Title: Stroke Associated with SARS-CoV-2 Infection and its Pathogenesis: A Systematic Review

Running title: SARS-CoV-2 and Stroke

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Abstract

In this systematic review, in addition to pluralization of almost all reports of stroke cases from the outbreak of the SARS-CoV-2 pandemic to 2 July 2020, we will discuss the change of stroke incidence during the pandemic period as well as the proposed mechanisms of this relationship between SARS-CoV-2 and stroke. Web of Science, PMC/Medline and Scopus databases were searched up to July 2020 without any time and language limitation. After quality assessment, 22 articles were included in this study. Based on the results of all studies, it is certainly impossible to conclude the rising or decreasing stroke frequency or the shift in the ischemic and hemorrhagic ratio. It appears that SARS-CoV-2 infection has some correlation with stroke. The supposed mechanisms for the SARS-CoV-2-related hemorrhagic stroke include 1) SARS-CoV-2-related vasculopathy with the endothelial damage of small vessels, 2) viral infection induced platelet dysfunction or thrombocytopenia, and 3) activation of the pro-inflammatory cascade leading to coagulopathy. Receiving therapeutic anticoagulation for high D-dimer or for a known thrombus due to SARS-CoV-2 infection as well as using extracorporeal membrane oxygenation (ECMO) in some patients are intended helpful strategies. Furthermore, the possible mechanisms for ischemic stroke include 1) dysregulation of ACE2 (key host cellular receptor for SARS-CoV-2)-related physiologic functions, 2) endothelial cell damages, 3) thrombo-inflammation, 4) coagulopathy and coagulation abnormalities related to SARS-CoV-2 infection. A better understanding of the SARS-CoV-2 pathogenesis and its relation to neurologic abnormalities such as stroke can be considered to prevent SARS-CoV-2 and improve new therapeutic approaches.

Keywords: SARS-CoV-2, Stroke, Angiotensin Converting Enzyme 2, Blood Coagulation Disorders, Cerebrovascular Disorders
Introduction

Cerebrovascular disorders include cerebral infarction due to thrombosis or emboli, and intracranial hemorrhage is one of the common causes of morbidity and mortality (Ashtari F, Saberi A et al. 2007a). On average, every 40 seconds someone in the United States has a stroke. Stroke mortality is particularly high in Eastern Europe and Asia. Factors that increase the risk for ischemic stroke include aging, male gender, ethnicity, family history, prior history of stroke, lack of physical activity, cigarette consumption, alcohol abuse, illicit drug use, low socioeconomic status, arterial hypertension, dyslipidemia, heart disease, and carotid artery disease, sickle cell disease, diabetes mellitus (DM), hyperhomocysteinemia, atrial fibrillation and left ventricular hypertrophy (José Biller 2016).


Different mechanisms explain the relationship between stroke and SARS-CoV2 infection, such as coagulopathy especially thrombophilia, expression of angiotensin-converting enzyme 2 (ACE2) on CNS cells, and interaction with SARS-CoV2, endothelial dysfunction and microthrombosis and cytokine storm, which could result in cerebrovascular disease (Al Saiegh F, Ghosh R et al. 2020, Hess DC, Eldahshan W et al. 2020, Zhou P, Yang XL et al. 2020).

In this study, in addition to pluralizing nearly all reports of stroke cases from the outbreak of the SARS-CoV-2 pandemic to 2 July 2020, we discuss the incidence of stroke during the SARS-CoV-2 pandemic period, and demonstrate the proposed mechanism of the relationship between SARS-CoV-2 and stroke.

Materials and Methods

Research question and inclusion/exclusion criteria

The primary question was that what incidence of stroke during the SARS-CoV-2 pandemic period. The secondary question was that whether SARS-CoV-2 infection the increase or decrease of stroke frequency or changes in the ischemic to hemorrhagic ratio.

Inclusion criteria for this review includes: studies with human subjects, evaluating or reporting of the SARS-CoV-2 patients with stroke.
Exclusion criteria for this review includes: studies focused on associated of other neurological diseases with stroke, animal models; studies had no extractable data or wrong type of study design.

**Search strategies**

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Moher D, Liberati A et al. 2009). All the studies were obtained from databases around the world, including Medline/PMC (via PubMed), Web of Science, and Scopus. Documents were carefully searched at the databases with no time and study type limit, until 2 July 2020. In addition, the search was done without language limitation.

**Keywords**

Table 1 describes the search strategy. The search terms with similar meanings were combined using the OR logic, and the search terms were coupled using the AND logic. For every database, the search strategy was updated and personalized.

<table>
<thead>
<tr>
<th>Database</th>
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<td>Scopus</td>
<td>(TITLE-ABS-KEY (stroke) AND TITLE-ABS-KEY (covid-19) OR TITLE-ABS-KEY (sars-cov-2) OR TITLE-ABS-KEY (coronavirus)) AND (LIMIT-TO (DOCTYPE, &quot;ar&quot;))</td>
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<td>PubMed</td>
<td>(((stroke[Title/Abstract]) AND (covid-19[Title/Abstract])) OR (sars-cov-2[Title/Abstract])) OR (coronavirus[Title/Abstract]) Filters applied: Full text, Clinical Trial, Randomized Controlled Trial.</td>
</tr>
</tbody>
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| Web of Science | TITLE: (stroke) AND TITLE: (covid-19) Refinded by: DOCUMENT TYPES: (ARTICLE)  
TITLE: (stroke) AND TITLE: (sars-cov-2) Refinded by: DOCUMENT TYPES: (ARTICLE)  
(stroke) AND TITLE: (coronavirus) Refinded by: DOCUMENT TYPES: (ARTICLE) |

**Quality assessment**

To help interpretation of results and limit bias of the review, we assessed the quality of selected articles using STARD (Requirements for Diagnostic Accuracy Reporting), which included criteria for the quality of completeness and consistency of the reporting of diagnostic accuracy studies (Cohen JF, Korevaar DA et al. 2016). Only those studies meeting the inclusion criteria for the analysis were conducted with quality assessment. Two reviewers independently evaluated the methodological consistency of the studies according to the criteria of Downs and Black (Downs SH and N. 1998). Any disputes were resolved by consensus, and a third reviewer checked them out. Each article received a total quality score, which was used in data synthesis and interpretation of review results.

**Data extraction**

Two investigators extracted the data using an extraction form independently and in duplicate. The following data were extracted from the selected articles: the first author’s name, the year of publication, location of the studies, the study type, number of cases participated, stroke type, gender, National Institute of Health Stroke Scale (NIHSS), D-Dimer, C-reactive protein (CRP), white blood cell (WBC), diagnosis test and risk factors concern correlation between stroke and SARS-CoV-2 in patients. Two authors examined the papers found through the search strategy for eligibility based on title and abstract. Differences between authors in the extraction of data were resolved by consensus.

**Results**
Translucently, a total of 164 reports were screened to analyze patients with stroke and SARS-CoV-2. Additionally, 154 articles were collected and analyzed after deleting the duplicates. After removing 86 unrelated reports, 37 full texts were assessed for eligibility. Figure 1 demonstrates the search strategy based on the PRISMA Flow Diagram.

Table 2 provides a description of the included articles. According to the results of 22 studies around the world, the following pluralization was obtained: 81 cases of ischemic stroke and 61 cases of hemorrhagic stroke from published studies were presented. From these 142 cases, 125 cases were positive for SARS-COV 2 by polymerase chain reaction (PCR) or typical findings of chest CT scan or both examinations. One case of transient ischemic attack (TIA), one case of cerebral venous thrombosis (CVT) and one case reversible cerebral vasoconstriction syndrome (RCVS) who were positive for SARS-COV 2 were reported. In addition, one cohort study reported 406 stroke and TIA cases among 40,469 patients who were positive for SARS-COV 2.
<table>
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<tr>
<th>Author, Year, Country</th>
<th>Study type</th>
<th>Treated no. Patients</th>
<th>Stroke type (Stroke patients no.)</th>
<th>Stroke SARS-CoV-2 patients no.</th>
<th>Gender (Stroke + SARS-CoV-2 patients no.)</th>
<th>NIHSS</th>
<th>D-Dimer</th>
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<th>WBC</th>
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<td>Agarwal, et al. (Agarwal A, Vishnu VY et al. 2020)</td>
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<td>25</td>
<td>11</td>
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<td>Al Saiegh, et al. (Al Saiegh F, Ghouz B et al. 2020)</td>
<td>Case Report</td>
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<td>Delmedina, et al.(Delmedina J, Abdellatif M et al. 2020)</td>
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<td>Qin, et al.(Qin L, Chiu H et al. 2020)</td>
<td>Case Report</td>
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<td>Hazuki, et al. (Hazuki R, Rego-Pa et al. 2020)</td>
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**Notes:**
- SARS-CoV-2: Severe Acute Respiratory Syndrome coronavirus 2
- NIHSS: National Institute of Health Stroke Scale
- CRP: C-reactive protein
- IS: Ischemic
- ICH: Intracerebral hemorrhage
- CVT: Cerebral venous thrombosis
- TIA: Transient ischemic attack
- RCVS: Reversible cerebral vasoconstriction syndrome
- RT-PCR: Real-time polymerase chain reaction
- CT: Computed tomography
- PCR: Polymerase chain reaction
Discussion

In the present study, the stroke cases, including ischemic (arterial and venous) and hemorrhagic (intracranial and subarachnoid) ones during the SARS-CoV-2 pandemic period to July 2020 have been reported. Overall, 142 cases including 81 cases of ischemic stroke and 61 cases of hemorrhagic stroke from published studies were presented. Furthermore, 125 patients included in this report were positive for the SARS-CoV-2 detected by PCR and typical findings of chest CT scan or both examinations. Moreover, one case of TIA, one case of CVT and one case RCVS who were positive for SARS-CoV-2 were reported. Additionally, one cohort study indicated that 406 stroke and TIA cases among 40,469 patients were positive for SARS-CoV-2 (Nalleballe K, Onteddu SR et al. 2020). It is not definitely possible to conclude the increase or decrease of stroke frequency, but it appears that there are some relationships between SARS-CoV-2 infection and stroke. Some studies demonstrated decreased occurrence of stroke, but their reasons were almost social and psychological, and there was not any pathophysiological mechanism.

Naccarato et al. reported that admission of stroke was decreased beyond 45% during the study period in 2020, compared to the same period in 2019. None of the patients was positive for SARS-CoV-2. In general, a lower absolute number of ‘code stroke’ activation and intravenous thrombolytic therapy (rtPA) treatments were identified in 2020 than in 2019 (Naccarato M, Scali I et al. 2020). Questions may arise as to whether the seasonal pattern of stroke incidence may play a role in our outcomes, but there is contradictory evidence. Some studies have revealed that ischemic stroke occurrences during spring and autumn are substantially higher than those in the summer. Thus, this reduction rate can be related to the failure of emergency services to transfer stroke patients, because of focusing on the transfers of SARS-CoV-2 patients. Furthermore, it is possible that fear could also delay stroke activation by patients or their families (Tejada Meza and al. 2020) and greater social isolation and/or avoid seeking healthcare services due to employment concerns and loss of insurance (Siegler and al.).

Hemorrhagic stroke

In some studies, the cases of hemorrhagic stroke were presented. According to our results, it appears that the ratio of hemorrhagic stroke to ischemic stroke (3/4) has been increased compared to the routine (1/3) ratio (José Biller 2016), which may be due to more inclination to hemorrhagic stroke reported in the period of the SARS-CoV-2 pandemic.

The potential possibilities leading to ICH include an infective arteriopathy, platelet dysfunction or thrombocytopenia, consumption coagulopathy and renal and hepatic dysfunction which lead to hypertension (Agarwal A, Vishnu VY et al. 2020). Receiving therapeutic anticoagulation for a high D-dimer or for a known thrombus due to SARS-CoV-2 infection is another cause (Dogra S, Jain R et al. 2020). Intraparenchymal hemorrhages have been reported with ECMO. Postulated mechanisms include
disruption in hemostasis likely potentiated by concomitant anticoagulation during ECMO, and hemodynamic dysfunction with loss of cerebral perfusion auto-regulation (Zahid MJ, Baig A et al. 2020).

Additionally, Dakay et al. reported a case of RCVS and dissection in the setting of SARS-CoV-2 infection resulting in convexal subarachnoid hemorrhage (cSAH). In this case, a week before the presentation, she had cough, which possibly precipitated the dissection, leading to subsequent RCVS and cSAH. Extracranial dissection associated with RCVS is rare, but it was reported that dissection could result in precipitating the RCVS through release of vasoactive substances. CSAH in RCVS is possibly due to complex vessel wall changes, with vasoconstriction accompanied by vasodilatation resulting in damage to the reperfusion and bleeding. However, SARS-CoV-2 can also cause vasoconstriction; blood pressure spikes can lead to a loss of cerebral autoregulation, which is the proposed RCVS mechanism. SARS-CoV-2 in particular down-regulates the ACE2 receptor, which acts to suppress sympathetic sound, increases vasodilatation and exerts antihypertensive effects. SARS-CoV-2 results in ACE2 down-regulation, which can cause the classic renin-angiotensin axis to over-activate and result in vasoconstriction (Dakay K, Kaur G et al. 2020).

Ischemic stroke

In some reports the cases of ischemic stroke were presented as a thrombotic event increased by SARS-CoV-2 infection (Cantador E, Núñez A et al. 2020, Chibane S, Gibeau G et al. 2020), therefore, increasing the chance of ischemic stroke is inevitable. The supposed mechanisms of ischemic and thrombotic events are as follows:

SARS-CoV-2 receptor for cell entry: ACE2

Upper and lower respiratory tracts are a major location of SARS-CoV-2 infection and disease morbidity (Huang, Chen et al. 2020, Sungnak, Huang et al. 2020). ACE2, the key host cellular receptor for SARS-CoV-2, is expressed in human lung parenchyma and alveolar epithelial cells, capillary endothelium of the lungs as well as alveolar macrophages (Jia, Look et al. 2005, Kuba, Imai et al. 2006). In addition to the lungs, it has been demonstrated that ACE2 is widely expressed in multiple extra-pulmonary tissues, including neurons, endothelial and arterial smooth muscle cells in the brain, epithelial cells of oral mucosa, small intestine and colon, and many other tissues (Xia and Lazartigues 2008, Chen, Li et al. 2020, Fan, Li et al. 2020, Li, Li et al. 2020, Shen, Xiao et al. 2020, Xu, Zhong et al. 2020). In this regard, the level of expression of ACE2 from the highest to lowest levels may vary in various human tissues (Li, Li et al. 2020), and the extra-pulmonary complications of SARS-CoV-2 might be followed secondarily after SARS-CoV-2 infection (Gupta, Madhavan et al. 2020). The coronavirus spike (S) protein facilitates the entry of SARS-CoV-2 via ACE2 into target cells. This interaction is mediated by a defined receptor binding domain (RBD) on the S protein (Li, Li et al. 2005).

There is strong evidence that SARS-CoV-2 and its structure has similarity to other coronavirus species found in bats, and the reported SARS-CoV-2 genome sequence for has a closely resembles with
other beta-coronaviruses such as SARS-CoV-1 (Ather, Patel et al. 2020, Zhou, Yang et al. 2020). In addition, it has been demonstrated that SARS-CoV-1 and SARS-CoV-2 using the same ACE2 receptor for cell entry (Ge, Li et al. 2013, Zhou, Yang et al. 2020), while the binding affinity of SARS-CoV-2 to ACE2 is higher than that of SARS-CoV-1, which may partly explain the increased SARS-CoV-2 transmissibility (Wang, Zhang et al. 2020). ACE2 binds with SARS-CoV-2 with an affinity of 15 nM, approximately 10–20 times higher than that of SARS-CoV-1, and this might clarify its greater virulence (Wrapp, Wang et al. 2020). Additionally, cell entry involves the priming of the S protein by the cellular serine protease TMPRSS2 or other proteases, which entails the S protein cleavage at S1/S2 and S2 sites and allows the fusion of viral and cellular membranes, a process driven by the subunit of S2. To complete this entry process, the co-expression of ACE2 and TMPRSS2 is required. Analysis of the receptor binding motif (RBM), a portion of RBD connected with ACE2, indicated that most of the amino acid residues necessary for the SARS-S protein binding with ACE2 were conserved in the SARS-2-S protein (Hoffmann, Kleine-Weber et al. 2020).

**Dysregulation of ACE2-related physiologic functions induced by SARS-CoV-2**

The major mechanisms that may be correlated with ACE2 in the pathophysiology of CoV-2 include dysregulation of the renin-angiotensin-aldosterone system (RAAS) and the direct viral toxicity mediated by ACE2 (Alsufyani and Docherty 2020). ACE2-mediated cell entry and subsequent tissue damage as well as dysregulation of RAAS may be unique to SARS-CoV-2. RAAS includes the cascade of regulatory and vasoactive factors orchestrating key human physiological processes such as cardiovascular system, hydro-electrolyte control, blood-pressure regulation, vascular permeability, pulmonary epithelial membrane stability, and tissue growth (Alsufyani and Docherty 2020). ACE2 is an important RAAS path regulator through cleavage of angiotensin I and II into inactive angiotensin 1-9 and angiotensin 1-7, respectively, which have vasodilator, anti-proliferative and anti-fibrotic characteristics (Santos, Sampaio et al. 2018). SARS-CoV-2 causes the down-regulation of the ACE2 expression on alveolar epithelial cells, capillary endothelium of the lungs and alveolar macrophages, and then leads to excessive production of angiotensin I and II that has been suggested to increase pulmonary vascular permeability and disease development to ARDS (Kuba, Imai et al. 2006, Silhol, Sarlon et al. 2020). ARDS development is associated with the up-regulation of pro-inflammatory cytokines and chemokines, known as cytokine release syndrome or cytokine storm phenomenon, which lead to tissue damage and severe inflammation induced by overwhelming immune cells migration into the lungs and their unspecific activation (Ragab, Salah Eldin et al. 2020). It has been illustrated that ACE2 deficiency impaired the endothelium function in cerebral arteries (Silva, Chu et al. 2012), indicating that ACE2 plays a protective role in endothelium. Furthermore, ACE2 is a brain hemostasis regulator through the RAAS regulation (Santos, e Silva et al. 2003). In addition, production of angiotensin 1-7 induced by ACE2 promotes the brain angiogenesis, oxidative stress inhibition, and neuro-inflammation resistance and improves the cerebral blood flow (Kangussu, Marzano et al. 2019).
Therefore, the down-regulation of ACE2 induced by SARS-CoV-2 frustrates the normal functions of CNS.

Coagulopathy related to SARS-CoV-2

According to the official data released by the Chinese Health Commission, the frequency of newly diagnosed SARS-CoV-2 patients has been decreased, and the pandemic is being steadily managed. Although most patients have mild-moderate symptoms with good prognosis, some others develop serious illness and die from multi-organ failure due to the diffuse micro-vascular damage (Lin, Lu et al. 2020, Tang, Li et al. 2020, Zheng, Feng et al. 2020). It is stated that disseminated intravascular coagulation (DIC) and ischemic changes may occur in the severe form of SARS-CoV-2 patients, and some studies are proposed as an anti-coagulation therapy to control the disease (Kollias, Kyriakoulis et al. 2020, Lin, Lu et al. 2020). It has also been shown that elevation of D-dimer (as a coagulation parameter) and extreme thrombocytopenia in critically ill SARS-CoV-2 patients may render the patients prone to acute cerebrovascular events (Wang, Wang et al. 2020, Wu, Xu et al. 2020). Recently, a retrospective analysis of 21 deaths by SARS-CoV-2 demonstrated that 71% of patients who died had DIC during their hospital stay. They showed that abnormal coagulation results, especially markedly elevated D-dimer and fibrin degradation product (FDP), are typical in deaths with SARS-CoV-2 (Tang, Li et al. 2020). The data suggested that acute coagulation disorders are crucial risk factors for increased in-hospital mortality. Cui et al. reported that elevation of D-dimer levels might be indicative of thrombosis and could be used to predict venous thromboembolism (VTE). They showed a 25% incidence of VTE in severe SARS-CoV-2 patients (20 patients among 81 ICU-patients), and 8 of which died from VTE events (Cui, Chen et al. 2020). Patients with hyper-coagulable state may exhibit normal or enhanced platelet counts with reasonably activated partial thromboplastin time, significantly increased D-dimer and fibrinogen, increased CRP levels, factor VII as well as the von Willebrand factor (Panigada, Bottino et al. 2020), whereas in this case, Klok et al. reported that thrombotic complications occurred in 31% of critically ill ICU-patients with SARS-CoV-2 (Klok, Kruip et al. 2020).

Endothelial cell damages and thrombo-inflammation correlated to SARS-CoV-2

Other proposed SARS-CoV-2 pathophysiological mechanisms related to the ACE2-mediated entry are endothelial cell damage and thrombo-inflammation (Ackermann, Verleden et al. 2020). As mentioned earlier on the expression of ACE2 in the arterial and venous endothelium of various organs, it has been shown that SARS-CoV-2 particles are detected in lungs endothelial cells and other tissues (Ackermann, Verleden et al. 2020). After SARS-CoV-2 endothelial cell infection, endothelial injury and endothelialitis developed in multiple vascularized tissues, and these pathological conditions were accompanied by elevation of the von Willebrand factor and recruitment of activated immune cells such as neutrophils, monocytes and macrophages (Varga, Flammer et al. 2020). Ultimately, excessive thrombin production and complement activation are triggered, leading to thrombo-inflammation and...
vascular dysfunction (Engelmann and Massberg 2013, Bikdeli, Madhavan et al. 2020). Magro et al. illustrated that hyper-coagulability and micro-vascular thrombosis related to SARS-CoV-2 were associated with complement-mediated endothelial injury (Magro, Mulvey et al. 2020). In severe SARS-CoV-2 patients, they showed a pattern of the lung and skin damage consistent with the complement-mediated micro-vascular injury. Their demonstration of the striking deposition of terminal complement components C5b-9 (membrane attack complex), C4d, and mannose binding lectin-associated serine protease 2 (MASP2) in the microvasculature of organs is consistent with the profound activation of both alternative and lectin-based pathways of the complement system (Magro, Mulvey et al. 2020). Another mechanism correlated with the SARS-CoV-2 associated hyper-coagulability is the cytokine-induced systemic inflammatory response. Rannucci et al. demonstrated interleukin (IL)-6 as a coagulation parameter in critically ill patients with ARDS. A significant finding from their study was the direct correlation between IL-6 and fibrinogen levels, confirming the link between inflammation and pro-coagulant modifications. All of their patients had dramatically increased levels of blood IL-6 (Ranucci, Ballotta et al. 2020). Thus, in the proposed way, utilizing novel anti-inflammatory agents such as IL-6- and IL-1-antagonists as additional therapy alongside with anti-coagulation therapies, treat the cytokine storm and this may be critical in reducing thrombo-inflammatory responses and subsequent tissue injury (Connors and Levy 2020). Furthermore, immune cells activation and their cross-interaction with platelets in the situation of thrombo-inflammation could be a major inducer of pro-inflammatory effects such as cytokine over-production, neutrophil extracellular traps (NETs) and fibrin formation (Semple, Italiano et al. 2011, Engelmann and Massberg 2013). Moreover, following the increased neutrophil-lymphocyte ratio occurred in SARS-CoV-2 patients in intensive care units (ICU), NET formation as a protective role against microorganisms inappropriately damages the endothelium and activates coagulation pathways through activation of surrounding immune and non-immune cells to induce inflammatory cytokines secretion and to promote thrombus formation (Leppkes, Knopf et al. 2020, Tomar, Anders et al. 2020). A brief report in the New England Journal of Medicine has demonstrated the occurrence of anti-phospholipid antibodies in SARS-CoV-2 ICU-patients. They showed in a case report that the existence of anti-phospholipid antibodies (anti-cardiolipin IgA and anti-β2-glycoprotein IgG/IgA antibodies) may rarely lead to thrombotic events like DIC (Zhang, Xiao et al. 2020). In summary, SARS-CoV-2 associated coagulopathy may involve immune system components such as immune cells, pro-inflammatory cytokines, complement system and pathologic antibodies.

SARS-CoV-2-induced coagulation abnormalities and the risk of stroke

Raised levels of CRP and D-dimer in severe infected-patients exhibiting a high inflammatory condition and coagulopathy may play a major role in stroke pathogenesis in the context of SARS-CoV-2. Although ACE2 is expressed in the nervous system, other pathways such as direct damage of BBB,
hypoxia and immune-related injuries have been proposed to declare the entry of SARS-CoV-2 into CNS (Steardo, Steardo Jr et al. 2020, Wu, Xu et al. 2020). The possible cause of cerebrovascular injuries associated with SARS-CoV-2 infection could be hyper-coagulability resulting in macro and micro thrombus formation in the vessels (Avula, Nalleballe et al. 2020). In this context, Barrios-Lopez et al. demonstrated that the hyper-coagulable condition associated with the hyper-inflammatory response triggered by SARS-CoV-2 could be considered a possible cause of ischemic stroke (Barrios-López, Rego-García et al. 2020). However, they noted that studies with larger samples were necessary to confirm the hypothesis. Another research revealed smokers’ vulnerability to cerebrovascular diseases linked to SARS-CoV-2, including stroke. They showed an increased ACE2 expression in ischemic brains and vessels exposed to smoking, rendering them vulnerable to CNS infection with SARS-CoV-2 (Ji-Young, Hye-Kyung et al. 2020). Thus, the modification of the ACE2 expression in the CNS of high risk groups (diabetes and smokers) has occurred.

SARS-CoV-2 patients with cerebrovascular diseases often present with complications such as hypertension and other stroke risk factors. Pro-inflammatory changes during SARS-CoV-2 are associated with stroke risk factors and under inflammatory stimulation, leukocyte activation and following cerebrovascular thrombosis are arisen. The accumulation of inflammatory immune cells in the vascular wall leads to BBB disruption, and this process may lead to thrombosis, thereby increasing the risk of stroke (Fan, Tang et al. 2020). One possible mechanism correlating with the SARS-CoV-2 associated stroke is the pro-inflammatory cytokine storm phenomenon. Different viruses trigger hyper-cytokinemia through various mechanisms. For instance, SARS-CoV-1 related cytokine storm are mainly associated with IL-1β, IL-6, IL-12, interferon (IFN)-γ and monocyte chemo-attractant protein-1 (MCP-1) (Wong, Lam et al. 2004). Indeed, the cytokine storm correlated with MERS-CoV is related primarily to IFN-γ, tumor necrosis factor (TNF)-α, IL-15 and IL-17, a pattern of T helper-1 (Th1) and Th17 lymphocytes (Mahallawi, Khabour et al. 2018). Furthermore, the cytokine storm pattern in severely ill SARS-CoV-2 patients is related to significant enhancement of IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), MCP-1, and TNF-α (Huang, Wang et al. 2020). Furthermore, decrease in CD4+ and CD8+ T cells and high production of IL-6 and IL-10 were observed in the severe form of SARS-CoV-2 (Wan, Yi et al. 2020). After appearance of hyper-inflammation during the cytokine storm, the permeability of BBB is enhanced. Then, SARS-CoV-2 attracts CD68+ monocyte/macrophages and CD3+ T cells into the infected brain; however, a large number of inflammatory cytokines are released after SARS-CoV-2 related brain injury, which finally promotes thrombosis and stroke (Fugate, Lyons et al. 2014, Fan, Tang et al. 2020).

Extra-pulmonary complications and pathophysiology of neurologic damages related to SARS-CoV-2

Unlike the extensive literature on the pathophysiology of complications caused mainly by SARS-CoV-2 specifically severe respiratory disorders, certain extra-pulmonary manifestations such as
thrombotic complications, myocardial failure and arrhythmia, acute coronary syndromes, acute kidney injury, gastrointestinal symptoms, hepatocellular damage, hyperglycemia and ketosis, neurological diseases, ocular symptoms and dermatological complications can occur concerning the SARS-CoV-2 infection (Gupta, Madhavan et al. 2020). Among these issues, the extent of the SARS-CoV-2 involvement in CNS is not well known, and the existence or the absence of SARS-CoV-2 in the CNS is a subject of debate. The extra-pulmonary pathogenesis of SARS-CoV-2 is still incompletely understood with an emphasis on neurologic manifestations. It is stated that SARS-CoV-2 can be detected in the brain and cerebrospinal fluid (CSF) of COVID-19 patients, and there is a short study reporting the absence of SARS-CoV-2 in the CSF of COVID-19 patients with concurrent serious neurological symptoms. Additionally, in such cases, an underlying inflammatory and hyper-coagulable state may provoke cerebrovascular syndrome without disruption of BBB (Al Saiegh F, Ghosh R et al. 2020). The neuro-infection could be occurred due to the considerable similarity between SARS-CoV-1 and SARS-CoV-2, and it is reported that SARS-CoV-2 exhibits neurotropic characteristics and may also cause neurological harm (Wu, Xu et al. 2020). Recently, the first case of the viral encephalitis caused by SARS-CoV-2 has been identified in which the virus attacks CNS and illustrates that CoV-2 has potential to cause nervous system injury (Xiang P, Xu X et al. 2020). It has also been advised that SARS-CoV-2 similar to the influenza virus can aggravate ischemic brain injury by triggering a cytokine storm and raising the risk of intra-cerebral hemorrhage, indicating that blocking cytokine cascade is an effective approach to treat stroke in a pro-inflammatory context (Muhammad S, Haasbach E et al. 2011). Consequently, the cytokine storm syndrome caused by SARS-CoV-2 may be one of the major factors associated with SARS-CoV-2 cerebral disorders.

Conclusion

Although it is impossible to conclude the increase or decrease of stroke frequency or changes in the ischemic to hemorrhagic ratio in association with SARS-CoV-2, it seems that SARS-CoV-2 infection is associated with stroke in some aspects. For hemorrhagic stroke, the supposed mechanisms include SARS-CoV-2 related vasculopathy with endothelial damage of small vessels viral infection induced platelet dysfunction or thrombocytopenia, activation of pro-inflammatory cascade leading to consumption coagulopathy, receiving therapeutic anticoagulation for a high D-dimer or for a known thrombus due to SARS-CoV-2 infection and using ECMO in some patients. The possible mechanisms for ischemic stroke include presence of ACE2 receptor on neurons as the key host cellular receptor for SARS-CoV-2, dysregulation of ACE2-related physiologic functions, cerebral endothelial and arterial smooth muscle dysfunction, coagulopathy and thrombo-inflammation related to SARS-CoV-2.

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Compliance with ethical standards

Conflict of interest
All authors declare that they have no conflict of interest.

**Ethical approval**

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