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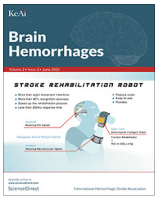

Review article

COVID-19 and stroke: A review

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ABSTRACT

COVID-19 patients have presented with a wide range of neurological disorders, among which stroke is the most devastating. We have reviewed current studies, case series, and case reports with a focus on COVID-19 patients complicated with stroke, and presented the current understanding of stroke in this patient population. As evidenced by increased D-dimer, fibrinogen, factor VIII and von Willebrand factor, SARS-CoV-2 infection induces coagulopathy, disrupts endothelial function, and promotes hypercoagulative state. Collectively, it predisposes patients to cerebrovascular events. Additionally, due to the unprecedented strain on the healthcare system, stroke care has been inevitably compromised. The underlying mechanism between COVID-19 and stroke warrants further study, so does the development of an effective therapeutic or preventive intervention.

1. Introduction

Despite being a severe acute respiratory syndrome, coronavirus disease 2019 (COVID-19) can present in various ways not restricted to pulmonary symptoms. A wide range of symptoms has been reported from asymptomatic disease to kidney injuries, cardiac damages, and neurological manifestations. Neurological symptoms, including headache, dizziness, cranial nerves damage such as anosmia, confusion, cerebrovascular diseases, and encephalopathies, can be the initial presentation of COVID-19 or concur with respiratory symptoms.[1–3] Neurological involvement has been observed in up to 36% of COVID-19 patients.[4,5] In severe cases, cerebrovascular diseases are among the most prevalent comorbidities and are presented as an independent risk factor for poor prognosis.[6,7] Preliminary evidence indicates that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could cause ischemic stroke through hypercoagulative state, endothelial injury, and cardiogenic embolism.[8] Stroke has previously been observed in severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) and Middle East Respiratory Syndrome (MERS) patients.[9,10] Currently, numerous cases of COVID-19 patients complicated with stroke have been reported; some patients had stroke symptoms as the initial presentation.[11,12] This has raised the recognition of SARS-CoV-2 infection manifesting as a cerebrovascular incident. As SARS-CoV-2 swept through the world, the COVID-19 pandemic has called increasing attention to neurological providers as the novel coronavirus infection causes a higher rate of stroke compared to the regular population. We hereby conducted a literature review and presented current studies, case series, and understanding of COVID-19 and stroke.

2. Cohort studies, case series, and case reports of stroke complicated COVID-19 infection

We have conducted a search of literature through PubMed and Google Scholar with the following keywords "SARS-CoV-2", "COVID-19", "stroke," and "neurological symptoms." Publications of cohort studies, case series, and case reports of stroke (both ischemic and hemorrhagic stroke) complicated with COVID-19 infections have been included from January of 2020 to July of 2020. Studies that were not focused on stoke and Covid-19 infec-

Abbreviations: COVID-19, Coronavirus disease 2019; ACE2, Angiotensin-converting enzyme 2; aPL, Antiphospholipid; aPTT, Activated partial thromboplastin time; CPR, C-reactive protein; CVD, Cerebrovascular disease; DIC, Disseminated intravascular coagulation; ECMO, Extracorporeal membrane oxygenation; ICH, Intracranial hemorrhage; IL-6, Interleukin-6; MERS, Middle East Respiratory Syndrome; NIHSS, National Institutes of Health Stroke Scale; PT, Prothrombin time; rt-PCR, Reverse transcription polymerase chain reaction; SARS-CoV-1, Severe acute respiratory syndrome coronavirus 1; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; TNF-alpha, Tumor necrosis factor-alpha; vWF, Von Willebrand Factor.

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tion have been excluded. A total of sixteen studies with authors, journals, publication dates, characteristics, and outcomes are listed (Table 1).

3. Stroke presentation in COVID-19 patients

During the pandemic, a decreased volume of stroke emergencies has been observed by independent institutions across the globe, which has persisted even after the number of confirmed COVID-19 cases decreased.[13,14] Siegler et al. reported a 38% fall in newly diagnosed stroke patients and 25% fewer consultations via stroke telemedicine at the local institution.[13] This phenomenon has been attributed to the possibility that the fear of contracting SARS-CoV-2 while being exposed to a healthcare facility has deterred patients with mild symptoms from seeking medical attention and treatment.[1,14,15] Although further study is warranted to attest to this hypothesis. Additionally, among patients treated for ischemic stroke during the pandemic, Meza et al. reported that there was no difference in the number of patients received intravenous thrombolysis compared to those received endovascular therapy. However, the onset-to-door time of stroke patients during the emergency-state lockdown had increased while being compared to non-emergency state.[14]

In a systemic review conducted in May of 2020, Ghannam et al. reported that 48.8% of neurological involvement in Covid-19 patients were cerebrovascular incidents, which consisted of 87.5% ischemic stroke, 5% cerebral venous thrombosis, 5% intraparenchymal hemorrhage, and 2.5% subarachnoid hemorrhage.[3] The majority of ischemic stroke subtype was large vessel occlusion, which consisted of 77% within a total pooled sample of 35 ischemic stroke cases. However, in a retrospective cohort study examining COVID-19 and stroke from a New York Healthcare system conducted in July of 2020, Yaghi et al. reported that large vessel disease consisted of only 6.2% out of total 32 ischemic stroke cases, and the majority of stroke subtypes was cryptogenic. Intracranial hemorrhages (ICH) have been reported in Covid-19 patients as well. Dogra et al. identified 33 COVID-19 patients afflicted with ICH, of which 75.8% was receiving anticoagulation either for therapeutic or prophylactic purpose.[16] In severe cases requiring extracorporeal membrane oxygenation (ECMO) support with continuous anticoagulation, intraparenchymal hemorrhage with a poor prognosis has been observed.[17] Nonetheless, macrothrombosis, microangiopathy, venous thrombosis, and hemorrhagic stroke have all been observed in patients infected with SARS-CoV-2. The incidence of ischemic stroke among COVID-19 patients is reported to be at 1.6% by Klok et al. and 2.5% by Lodigiani et al. in studies from two different institutes.[18,19] The disparity of incidence can be attributed to the small number of samples, timing of the study, and study methods. Of note, both studies targeted COVID-19 patients required treatment in the ICU, which had automatically excluded mild to moderate COVID-19 patients. Therefore, the actual incidence of stroke in COVID-19 patients could be higher.[20] This calls for further investigation as SARS-CoV-2 poses a continuing threat to the neurological well-being of COVID-19 patients.

In general, levels of D-dimer, interleukin-6 (IL-6), C-reactive protein (CRP), fibrinogen, and platelet were increased in COVID-19 patients.[21] Stroke patients with COVID-19 were found to be generally younger with higher admission National Institutes of Health Stroke Scale (NIHSS) score than their counterparts without COVID-19.[1] This could be attributed to the hypercoagulative state that predisposes COVID-19 patients to thromboembolic incidents.

Cerebrovascular disease (CVD) as a prognostic factor in COVID-19 patients have been systemically reviewed and analyzed in different studies. Prananta et al. [22] reported that CVD was associated with mortality in COVID-19 patients. The risk ratio (RR) was 2.38 [1.92,2.96], which means COVID-19 patients with cerebrovascular events have poor outcomes. However, the association between cerebrovascular disease and severe COVID-19 was borderline significant (RR1.88[1.00,3.51]). This is in stark contrast with the finding from Aggarwal et al., who had reported an increased odd of association between CVD and severe COVID-19 infection and no statistical significance in the association between CVD and mortality in severe COVID-19 patients.[23] The disparity of the conclusions between the two studies could be caused by the fact that both studies pooled data from selected published literature, in which the number of studies was limited, and the sample size was small. Furthermore, severe COVID-19 patients tend to develop multiorgan impairment, which could potentially confound the association between CVD and severity of COVID-19. For stroke patients of mild to moderate COVID-19 patients, although single institute studies and case reports have reported optimistic outcomes,[4] systemic reviews are still lacking in this patient group.

4. Mechanism of stroke in COVID-19 patients

The genome sequence of SARS-CoV-2 shares 89.1% similarity with a group of SARS-like coronaviruses.[24] Unsurprisingly, similar to SARS-CoV-1, SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) receptor with viral surface spike (S) proteins and gains entry to host cells.[25,26] ACE2 is widely expressed in human body,[27,28] specifically the neurons, glial cells, endothelial cells, and arterial smooth muscles in the central nervous system.[25,29,30] This renders them vulnerable targets to SARS-CoV-2. Although the neurotropism of SARS-CoV-2 is still disputable, the affinity of SARS-CoV-2 S protein to ACE2 receptor is 10- to 20-fold higher than that found in SARS-CoV-1,[31] which potentially explains many of the neurological manifestations such as anosmia in COVID-19 infection. The cause of stroke, however, is plausibly multifactorial. Coagulopathy and hypercoagulability as a result of systemic response to SARS-CoV-2 infection, endothelial injury caused by direct viral invasion, and venous stasis due to immobilization are all implicated in CVD in COVID-19 patients (Fig. 1).

Coagulopathy attributes to thrombotic events and has been widely observed in COVID-19 patients regardless of severity. More than 95% of severe COVID-19 patients have elevated levels of D-dimer and fibrinogen.[32,33] However, classical coagulation markers, prothrombin time (PT), and activated partial thromboplastin time (aPTT) are normal or only slightly prolonged and do not reflect the procoagulant state, which is distinct from disseminated intravascular coagulation (DIC). In fact, severe COVID-19 patients rarely progress to an overt DIC.[34] Additionally, antiphospholipid antibodies (aPL) were detected in some severe cases, which is associated with thrombosis.[33,35]

Hypercoagulability as well has been reported in both severe and mild COVID-19 patients. Clot waveform analysis (CWA) demonstrated hypercoagulability that precedes or coincides with severe illness.[36] Hypercoagulability, along with a systemic inflammatory response to the viral infection, could lead to macro- and microthrombi formation, ultimately eliciting cerebrovascular incidents.[37,38] A thromboelastography study of the coagulation profile in critical COVID-19 patients yielded consistency with a hypercoagulative state. It's been postulated that substantially increased factor VIII is associated with COVID-19 related hypercoagulability.[37] Activation of the complement pathway, inflammatory cytokines, as well as cytoplasmic microparticles originated from platelets or lymphocytes could also induce hypercoagulative state.[39–41]

Hyperviscosity is another risk factor for thrombosis. This has been demonstrated in a case series of critically ill COVID-19 patients. Fifteen patients had their plasma viscosity assessed with

Table 1
Summary of literature with a focus on stroke in COVID-19 patients.

Authors	Journal	Publication Date	Study type	Number of Stroke Patients	Age (Median)	Sex	Characteristics	Outcome
Yaghi et al. [1]	Stroke	Jul-20	Cohort study	32	62.5[52.0–69.25]	23 Male 9 Female	0.9% (32/3556) hospitalized COVID-19 infection identified with stroke Median time from COVID-19 Symptoms to stoke 10 days [5–16.5] 43.8% (14) admitted for stroke; 56.2% (18) admitted for COVID-19 related symptoms 21.9% (7) cardioembolic; 6.3% (2) Large Vessel disease 65.6% (21) cryptogenic, 6.3% (2) other types of stroke Median D-dimer 3913 ng/mL (2549–10000); median CRP 101.1 ng/mL (38.8–214.3)	75.0% (24/32) deceased/critically ill
Morassi et al. [56]	Journal of Neurology	Apr-20	Case series	6	69[57–82]	5 Male 1 female	Four ischemic strokes; two hemorrhagic strokes Five males with severe COVID-19; one female with moderate COVID-19; Increased LDH, abnormal blood clotting tests in four patients	Death (83%) 5 (severe COVID-19 all died); severe neurological deficits (mRS:4)
Klok et al. [18]	Thrombosis Research	Apr-20	Cohort study	3	n/a[a]	n/a	Focused on thrombotic complications in critically ill COVID-19 patients. Reported 3 ischemic strokes.	n/a
Mao et al. [5]	JAMA Neurology	20-Apr	Cohort study	6	n/a	n/a	Study focused on neurological manifestations of COVID-19 patients; five ischemic stroke, one hemorrhagic stroke was reported; Five severe covid-19 cases, one non-severe COVID-19 case; Median time from COVID-19 symptoms to stroke 9 days (1 to 18)	One hemorrhagic stroke died; others unknown
Helms et al. [20]	The New England Journal of Medicine	Jun-20	Case series	3	n/a	n/a	Observation case series with a focus on neurological features. Reported three patients with ischemic stroke.	n/a
Helms et al. [33]	Intensive care Med	Apr-20	Cohort study	4	n/a	n/a	Focused on high thrombosis risks in COVID-19 patients, reported four stroke patients, no details regarding age and outcome etc.	n/a
Li et al.[4]	SSRN Electronic Journal	Jul-20	Retrospective observational study	13	72 [32–91]	7 Male 6 Female	Eleven acute ischemic strokes, 1 CVST[b], 1 cerebral hemorrhage 11 severe COVID-19; 2 non-severe COVID-19 Median time from COVID symptoms to stroke 9 days (0 to 28)	38.5% (5) death

Authors	**Journal**	**Publication date**	**Study type**	**Number of Stroke Patient**	**Age (median)**	**Sex**	**Characteristics**	**Outcome**
Merkler et al.[57]	JAMA Neurology	20-Jul	Retrospective observational study	31	69 (interquartile range, 66–78)	18 Male 13 Female	All presented with ischemic stroke; 8 patients presented with stroke initially.	n/a
Avula et al.[11]	Brain, Behavior, and Immunity	Apr-20	case report	4	81.5 [73–88]	1 Male 3 Female	All patients presented with acute ischemic stroke with COVID-19; Of patients who had D-dimer and CRP[c] tested, they are all increased; D-dimer CRP levels both elevated when data available	3 died; 1 discharged to rehab

Table 1 (*continued*)

Authors	Journal	Publication Date	Study type	Number of Stroke Patients	Age (Median)	Sex	Characteristics	Outcome
Valderrama et al.[53]	Stroke	Jul-20	Case report	1	52	Male	Patient presented with covid-19 symptoms, developed stroke on day 7 of COVID-19 symptoms; Angiography revealed partially occlusive left terminal internal carotid artery thrombus; Mechanical thrombectomy was performed; D-dimer and CRP were both high.	Discharged
Guillan et al.[58]	Thrombosis Research	Sep-20	Case report	1	67	Male	Simultaneous presentation of ischemic stroke and mild Covid-19; Cerebral infracts in multiple arterial territories; High D-dimer and CRP.	Favorable without new clinical events
Vu et al.[59]	Emergency Radiology	Mar-20	Case report	1	30	Male	Presented with dysarthria, right hemiparesis, right facial droop; CT showed acute left basal ganglia hemorrhage (hemorrhagic stroke); Asymptomatic COVID-19 (CT neck revealed nodules in both upper lobes of the lung, which led to covid-19 diagnosis eventually)	n/a
Fu et al.[60]	BMC Neurology	Jun-20	Case report	2	45	Male	Six days after mild covid-19 symptom (fever), patient developed stroke symptoms including dysarthria, weakness of left limbs, facial droop. CT revealed right corona radiata infarction; D-dimer and CRP were both high.	Recovered, discharged
					50	Male	Patient presented with left side weakness after 9 days of fever; Confirmed with COVID-19 with rt-PCR[d]; CT showed right basal ganglia infarction; D-dimer and CRP both high.	Discharged with residual neurological deficits
Gunasekeran et al.[61]	QJM	May-20	Case report	1	40	Female	Seven days after intubation, patient showed sluggish pupils and absent corneal responses. CT revealed a large middle cerebral artery territory infarct with extensive mass effect, including midline shift and downward herniation. Patient had diabetes insipidus which was deemed the cause of the massive stroke.	Deceased

Authors	**Journal**	**Publication date**	**Study type**	**Number of Stroke Patient**	**Age (median)**	**Sex**	**Characteristics**	**Outcome**
Oxley et al.[62]	The New England Journal of Medicine	Apr-20	Case Report	5	39 [33–49]	4 Male 1 Female	Moderate to mild COVID-19 infection; all had large vessel disease; mean NIHSS upon admission was 19;	3 discharged home or rehab, 1 in ICU, 1 in stroke unit
Beyrouti et al.[63]	J neurol Neurosurg Psychiatry	May-20	Case report	6	68.5 [53–85]	5 Male 1 Female	Five severe and one moderate COVID-19 infection; CT or MRI confirmed ischemic stroke; CRP all elevated; antiphospholipid antibodies were all detected.	1 died; others unknown

(*continued on next page*)

Table 1 (*continued*)

Authors	Journal	Publication Date	Study type	Number of Stroke Patients	Age (Median)	Sex	Characteristics	Outcome
Sharifi-Razavi et al.[64]	New Microbes and New Infections	Mar-20	Case report	1	79	Male	Three days after COVID-19 symptoms (fever, cough), patient presented with loss of consciousness, hemorrhagic stroke confirmed with CT, rt-PCR confirmed Covid-19.	unknown
TUNÇ et al.[65]	Journal of clinical Neuroscience	20-May	case report	4	69.5 [45–77]	2 Male 2 Female	Median 1.5 days (1–4) stroke presentation after COVID-19 symptoms; COVID-19 non-severe; two patients had large vessel disease; two patients had small vessel disease.	2 discharged well; 2 bedridden, all survived.
Goldberg et al.[66]	AJNR Am J Neuroradiol	May-20	case report	1	64	Male	Sixteen days after onset of COVID-19 symptoms, patient woke up with hemiparesis. CT confirmed right middle cerebral artery and bilateral anterior cerebral artery territories acute ischemic infarction; high D-dimer and antiphospholipid antibodies.	n/a
Hughes et al.[12]	European Journal of Case Report in Internal Medicine	20-Apr	case report		59	Male	Presented with right hemiparesis, dysphasia 4 days after COVID-19 confirmation, was diagnosed with cerebral venous sinus thrombosis.	Recovered
Carroll et al.[67]	Neurocrit care	Jun-20	Case report	2	66 [62–72]	Male	Two severe COVID-19 cases under intubation were absent of brainstem reflexes; CT revealed multifocal hemorrhages and severe diffuse cerebral edema.	Deceased
Authors	**Journal**	**Publication date**	**Study type**	**Number of Stroke Patient**	**Age (median)**	**Sex**	**Characteristics**	**Outcome**
Fara et al.[68]	Journal of Thrombosis and Haemostasis	May-20	Case report	3	33	Female	Patient with no medical history presented with left hemiplegia and left facial hypoesthesia; MRI revealed acute infarction in the right middle cerebral artery territory. Treated with anticoagulation.	Near-complete resolution of thrombosis.
					77	Female	Patient with history of hypertension and hyperlipidemia presented with sudden onset of aphasia, left hemiparesis. Found to have non-occlusive thrombosis of the distal right common carotid artery. (coughing led to confirmation with COVID-19, no fever, no oxygenation supplementation required).	Thrombosis had completely resolved
					55	Male	Patient with history of diabetes presented with left hemiparesis. CTA showed thrombosis of right common carotid artery. Conventional angiography showed the thrombosis as non-occlusive, and he was treated with anticoagulation. Low-grade fever at presentation and required supplemental oxygenation, but did not develop significant respiratory distress.	n/a

Table 1 (*continued*)

Authors	Journal	Publication Date	Study type	Number of Stroke Patients	Age (Median)	Sex	Characteristics	Outcome
Zahid et al.[17]	Journal of Stroke	Jun-20	Case report	1	38	Male	Patient had severe Covid-19, was intubated and later on put on ECMO[e] support with continuous heparin infusion. Patient developed encephalopathic and head CT revealed left sub-insular parenchymal hemorrhage.	Obtained overall substantial clinical improvement.

[a] n/a: not available (data not provided in the original publications);
[b] CVST: Cerebral venous sinus thrombosis;
[c] CRP: C-reactive protein;
[d] rt-PCR: reverse transcription polymerase chain reaction;
[e] ECMO: extracorporeal membrane oxygenation.

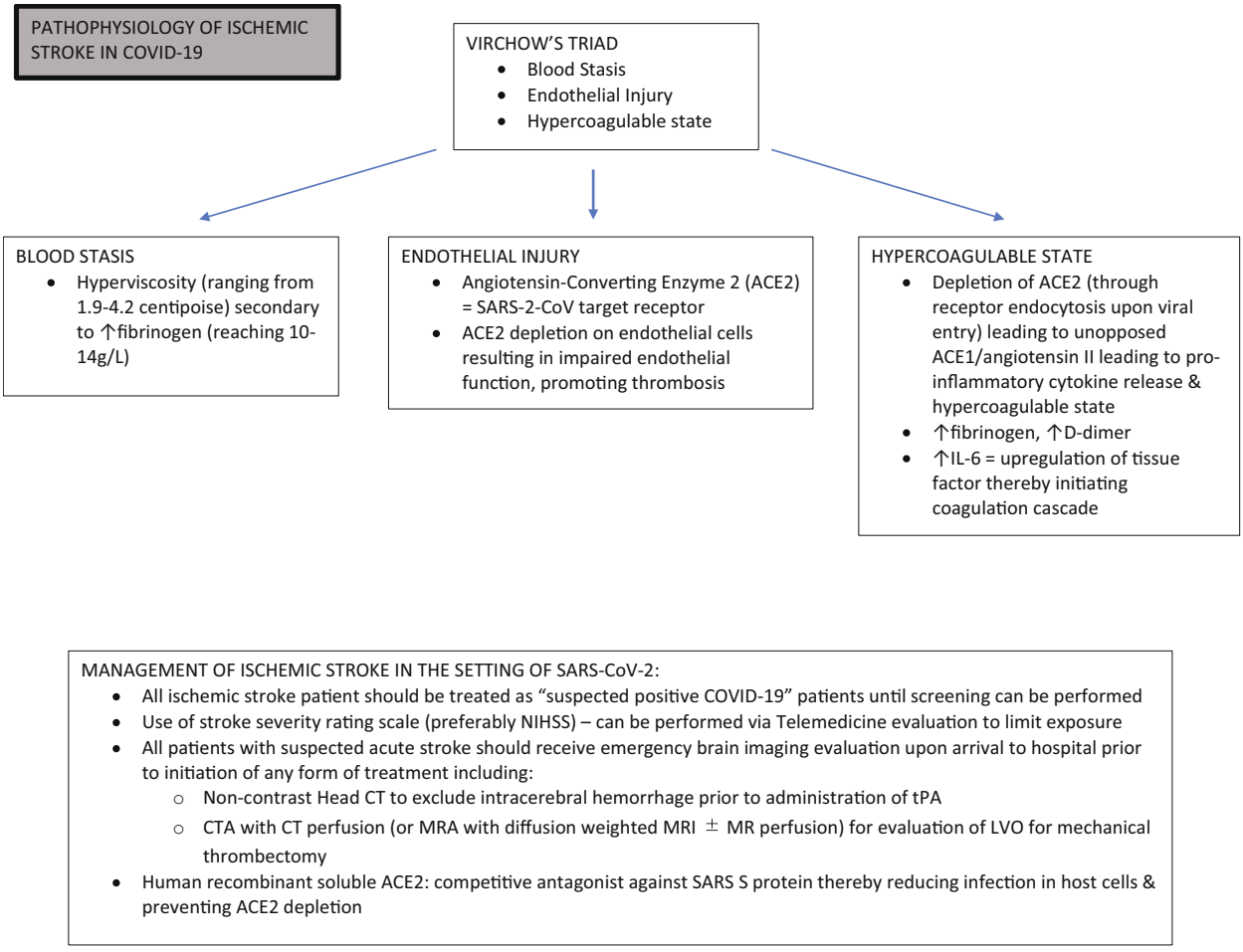

Fig. 1. Pathophysiology and Management of Ischemic Stroke in COVID-19.

traditional capillary viscometry, which was ranging from 1.9 to 4.2 centipoise (normal range 1.4–1.8 centipoise).[42] Although it is commonly seen in monoclonal gammopathies, hyperviscosity can be caused by substantially increased fibrinogen, which is consistent with observations in COVID-19 patients. Furthermore, SARS-CoV-2 rapidly activates immune response through the angiotensin 2 pathway and induces an imbalanced systemic inflammatory cascade, followed by a cytokine storm with high IL-6 and tumor necrosis factor-alpha (TNF- α).[43,44] Apart from direct impairment of organ function, a cytokine storm contributes to hyperviscosity as well. In return, hyperviscosity impairs endothelium and promote hypercoagulative state.[45]

Endothelial impairment is evidenced by elevated von Willebrand factor (vWF) and soluble P-selectin in COVID-19 patients as well. Specifically, the elevation of vWF is associated with the severity of the disease.[46] Overexpression of ACE2 in neuronal cells and endothelia prevents the development of ischemic stroke; this protective function is counteracted by the depletion of ACE2 as it serves as the target of SARS-CoV-2 spike protein.[47–49] Autopsy from SARS-CoV-1 have revealed vasculitis of venules in brain tis-

sue. This could be equally true in COVID-19 patients.[50] Through direct viral invasion and inflammatory response, SARS-CoV-2 facilitates endotheliitis, leads to microvascular dysfunction and a procoagulant state, and further increases risks of thrombotic events. Moreover, endothelial dysfunction compounded with anticoagulant treatment and preexisting comorbidities could lead to hemorrhagic stroke and hemorrhagic transformation of ischemic stroke in COVID-19 patients.[16]

5. Management of stoke amid COVID-19 pandemic

Response to stroke code amid the pandemic is challenging due to the potential exposure to COVID-19, requirement of isolation, and relative shortage of healthcare resources. A preplanned protocol is strongly recommended for institutes of different levels (Fig. 1). If patients are unable to provide essential information because of altered mental status, aphasia, or few witnesses, screening for COVID-19 could be difficult due to limited history of illness. In this case, stroke patients should be treated as potentially infected, and full personal protective equipment should be implemented. Stroke team members could have been redesignated to meet the increasing need for care of COVID-19, which forces the stroke team to operate with less staff. These all pose a threat to the delivery of healthcare to stroke patients with or without COVID-19. There is a high mortality rate in acute ischemic stroke in spite of timely treatment achieving revascularization. In one series, the mortality rate reaches 31%, while a pooled analysis revealed a dire 50% in COVID-19 patients complicated with acute ischemic stroke.[51] Nevertheless, no efforts should be spared in adhering to published stroke care guidelines. Telemedicine is superior at maximizing social distancing and physical isolation, and it should be made widely available. The NIHSS can be efficiently conducted via telemedicine.[52] It also shortens the time from symptoms onset to initial evaluation.

COVID-19 patients with ischemic stroke should undergo a full diagnostic work-up, including brain imaging, vascular imaging, cardiac evaluation. Coagulation profile should be ordered, such as D-dimer, fibrinogen, cytokines, and CRP.[53] In hospitalized COVID-19 patients with high levels of D-dimer indicating hypercoagulative state, anticoagulation therapy can be implemented to mitigate thrombotic complications, including ischemic stroke.[1] Intravenous recombinant tissue plasminogen activator (rt-PA) is recommended for selected patients following guidelines,[54] although the hypercoagulative profile predisposes patients to a higher rate of mortality or disability.[55] Mechanical thrombectomy is recommended for large vessel occlusion within six hours of symptom onset. The challenge lies in the transition from triage to angiographic suite while being compliant with the isolation policy.

Exogenous ACE2 with human recombinant soluble ACE2 is a novel treatment for COVID-19 patients with stroke. It competes with spike protein on SARS-CoV-2 and inhibit SARS-CoV-2 infections of the blood vessel, impedes viral related ACE2 depletion on endothelium and preserve its protective function. Collectively, exogenous ACE2 could prevent or reverse direct impairment of endothelial function enacted by SARS-CoV-2.[48] Other treatments targeting the renin-angiotensin system are also under investigation as a promising preventive treatment for stroke in COVID-19 patients.

6. Summary

COVID-19 patients have presented with a wide range of neurological disorders, among which stroke is the most devastating. SARS-CoV-2 infection induces coagulopathy, disrupts endothelial function, and promotes hypercoagulative state. Severe COVID-19 infection renders patients bedridden, and in certain cases requiring instrumental support. Collectively, it predisposes patients to cerebrovascular events. Due to the unprecedented strain on the healthcare system, stroke care has been inevitably compromised from initial encounter, treatment, to rehabilitation. The understanding of the underlying mechanism between COVID-19 and stroke warrants further study, so does the development of an effective therapeutic or preventive intervention.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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