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

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ABSTRACT

Introduction: The change of stroke incidence during the COVID-19 pandemic period and the proposed mechanisms of the relationship between SARS-CoV-2 and stroke is reviewed.

Methods: Web of Science, PMC/Medline, and Scopus databases were searched until July 2020 without time and language limitations. After quality assessment, 22 articles were included in this study.

Results: Based on the results, it is impossible to conclude any definite relationship between the rising or decreasing stroke frequency or the shift in the ischemic and hemorrhagic ratio and SARS-CoV-2 infection. However, 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 proinflammatory cascade leading to coagulopathy. The helpful strategies are receiving therapeutic anticoagulation for high D-dimer or a known thrombus due to SARS-CoV-2 infection, as well as using extracorporeal membrane oxygenation (ECMO) in some patients. Furthermore, the possible mechanisms for the SARS-CoV-2-related ischemic stroke include 1) dysregulation of angiotensin-converting enzyme 2 (a key host cellular receptor for SARS-CoV-2)-related physiologic functions, 2) endothelial cell damages, 3) thrombo-inflammation, and 4) coagulopathy and coagulation abnormalities related to SARS-CoV-2 infection.

Conclusion: A better understanding of the SARS-CoV-2 pathogenesis and its relation to neurologic abnormalities such as stroke can help to design new therapeutic approaches.

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Highlights

- According to our study, there is not a definite relationship between COVID-19 and stroke incidence.
- It appears that the ratio of the hemorrhagic stroke to ischemic stroke has enhanced, which may be due to the COVID-19.
- The frequency of thrombotic reactions due to the severe SARS-CoV-2 infection is seem to be increased.

Plain Language Summary

Since the onset of the COVID-19 pandemic, many case-report studies have shown that severe or critically ill COVID-19 can lead to thrombotic disorders and stroke. It seems that a relationship exists between COVID-19 and stroke in human societies, and accordingly, in the present study we have tried to provide a comprehensive and systematic review for this global concern. Based on our findings in a limited timeline and according to our knowledge, there is not necessarily a clear correlation between COVID-19 and the stroke prevalence, but this relationship is likely to exist. Also, in the present study we have described the supposed mechanisms for SARS-CoV-2-related stroke in a detail. It appears that the SARS-CoV-2 infection causes coagulation abnormalities, vascular damage and progression of inflammatory cascades leading to a stroke and multi-organ injury. Consequently, for the better understanding, further studies in this context are required.

Introduction

Cerebrovascular disorders include cerebral infarction due to thrombosis or emboli. Also, intracranial hemorrhage is one of the common causes of morbidity and mortality (Ashtari, et al. 2007). 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 smoking, alcohol abuse, illicit drug use, low socioeconomic status, arterial hypertension, dyslipidemia, heart disease, carotid artery disease, sickle cell disease, diabetes mellitus, hyperhomocysteinemia, atrial fibrillation and left ventricular hypertrophy (Boehme, Esenwa, & Elkind, 2017).

Nowadays, the role of infection in the occurrence of stroke has been mainly considered. In addition, many infectious agents were regarded as a risk factor for stroke (Ashtari et al. 2006; Ashtari et al. 2006b, Ashtari et al. 2007a; Ashtari et al. 2007b; Ashtari, Shayegannejad, Saberi, & Rabiee, 2008; Saberi, Akhondzadeh, Kazemi, & Kazemial, 2021).

In December 2019, the first case of Coronavirus Disease 2019 (COVID-19), an illness caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported from Wuhan, Hubei Province in China (Li, Li, Zhang, & Wan, 2020). The World Health Organization (WHO) declared SARS-CoV-2 disease (COVID-19) a pandemic on March 11, 2020. According to various reports from around the world, this virus plays a role in stroke occurrence (Agarwal et al., 2020; Avula et al., 2020; Barrios-López et al., 2020; Cantador et al., 2020; Chibane et al., 2020; Chougar, Mathon, Weiss, Degos, & Shor, 2020; Dakay et al., 2020; Deliwala, Abdulhamid, Abusalih, Al-Qasmi, & Bachuwa, 2020; Dogra et al., 2020; Gill, Chan, & Fitzpatrick, 2020; Hanafi et al., 2020; Jain et al. 2020; Klein, Libman, Kirsch, & Arora, 2020; Morassi et al., 2020; Moshayedi, Ryan, Mejia, Nour, & Liebeskind, 2020; Naccarato et al., 2020; Nalleballe et al., 2020; Oxley et al., 2020; Rudilosso, Esteller, Urra, & Chamorro, 2020; Zahid, Baig, Galvez-Jimenez, & Martinez, 2020; Shahjouei et al., 2020). Other members of the coronaviridae family are Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV). They are supposed to contribute to stroke pathophysiology and occurrence (Algahtani, Subahi, & Shirah, 2016; Venketasubramanian & Hennerici, 2020).

Different mechanisms explain the relationship between stroke and SARS-CoV-2 infection, such as coagulopathy (especially thrombophilia), expression of Angiotensin-Converting Enzyme 2 (ACE2) on Central Nervous System (CNS) cells, and interaction with SARS-CoV-2, endothelial dysfunction, microthrombosis, and cytokine

storm, which could result in cerebrovascular disease (Pourgholaminejad, Kazemi, & Saberi, 2021; Al Saiegh et al. 2020; Hess, Eldahshan, & Rutkowski, 2020; Zhou et al., 2020).

In this study, in addition to collecting nearly all reports of stroke cases since the outbreak of the SARS-CoV-2 pandemic until July 2, 2020, we discuss the incidence of stroke during the SARS-CoV-2 pandemic period and explain the proposed mechanisms of the relationship between SARS-CoV-2 and stroke.

2. Methods

Research question and inclusion/exclusion criteria

The first question is the incidence of stroke during the SARS-CoV-2 pandemic period. The second question asks about the relationship between SARS-CoV-2 infection with the increase/decrease of stroke frequency or changes in the ischemic to hemorrhagic ratio. The inclusion criteria for this review include studies with human subjects evaluating or reporting the SARS-CoV-2 patients with stroke. The exclusion criteria include studies focused on other neurological diseases with stroke, studies with animal models, studies with no extractable data, or the wrong type of study design.

Search strategies

This study was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Hutton et al., 2015). All studies were obtained from Medline/PMC (via PubMed), Web of Science, and Scopus. Documents were carefully searched at the databases with no time and study type limit until July 2, 2020. In addition, the search was conducted without language limitations.

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.

Quality assessment

To help interpretation of results and limit the review bias, 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 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 & Black, 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, NIHSS (National Institute of Health Stroke Scale), D-Dimer, C-reactive protein (CRP), White Blood Cell (WBC), diagnostic test and risk factors concerning the correlation between stroke and SARS-CoV-2 in patients. Two authors examined the found papers through the search strategy for eligibility based on their titles and abstracts. Differences between authors in the extraction of data were resolved by consensus.

3. Results

Total of 164 reports were found that studied the patients with stroke and SARS-CoV-2. After deleting the duplicates, 154 articles remained. After removing 86 unrelated reports, 37 full texts were assessed for eligibility. Figure 1 shows 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 worldwide, the following information was obtained: 81 cases of ischemic stroke and 61 cases of hemorrhagic stroke from published studies were presented. Of 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. One case of Transient Ischemic Attack (TIA), one case of Cerebral Venous Thrombosis (CVT), and one case of Reversible Cerebral Vasoconstriction Syndrome (RCVS) were reported because they were positive for SARS-CoV-2. In addition, one cohort study reported 406 strokes and TIA cases among 40469 patients who were positive for SARS-CoV-2.

3. Discussion

In the present study, the stroke cases, including ischemic (arterial and venous) and hemorrhagic (intracranial and subarachnoid) ones since the emergence of the SARS-CoV-2 pandemic until 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 these reports 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 40469 patients were positive for SARS-CoV-2 (Nalleballe et al., 2020). It is not possible to conclude a definite relationship between increase or decrease of stroke frequency and COVID-19, but it appears that some relationships exist between SARS-CoV-2 infection and stroke. Some studies demonstrated the decreased occurrence of stroke, but their reasons were almost social and psychological, and there were no pathophysiological mechanisms (Nalleballe et al., 2020).

Naccarato et al. reported that stroke admission decreased under 45% during the study period in 2020, compared to the same period in 2019. None of the patients were 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 et al., 2020). Questions may arise as to whether the seasonal pattern of stroke incidence may play a role in our findings, 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. In addition, anxiety can delay the activation of stroke by patients and their families (Tejada et al., 2020) increased social isolation and non-use of medical services due to employment problems and loss of insurance (Siegler, Heslin, Thau, Smith, & Jovin (2020).

Hemorrhagic stroke

In some studies, cases of hemorrhagic stroke were presented. According to our results, it appears that the ratio of the hemorrhagic stroke to ischemic stroke (¾) has increased compared to the routine (1/3) ratio (Boehme, Esenwa, & Elkind, 2017), which may be due to more inclination to hemorrhagic stroke reported in the period of the SARS-CoV-2 pandemic.

The potential causes of Intracerebral Hemorrhage (ICH) include an infective arteriopathy, platelet dysfunction or thrombocytopenia, consumption coagulopathy, and renal and hepatic dysfunction, which lead to hypertension (Agarwal et al., 2020). Receiving therapeutic anticoagulation for a high D-dimer or a known thrombus due to SARS-CoV-2 infection is another cause (Dogra et al., 2020). Intraparenchymal hemorrhages have been reported with Extracorporeal Membrane Oxygenation (ECMO). Postulated mechanisms include disruption in hemostasis, which is likely potentiated by concomitant anticoagulation during ECMO, and hemodynamic dysfunction with loss of cerebral perfusion auto-regulation (Zahid 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, one week before the presentation, the patient had a cough, which possibly precipitated the dissection, leading to subsequent RCVS and cSAH. Extracranial dissection associated with RCVS is rare, but it has been reported that dissection could precipitate the RCVS by releasing 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. In particular, SARS-CoV-2 down-regulates the ACE2 receptor, which suppresses 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 cause vasoconstriction (Dakay 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 et al., 2020; Chibane 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

The upper and lower respiratory tracts are the main targets of SARS-CoV-2 infection and disease morbidity (Huang et al., 2020; Sungnak et al., 2020). ACE2, the critical host

Table 1. Search strategy applied in the PubMed, Scopus, and Web of Science databases

Database	Syntax
Scopus	(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, "ar"))
PubMed	(((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.
Web of Science	TITLE: (stroke) AND TITLE: (COVID-19) Refined by: DOCUMENT TYPES: (ARTICLE) TITLE: (stroke) AND TITLE: (SARS-CoV-2) Refined by: DOCUMENT TYPES: (ARTICLE) TITLE: (stroke) AND TITLE: (coronavirus) Refined by: DOCUMENT TYPES: (ARTICLE)

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cellular receptor for SARS-CoV-2, is expressed in the human lung parenchyma, alveolar epithelial cells, capillary endothelium of the lungs, and alveolar macrophages (Jia, Look et al. 2005; Kuba, Imai, & Penninger, 2006). In addition to the lungs, it has been demonstrated that ACE2 is widely expressed in multiple extrapulmonary tissues, including neurons, endothelial and arterial smooth muscle cells in the brain, epithelial cells of the oral mucosa, small intestine and colon, and many other tissues (Xia & Lazartigues 2008; Chen, Li, Chen, Feng, & Xiong, 2020; Xiao et al., 2020; Xu et al., 2020). In this regard, the expression of ACE2 from the highest to lowest levels may vary in various human tissues (Li et al., 2005), and the extrapulmonary complications of SARS-CoV-2 might be followed secondarily after SARS-CoV-2 infection (Gupta 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 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 has closely resembled other beta-coronaviruses such as SARS-CoV-1 (Ather et al., 2020; Zhou et al., 2020). In addition, SARS-CoV-1 and SARS-CoV-2 use the same ACE2 receptor for cell entry (Ge, Li et al. 2013; Zhou al., 2020). However, 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 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 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 are conserved in the SARS-2-S protein (Hoffmann et al., 2020).

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

The major mechanisms that may be associated 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 & 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 & 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. They have vasodilator, anti-proliferative and anti-fibrotic characteristics (Santos et al., 2018). SARS-CoV-2 down-regulates 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 increase pulmonary vascular permeability and disease development to acute respiratory distress syndrome (ARDS) (Kuba et

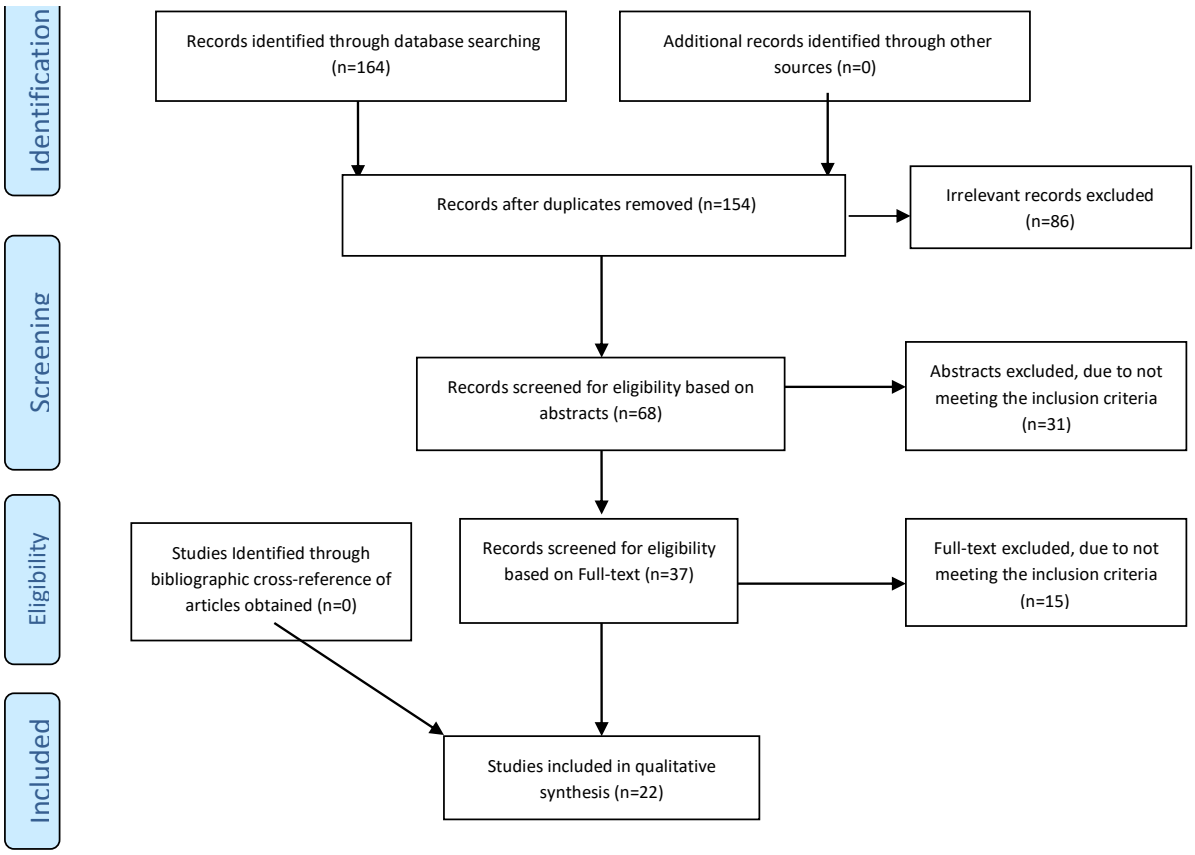

Figure 1. Flow chart of literature search and study selection

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al., 2006; Silhol et al., 2020). ARDS development is associated with the up-regulation of proinflammatory cytokines and chemokines, known as cytokine release syndrome or cytokine storm phenomenon. This reaction leads to tissue damage and severe inflammation induced by overwhelming immune cells migration into the lungs and their unspecific activation (Ragab et al., 2020). It has been illustrated that ACE2 deficiency impaired the endothelium function in cerebral arteries, indicating that ACE2 plays a protective role in the endothelium. Furthermore, ACE2 is a brain hemostasis regulator through the RAAS regulation (Santos et al., 2003). In addition, the production of angiotensin 1-7 induced by ACE2 promotes brain angiogenesis, oxidative stress inhibition, and neuro-inflammation resistance and improves cerebral blood flow (Kangussu et al., 2019). Therefore, the down-regulation of ACE2 induced by SARS-CoV-2 impairs the normal functions of the 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 to moderate symptoms with a good prognosis, others develop severe illnesses and die from multi-organ failure due to diffuse microvascular damage (Lin et al., 2020, Tang et al., 2020, Zheng et al. 2021). It is stated that disseminated intravascular coagulation (DIC) and ischemic changes may occur in the severe form of SARS-CoV-2, and some studies proposed as an anticoagulation therapy to control the disease (Kollia 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 an elevated D-dimer and fibrin degradation product, are typical in deaths with SARS-CoV-2 (Tang 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 indicate thrombosis and could be used to predict venous thromboembolism (VTE). They showed

Table 2. Summary of studies included in the systematic review of stroke associated with SARS-CoV-2

Author, Year, Country	Study Type	Total No. Population	Stroke Type (Stroke Patients No.)			Stroke + SARS-CoV-2 Patients No.	Gender (Stroke + SARS-CoV-2 Patients No.)		NIHSS	D-Dimer	CRP	WBC	Diagnostic test	Risk Factors
			IS	ICH	Others		Male	Female						
Agarwal et al. 2020 India	Original Article	25	11	14	-	2	2	-	NA	NA	M: 4.11 (<1) (mg/dL) M: NA (mg/dL)	NA	RT-PCR of a nasopharyngeal swab specimen	-Hypertension -Smoking -Diabetes mellitus
Al Saiegh, et al. 2020, USA	Case Reports	2	1	-	-	1	-	1	NA	NA	NA	NA	Chest X- ray RT-PCR	NA
Avula et al. 2020, USA	Case Reports	4	-	-	-	4	1	3	M: NA F: 16 F: 36 F: NA	M: NA F: NA F: 13,966 (ng/mL) F: 3442 (ng/mL)	M: 26.22 (mg/dL) F: NA F: 16.24 (mg/dL) F: 12.7 (mg/dL)	M: 12.32 (K/µL) F: 4.95(K/µL) F: 18.89(K/µL) F: 7 (K/µL)	Chest imaging Serology test RT-PCR	-Hypertension -Dyslipidemia -Carotid stenosis -Urinary tract infections -Diabetes mellitus type 2 -Neuropathy -Chronic kidney disease -Hyperlipidemia
Barrios-Lópeza, et al. 2020 Spain	Case Reports	4	4	-	-	4	2	2	M: 7 M: 6 F: 8 F: 16	M: 104.99 (mg/L) M: 7.59 (mg/L) F: 0.51 (mg/L) F: 0.72 (mg/L)	M: 282.4 (mg/L) M: 11.6 (mg/L) F: 23.7 (mg/L) F: 12.9 (mg/L)	NA	RT-PCR Serology test Chest imaging	-Diabetes mellitus type 2 -Former smoker -Obesity -Hypertensive heart disease -Asthma -Permanent atrial fibrillation -Ischemic heart disease -Arterial hypertension
Dakay, et al. 2020 USA	Case Report	1	-	-	RCVS	1	-	1	NA	NA	NA	NA	RT-PCR of a nasopharyngeal swab specimen	-Migraines
Deliwala, et al. 2020 USA	Case Report	1	1	-		1	-	1	NA	2.72 (1st draw) , 3.64 (2nd draw)	38.09 (1st draw) , 161.54 (2nd draw)	9.9	Chest CT	None

Author, Year, Country	Study Type	Total No. Population	Stroke Type (Stroke Patients No.)			Stroke + SARS-CoV-2 Patients No.	Gender (Stroke + SARS-CoV-2 Patients No.)		NIHSS	D-Dimer	CRP	WBC	Diagnostic test	Risk Factors
			IS	ICH	Others		Male	Female						
Dogra, et al. 2020 NY, USA	Cohort	3824	-	33	-	33	26	7	NA	2204 (1232_3074)	NA	NA	NA	-Congestive heart failure -Coronary artery disease -Diabetes -Hyperlipidemia -Hypertension -Hypothyroidism -Liver disease -Prior malignancy -Prior stroke -Renal disease
Gillet al 2020, USA	Case Report	1	1 (with some hemorrhagic conversion)	-	-	1	-	1	21	8.24	50 (mg/L)	NA	AP chest	-Hypertension -Hyperlipidemia -Diabetes
Hanafi et al. 2020, France	Case Report	1	1	-	-	1	1	-	NA	NA	60 (mg/L)	NA	Non-contrast chest CT RT-PCR of a nasopharyngeal swab specimen	NA
Jain et al. 2020, USA	Cohort	3218	26	9	-	35	NA	NA	NA	NA	NA	NA	RT-PCR of nasopharyngeal or oropharyngeal swab Chest X-rays	-Age -BMI -Hypertension
Klein et al. 2020, USA	Case Report	1	-	-	CVT (n=1)	1	-	1	NA	2876 (ng/L)	37 (mg/L)	8760 (cells per µL)	PCR	None

Author, Year, Country	Study Type	Total No. Population	Stroke Type (Stroke Patients No.)			Stroke + SARS-CoV-2 Patients No.	Gender (Stroke + SARS-CoV-2 Patients No.)		NIHSS	D-Dimer	CRP	WBC	Diagnostic test	Risk Factors
			IS	ICH	Others		Male	Female						
Morassi et al. 2020, Italy	Case Reports	6	4	2	-	6	5	1	NA	M: 7744 (ng/L) M: NA M: NA F: 1381 (ng/L) M: 2866 (ng/L) M: NA	M: 175 (mg/L) M: 46 (mg/L) M: 181 (mg/L) F: 12 (mg/L) M: 214 (mg/L) M: 21 (mg/L)	NA	RT-PCR of a nasopharyngeal swab specimen Chest CT	-Previous smoker -History of myocardial infarction -Arterial hypertension -Diabetes mellitus -Previous TIA -Aortic valve replacement -Previous stroke -Thrombocytosis
Moshayedi et 2020, USA	Case Report	1	1	-	-	1	1	-	NA	NA	NA	NA	PCR	NA
Naccarato, et al. 2020, Italy	Original Article	35	14	1	TIA (n=1)	16	6	10	n=10 (3-18) n=8 (>10)	NA	NA	NA	RT-PCR of a nasopharyngeal swab specimen	-Hypertension -Diabetes -Dyslipidemia -Atrial fibrillation -Ischemic cardiomyopathy
Nalleballe et al. 2020, USA	Cohort	40469	-	-	Stroke and TIA (n=406)	406	NA	NA	NA	NA	NA	NA	NA	NA
Zahid et al. 2020, USA	Case Report	1	-	1	-	1	1	-	NA	NA	NA	NA	Chest CT	None
Abdulkadir et al. 2020, Turkey	Case Reports	4	4	-	-	4	2	2	F: 16 F: 5 M: 10 M: 2	F: 803 (ugFEU/L) F: 1040 (ugFEU/L) M: 644 (ugFEU/L) M: 378 (ugFEU/L)	F: 142 (mg/L) F: 4 (mg/L) M: 33 (mg/L) M: 366 (mg/L)	NA	Chest CT PCR of oropharyngeal and nasopharyngeal swabs specimens	-Diabetes Mellitus -Hypertension

Kazemi, S., et al. (2021). COVID-19 and Stroke. *BCN, 12*(5), 569-586.

Author, Year, Country	Study Type	Total No. Population	Stroke Type (Stroke Patients No.)			Stroke + SARS-CoV-2 Patients No.	Gender (Stroke + SARS-CoV-2 Patients No.)		NIHSS	D-Dimer	CRP	WBC	Diagnostic test	Risk Factors
			IS	ICH	Others		Male	Female						
Rudilosso et al. 2020, Spain	Case Report	1	1 (Thalamic perforating artery)	-	-	1	1	-	NA	NA	NA	NA	NA	None
Oxley et al. 2020, USA	Case Reports	5	5	-	-	5	4	1	F:19 M:13 M: 16 M: 23 M: 13	F: 460 (ng/mL) M: 52 (ng/mL) M: 2230 (ng/mL) M: 13800 (ng/mL) M: 1750 (ng/mL)	NA	F: 7800 (cells per mm3) M: 9900 (cells per mm3) M: 5500 (cells per mm3) M: 9000 (cells per mm3) M: 4900 (cells per mm3)	NA	-Hyperlipidemia -Hypertension -Undiagnosed diabetes -Mild stroke -Diabetes
Cantador et al. 2020, Spain	Cohort	1419	6	-	TIA (n=2)	8	7	1	4 (1.5–4.75	2589 (735–8156) (ng/L)	100.5 (27–206) (mg/L)	NA	NA	-Hypertension -Diabetes -Hypercholesterolemia -Smoking
Chibane et al. 2020, Canada	Case report	1	1	-	-	1	-	1	NA	>4400 (µg/L)	NA	25.2 (× 109/L) (neutrophils)	Lung X-ray PCR	-Immune thrombocytopenia --Breast cancer surgery and chemotherapy -Splenectomy and radiotherapy following a Hodgkin's lymphoma -diagnosis -Raynaud's phenomenon, with negative antinuclear and extractable nuclear antigen antibodies and slightly positive rheumatoid factor (44 IU/mL)
Chougar et al. 2020, France	Case report	1	-	1	-	1	1	-	NA	NA	NA	30 (cells per mm3)	RT-PCR of a nasopharyngeal swab specimen	None

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; WBC, white blood cells; NA, not available; RT-PCR, real-time polymerase chain reaction; CT, computed tomography; TIA, transient ischemic attack; RCVS, reversible cerebral vasoconstriction syndrome; CVT, cerebral venous thrombosis.

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a 25% incidence of VTE in severe SARS-CoV-2 patients (20 out of 81 ICU patients), and 8 of which died from VTE events (Cui et al., 2020). Patients with the hypercoagulable state may exhibit average or enhanced platelet counts with reasonably activated partial thromboplastin time, significantly increased D-dimer and fibrinogen, increased CRP levels, factor VII and the von Willebrand factor (Panigada et al., 2020). In contrast, in this case, Klok et al. reported that thrombotic complications occurred in 31% of critically-ill ICU patients with SARS-CoV-2 (Klok et al., 2020).

Endothelial cell damages and thrombo-inflammation related 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 et al., 2020). As mentioned earlier on the expression of ACE2 in the arterial and venous endothelium of various organs, SARS-CoV-2 particles have been detected in lung endothelial cells and other tissues (Ackermann et al., 2020). After SARS-CoV-2 endothelial cell infection, endothelial injury and endothelialitis are developed in multiple vascularized tissues. These pathological conditions were accompanied by the elevation of the von Willebrand factor and the recruitment of activated immune cells such as neutrophils, monocytes, and macrophages (Varga et al., 2020). Ultimately, excessive thrombin production and complement activation are triggered, leading to thrombo-inflammation and vascular dysfunction (Engelmann & Massberg, 2013, Bikdeli et al., 2020). Magro et al. reported that hypercoagulability and microvascular thrombosis related to SARS-CoV-2 are associated with complement-mediated endothelial injury (Magro et al., 2020).

In severe cases of SARS-CoV-2, a pattern of lung and skin damage is seen consistent with the complement-mediated microvascular injury. 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 are consistent with the profound activation of both alternative and lectin-based pathways of the complement system (Magro et al., 2020). Another mechanism involved in the SARS-CoV-2 associated hypercoagulability is the cytokine-induced systemic inflammatory response. Rannuci 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 procoagulant modifications.

All of their patients had dramatically increased levels of blood IL-6 (Ranucci 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 anticoagulation therapies would treat the cytokine storm, which may be critical in reducing thrombo-inflammatory responses and subsequent tissue injury (Connors & Levy, 2020). Furthermore, immune cells activation and their cross-interaction with platelets in the situation of thrombo-inflammation could be a significant inducer of proinflammatory effects such as cytokine over-production, Neutrophil Extracellular Traps (NETs), and fibrin formation (Semple et al., 2011; Engelmann & Massberg, 2013). Besides, following the increased neutrophil-lymphocyte ratio occurring in SARS-CoV-2 patients in Intensive Care Units (ICU), NET formation as a protective role against microorganisms inappropriately damages the endothelium. It 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 et al., 2020).

A brief report in the New England Journal of Medicine has demonstrated the occurrence of antiphospholipid antibodies in SARS-CoV-2 ICU patients. They showed in a case report that the existence of antiphospholipid antibodies (anti-cardiolipin IgA and anti-β2-glycoprotein IgG/IgA antibodies) might seldom lead to thrombotic events like DIC (Zhang et al., 2020). In summary, SARS-CoV-2-associated coagulopathy may involve immune system components such as immune cells, proinflammatory cytokines, complement system, and pathologic antibodies.

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

The elevated levels of CRP and D-dimer in severely infected patients exhibit a high inflammatory condition, and coagulopathy may play a significant 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 the Blood-Brain Barrier (BBB), hypoxia, and immune-related injuries have been proposed for the entry of SARS-CoV-2 into CNS (Steardo et al., 2020; Wu et al., 2020). The possible cause of cerebrovascular injuries associated with SARS-CoV-2 infection could be hypercoagulability, resulting in macrothrombus and microthrombus formation in the vessels

(Avula et al., 2020). In this context, Barrios-Lopez et al. demonstrated that the hypercoagulable condition associated with the hyper-inflammatory response triggered by SARS-CoV-2 could cause an ischemic stroke (Barrios-López et al., 2020). However, they noted that studies with larger samples are necessary to confirm the hypothesis. Another research revealed smokers' vulnerability to cerebrovascular diseases is linked to SARS-CoV-2 and 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. Thus, the expression of ACE2 has been modified in the CNS of high-risk groups (diabetes and smokers).

SARS-CoV-2 patients with cerebrovascular diseases often present with complications such as hypertension and other stroke risk factors. Proinflammatory changes during SARS-CoV-2 are associated with stroke risk factors, and under inflammatory stimulation, leukocyte activation and following cerebrovascular thrombosis increase. 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 et al., 2020). One possible mechanism involved in the SARS-CoV-2-associated stroke is the proinflammatory cytokine storm phenomenon. Different viruses trigger hypercytokinemia through various mechanisms. For instance, SARS-CoV-1-related cytokine storms 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 of 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 et al., 2018). Furthermore, the cytokine storm pattern in severely-ill SARS-CoV-2 patients is related to significantly enhancing IL-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), MCP-1, and TNF-α (Huang et al., 2020). Besides, a decrease in CD4+ and CD8+ T cells and high production of IL-6 and IL-10 have been observed in the severe form of SARS-CoV-2 (Wan et al., 2020). After the appearance of hyperinflammation during the cytokine storm, the permeability of BBB increases. Then, SARS-CoV-2 attracts CD68+ monocyte/macrophages and CD3+ T cells into the infected brain. However, many inflammatory cytokines are released after SARS-CoV-2-related brain injury, which finally promotes thrombosis and stroke (Fugate et al., 2014).

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

Unlike the extensive literature on the pathophysiology of complications caused by SARS-CoV-2, specifically severe respiratory disorders, other extrapulmonary manifestations can occur. They comprise 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 (Gupta et al., 2020). Among these complications, the extent of the SARS-CoV-2 involvement in CNS is not well known, and the existence or absence of SARS-CoV-2 in the CNS is a subject of debate. The extrapulmonary 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 neurological severe symptoms.

Additionally, in such cases, an underlying inflammatory and hypercoagulable state may provoke cerebrovascular syndrome without disruption of BBB (Al Saiegh et al., 2020). The neuro-infection could occur 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 et al., 2020). Recently, the first case of viral encephalitis caused by SARS-CoV-2 has been identified in which the virus attacks CNS and illustrates that CoV-2 can cause nervous system injury (Xiang 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 increasing the risk of intracerebral hemorrhage, indicating that blocking cytokine cascade is an effective approach to treat stroke in a proinflammatory context (Muhammad 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.

4. Conclusion

Although it is impossible to conclude whether the increase or decrease of stroke frequency or changes in the ischemic to the hemorrhagic ratio is associated with COVID-19, it seems that SARS-CoV-2 infection has something to do 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 proinflamma-

tory cascade leading to consumption coagulopathy, receiving therapeutic anticoagulation for a high D-dimer, or a known thrombus due to SARS-CoV-2 infection and using ECMO in some patients. The possible mechanisms for ischemic stroke include the 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 COVID-19.

Ethical Considerations

Compliance with ethical guidelines

The present study is confirmed (No. 2696) from the Ethics Committee at Deputy of Research and Technology of Guilan University of Medical Sciences, Rasht, Iran. This study is a systematic review with no human or animal samples.

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Authors' contributions

Conceptualization and supervision: Alia Saberi, Arash Pourgholaminejad; Methodology: Samaneh Kazemi; Investigation: Alia Saberi, Samaneh Kazemi; Writing the original draft, review, and editing: All authors.

Conflict of interest

The authors declared no conflict of interest.

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