharge [78].

Acute Stroke Treatment of Stroke During the COVID-19 Pandemic

Thromboprophylaxis

Patients with COVID-19 are at heightened risk for thrombotic complications [79]. Given the concern for a pro-coagulant state in COVID-19 patients, a randomized clinical trial evaluated the efficacy of prophylactic anticoagulation in non-critically ill patients with COVID-19 and found that therapeutic anticoagulation with heparin increased the probability of survival to hospital discharge with reduced use of cardiovascular or respiratory organ support as compared with usual-care thromboprophylaxis [80]. However, among critically ill patients with COVID-19, the INSPIRATION trial found that intermediate dose prophylactic anticoagulation was not superior to standard-dose prophylaxis in reducing the risk of acute VTE, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or death [81]. In addition, recently published clinical trials have shown that prolonged therapeutic anticoagulation with 30 days of rivaroxaban in patients with COVID-19 and elevated D-dimer increased the risk of bleeding without improving outcomes compared to prophylactic anticoagulation [82]. Given these data, prophylactic anticoagulation should be considered for all hospitalized patients with COVID-19 not requiring ICU-level care. No study, however, has evaluated the efficacy of thromboprophylaxis in the prevention of stroke among patients with COVID-19. For patient discharged home from the hospital, there is no evidence of improved outcomes in continuing anticoagulation post-discharge [83]. Clinical trials are currently ongoing and clinical judgment should be used to evaluate the bleeding risk of anticoagulation in patients with COVID-19 [84].

Thrombolysis

Intravenous tPA appears to be safe and effective for patients with COVID-19 and acute ischemic stroke [74, 85]. This recommendation, however, comes with the caveat that patients with COVID-19 have been found to have a higher prevalence of elevated inflammatory (elevated C-RP and D-dimer), [86, 87] and these markers have been previously associated with increased risk of post-tPA intracerebral hemorrhage among patients with acute ischemic stroke without COVID-19 infection [88]. Another aspect that needs to be considered is hepatic dysfunction in patients with COVID-19 patients [89]. Some COVID-19 patients may present with elevated transaminitis, but normal coagulation markers (prothrombin time PT, international normalized ratio INR, and activated partial thromboplastin time APTT) [89]. Intravenous tPA is hepatically cleared, and in patients with reduced hepatic function, there is a potential increase in serum tPA levels and increased risk of ICH [90]. Moreover, advanced hepatic dysfunction may be associated with coagulopathy with elevation in PT, INR, and thromcytopenia [90]. Ultimately, delivery of tPA should follow standard guidelines as recommend by the American Heart Association/American Stroke Association and FDA [91]. We do not recommend basing the decision of whether to give IV tPA based on thromboelastography, D-dimer level, or any other testing that is not standard among patients with acute ischemic stroke without COVID-19.

Mechanical Thrombectomy

As mentioned above, LVOs are common in COVID-19 patients [13, 17, 20, 21]. LVOs place large cerebral territories at ischemic risk and cause high rates of morbidity and mortality without further treatment. An abundance of high-quality data over the past few years has shown the efficacy of mechanical endovascular thrombectomy for improving clinical outcomes in patients with LVOs [19]. Mechanical thrombectomy (MT) is an available and helpful procedure in patients with LVO due to COVID-19. A recent meta-analysis showed that MT is safe and equally successful in patients with COVID-19-related LVOs as it is in patients without COVID-19 who have LVOs [92]. Controversies still exist on MT for posterior circulation strokes and in particular clinical trials have failed to show superiority of MT compared to best medical management [93, 94]. An ongoing trial is looking at MT for basilar artery occlusion (BAO) between 6 and 24 h from symptom onset [95]. It remains uncertain whether COVID-19 patients with BAO may benefit from MT.

Systems of Care During the COVID-19 Pandemic

Stroke Patients' Accessibility to Urgent Stroke Treatment

During the COVID-19 pandemic, patients' accessibility to the emergency medical care has dramatically changed. At the height of the pandemic, the emergency department (ED) volume was down approximately 50% in the USA [96]. Paradoxically, despite the heightened risk for thrombotic complications, including stroke, the number of stroke admission decreased during the height of the pandemic. This "COVID-19 stroke paradox" was thought to be due to patients' increased fear of entering hospitals and contracting COVID-19 [15, 46, 97, 98]. Patients were more likely to prioritize avoiding exposure to SARS-CoV2 and ignore symptoms that may have previously led them to visit a hospital [99]. This fear of contracting COVID-19 led to decreased stroke admissions throughout the world [15, 96, 97]. For example, a study from central and south Texas showed that patient admission, treatment, and discharge volumes for acute stroke treatment decreased significantly when COVID-19-related shelter-at-home orders were issued [100]. With the increased patients' fear of accessing the EDs and the governments' suggestion to access the ED only if truly necessary, the patients with stroke who came to the ED were often more severe and/or outside the window for acute stroke interventions including tPA and mechanical thrombectomy [10, 100–102]. Delays in presentation to the hospital were not just related to fear of SARS-CoV2 exposure, but also use of social distancing and decreased human contact, especially among older persons, thus reducing the chance of prompt identification of a neurological deficit [2, 31•]. Finally, among patients hospitalized with COVID-19, delays in identification of stroke were due to frequent use of sedatives and paralytics which precluded prompt identification of stroke symptoms [2, 6]. Perhaps it is not a surprise then that initially there was a decreased overall rate of hospitalization for stroke during the COVID-19 pandemic, despite the virus' propensity for thrombotic complications [97]. All the aforementioned changes due to the COVID-19 pandemic, including the patients' fear to access the ED, the increased proportion of strokes arriving to the ED outside the treatment window, and the difficulties in identifying stroke symptoms in hospitalized COVID-19 patients, have posed significant challenges to stroke care for which we continue to seek new avenues to combat.

Health Care System Logistics

The COVID-19 pandemic has affected the protocols and safety guidelines put in place to protect patients, providers, and health care workers. Tight infection control, redeployment, and social distancing regulations have impacted the ability of stroke teams to promptly provide acute stroke interventions [91]. Application of personal protective equipment (PPEs), stringent sterilization requirements, and additional safety measures similarly delayed stroke

teams in assessing and treating patients presenting with acute stroke symtpoms [91, 103]. Finally, the shortage of hospital beds, and in particular of intensive care beds, has also impacted stroke care; post-tPA or mechanical thrombectomy patients were often relegated to non-ICU beds, limiting the frequency of neurological assessments in patients at high risk for complications [91, 104].

Regarding thrombectomy, the need of COVID-19 testing prior to entering the angiography suite, and the difficulties in obtaining consent due to the "no visitor hospital policies" caused significant delays in delivery endovascular therapy [74, 103, 104]. Another important consideration is whether COVID-19 patients should undergo mechanical thrombectomy under general anesthesia as opposed to monitored anesthesia care (MAC). While a consensus statement from the Society for Neuroscience in Anesthesiology and Critical Care has proposed that general anesthesia may be required in COVID-19 patients undergoing thrombectomy to reduce exposure risk, [105] preliminary data have shown that general anesthesia and intubation result in increased door-to-reperfusion time (138 vs 100 min) and are associated with higher in-hospital mortality (RR 1.87) and lower probability of functional independence at discharge (RR 0.53) [106]. In light of these findings, whenever possible, and if safe, MAC should be considered even for COVID-19 positive patients undergoing mechanical thrombectomy.

The Post-pandemic Lessons

The COVID-19 pandemic has impacted stroke care [107]. While there have been increased delays in the recognition and treatment of acute ischemic stroke in the ED, there have also been improvements in the delivery of care for outpatients, and specifically for patients in remote regions. The pandemic has led to major advances in the use of telemedicine: a readily available technology that has allowed patients to receive access to a neurologist or stroke expert. For example, patients in rural areas, who often have limited access to neurologists and stroke care in general, now have access to these experts in the comfort of their home or in their local EDs. While the pandemic has caused major economic, political, and social problems, a benefit has been the realization that telemedicine is an easy-to-use, expeditious way to provide specialty-level expertise with an improved utilization of healthcare resources. We believe that this positive outcome from the COVID-19 pandemic is here to stay and will lead to an overall reduction in the worldwide burden of cerebrovascular disease and neurological disability.

Declarations

Conflict of Interest
Marialaura Simonetto declares that she has no conflict of interest. Paul Wechsler declares that he has no conflict of interest. Alexander Merkler declares that he has no conflict of interest.

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