**Intracerebral Hemorrhage Involvement in COVID-19 and Potential Mechanisms: A brief Review**

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Abstract: In less than two years, the disease caused by acute respiratory syndrome type 2 coronavirus (SARS-COV-2) coronavirus disease (COVID-19) has confirmed 261329867 infections and 5209278 deaths worldwide, with a mortality rate of 2.0% (according to the real-time big data report, as of November 28).General medical complications have received the most attention during the COVID-19 pandemic, while only a few studies have addressed the potential direct effects and neurotrophic potential of SARS-COV-2 on cerebral hemorrhage.In the study of COVID-19, our purpose is to integrate a preliminary case series and a series of clinical observations to describe the participation of intracerebral hemorrhage and the performance of COVID-19 patients, so as to provide accurate insight for future research.

**Keywords: COVID-19, Intracerebral hemorrhage(ICH), SARS-CoV-2,ACE2**

**Introduction:**

In mid-December 2019, the first case of COVID-19 emerged in Wuhan, China, and spread rapidly around the world[1] .The 2019 outbreak of coronavirus is a disease caused by acute respiratory syndrome coronavirus type 2(sars-cov-2) and can be effectively transmitted from person to person. A total of 261329867 cases of infection and 5209278 deaths have been confirmed with a mortality rate of 2.0% (as of November 28, according to Real time big data reports).As a respiratory pathogen, it mainly has respiratory symptoms, such as cough, expectoration, fatigue and shortness of breath. It is reported that there are other neurological manifestations, including headache, loss of consciousness, seizures, hypotaste, hyposmell and dysphagia [2,3].

Although more and more studies have shown that ischemic stroke is associated with COVID-19 [4].The clinical characteristics of intracerebral hemorrhage in patients with COVID-19 are less.We believe that cerebral hemorrhage in COVID-19 patients may be a serious neurological manifestation in addition to ischemic stroke.The comprehensive treatment of intracerebral hemorrhage in patients with COVID-19 in emergency department is a comprehensive treatment of intracerebral hemorrhage.Here, we will discuss the clinical observation and possible pathophysiological mechanism of patients with cerebral hemorrhage and COVID-19.

**Clinical observation:**

More and more evidence shows that coronavirus may invade the central nervous system and lead to nervous system disorder [5].The nervous system symptoms related to COVID-19 infection can be divided into three categories: central nervous system (CNS) symptoms or diseases, peripheral nervous system (PNS) symptoms and muscle symptoms [5].Among patients with COVID-19, cerebrovascular disease (CVD) is the most common complication, especially serious cases.Cerebrovascular diseases mainly include cerebral hemorrhage and ischemic stroke.At present, a large number of literatures have reported that ischemic stroke is related to cerebral COVID-19, but there is little evidence that intracranial hemorrhage is related to COVID-19. So far, only individual cases have been reported [6-9].

Here, we synthesize the literature to emphasize clinical observations that suggest an important association between SARS-COV-2 infection and intracerebral hemorrhage.

A single-center retrospective study of 219 hospitalized COVID-19 patients found that approximate 5% of patients had complications of cerebrovascular disease, including 4.6% of patients with acute ischemic stroke, 0.5% cerebral venous sinus thrombosis,and 0.5% case with cerebral hemorrhage. Patients infected with coronavirus who are older and have more underlying diseases are more likely to develop cerebrovascular disease. Patients with intracerebral hemorrhage have elevated blood pressure (≥130/80mmhg) and more severe COVID-19 symptoms, eventually resulting in death[10].

Notably, James et al. summarized the findings of a multi-country observational cohort of patients with SARS-COV-2 and cerebrovascular disease in a report that focused more on assessing short-term functional outcomes and survival in patients with COVID-19 and related cerebrovascular disease than the above study.The main results of this multicenter retrospective cohort study are the incidence of cerebrovascular events, including acute ischemic stroke, intracranial hemorrhage and cortical venous sinus thrombosis(CVST).Among 14483 patients with COVID-19, there were 172 (1.13%) patients had acute cerebrovascular events (CVE).Among patients with CVE, acute ischemic stroke was the most common CVE, and 156 patients (1.08%;1080/100000, 95% CI 920-1260/100000)were observed, of which 28 patients(0.19%,190/100000,95% CI 130-280/100,000)were confirmed as primary intracerebral hemorrhage by imaging and 3 with CVST (0.02%; 20/100000, 95% CI 4–60/100000).The median time from ICH onset to death was 3.5 days (IQR 1-7), 11 of these patients died within 7 days (39.3%) .The in-hospital mortality of SARS-COV-2 related stroke was 38.1% and ICH was 58.3%.Although there is a small but significant risk between the aforementioned intra cerebral hemorrhage and COVID-19, active surveillance and early intervention should be undertaken to mitigate adverse outcomes [11].

Matthew's case series reparted that within 14 to 38 days aof the onset of COVID-19, five patients were diagnosed with cerebral hemorrhage by brain CT [12-13].From this case report, we found that the patient was younger than expected for traditional ICH, and that most of the intracerebral hemorrhage was located in the frontal lobe, which is supplied by the anterior circulation vessels, the median delay between the time of onset of COVID-19 symptoms and the time of ICH diagnosis was 32 days (14-38 days) [14].

Another case describes a COVID-19 patient who developed acute cerebral hemorrhage on the 23th day after fever, cough and fatigue.This is the first case of a COVID-19 patient complicated with intracerebral hemorrhage.The patient had a history of atrial fibrillation after taking warfarin for a long time, and changed to low molecular weight hepari after admission.On the 12th day after admission, the patient presented with altered consciousness, elevated blood pressure, creatinine, d-dimer, and PT.Head CT images showed hemorrhage in the right temporal occipital lobe and left frontal occipital parietal lobe, and extended to bilateral lateral ventricles.The patient continued to develop progressive multiple organ failure with worsening respiratory and renal failure, despite treatment with associated dehydration to reduce intracranial pressure and antiviral and antimicrobial infections.Finally, the patient died.This case report indicates that the SARS-COV-2 induced cytokine storm promoted progrssive multiple organ dysfunction syndrome and may have contributed to the patient’s intracerebral hemorrhage [15].

Specifically, there is a case describing a COVID-19 positive patient who was diagnosed with ischemic stroke and later suffered from acute cerebral hemorrhage during hospitalization.A 62 year old male with a history of hypertension and smoking was admitted to hospital for clinical manifestations of pulmonary infection. The nasopharyngeal swab was cCOVID-19 PCR positive.On the 10th day of admission, he was diagnosed with cerebral infarction and given aspirin and atorvastatin.However, his mental state continued to deteriorate until both pupils dilated and a CT scan of his head revealed a new 6.0cm intracerebral hematoma.Eventually, the patient died after being hospitalized for 27 days.From this case, we know that hemorrhagic stroke is associated with COVID-19 infection and a higher risk of death [16].

Interestingly, the clinical feature of COVID-19 patients with coronavirus disease is intracerebral hemorrhage.A 38-year-old male patient with no history or contact history with a confirmed COVID-19 patient was diagnosed with intracerebral hemorrhage by brain CT and underwent a left intracerebral hematoma removal with a left flap decompression dural resection.Although the patient had difficulty breathing and poor oxygen saturation at admission, and the chest CT reexamination showed patches and strips of high-density shadows on the back of both lungs, the first novel coronavirus antibody -IgG and IgM tests were negative.Unfortunately, despite the use of anti infective drugs during hospitalization, the patient's blood oxygen saturation could not be maintained, and the subsequent sputum test results showed that the SARS-COV-2 nucleic acid test was positive.The report suggests that novel coronavirus is highly contagious and that the first symptom in novel coronavirus patients may be cerebral haemorrhage[17].

A similar case in the Gabriel Baudouin’s report provides a unique example of how a patient with a large area of the intraparenchymal hemorrhage could develop complications during the pandemic, even patients with no risk factors for bleeding should be aware of this COVID-19.A 40 year old man, who had history of obesity, hypertension and type 2 diabetes, was admitted to hospital for mental disorder, drowsiness and respiratory distress.Cranial CT showed extensive pons and midbrain hemorrhage, intraventricular extension involving the third and fourth ventricles, early hydrocephalus, and positive for SARS-COV-2 rapid polymerase chain reaction (PCR).On admission, respiratory distress, multiple organ failure, worsening of consciousness and other symptoms occurred successively.Finally, the family received counseling and only chose comfortable measures.The report shows the possibility of intracranial hemorrhage in patients with COVID-19, although there is no obvious bleeding quality, such as hypertension emergency department, anticoagulant drug use or antiplatelet drug use.In contrast, a retrospective study of 33 patients with COVID-19 positive cerebral hemorrhage recorded by neuroimaging examined the use of anticoagulants in this population [18].

Patients with coronavirus disease (COVID-19) were prone to thrombotic events and elevated coagulation markers, which in turn was associated with increased mortality [4,19,20].Various anticoagulant treatment options are being considered for these patients[21].The biggest concern with increased use of anticoagulants is the increased risk of bleeding in general and intracranial hemorrhage in particular.33 patients with COVID-19 positive neuroimaging ICH were studied retrospectively, and the application of anticoagulant therapy in this population was examined [22].The average age of these patients with cerebral hemorrhage is 61.6 years (range37-83 years), 78.8% were male. Of these patients, there were 5 patients(15.2%) had mass effect and herniated parenchymal hemorrhage with a mortality rate of 100% .All 5 patients received therapeutic anticoagulation therapy, 3 patients (60%) received high d-dimer therapy and 2 patients (40%) received known thrombus therapy.All of these hemorrhages are considered to be primary ICH rather than hemorrhagic transformation of ischemic stroke.Of the other 28 patients, 7 (25%) had punctured bleeding, mainly involving the cortex, and 17 (60).7%) had small hemorrhage, 4 cases (14.3% of patients had large single site bleeding without signs of hernia, and 26 (80%) cases of bleeding were considered to be the hemorrhagic transformation of ischemic infarction.The case report shows that patients in COVID-19 can consider anticoagulation therapy. Although the risk of cerebral hemorrhage should be considered when making the treatment plan, it is best to do head CT in advance for patients who can't have a good neurological examination to avoid the risk of catastrophic hemorrhage due to accidental large-scale acute infarction [22].

**Potential mechanisms of SARS-COV-2 mediated cerebral hemorrhage:**

Known Pathophysiology of SARS-COV-2 and other human coronaviruses provide clues about possible mechanisms of nerve damage.The genome of SARS -COV-2 virus is in the form of positive single-stranded RNA [23].SARS-COV-2 RNA encodes at least 27 proteins, including 15 non structural, 4 structural and 8 helper proteins [24,25].Four structural proteins play an important role in infection, namely nucleocapsid protein (N) around the RNA genome and three membrane proteins: spike glycoprotein (S), matrix protein (M) and envelope protein (E)[26].S protein can bind to human angiotensin converting enzyme 2(ACE2) receptor through the transmembrane protease serine 2(TMPRSS2) and cause infection [27].ACE2 exists in arterial and venous endothelial cells and arterial smooth muscle cells of multiple tissues and organs, including respiratory system, airway and brain [25]. In addition, neurons and glial cells also express ACE2, which may be invaded by SARS-COV-2 [28-30].ICH patients are susceptible to SRAS-COV-2 infection and have serious complications due to infection [28].Available evidence strongly suggests that SARS-COV-2 infection may significantly increase the incidence of hemorrhagic stroke, especially in high-risk patients [31].In our review, we propose three possible mechanisms of intracranial hemorrhage in COVID-19 -19 patients (Fig. 1).

**1.Downregulate the expression of ACE2**

Similar to SARS-COV-1, SARS-COV-2 uses S Glycoprotein as its main receptor, affecting the activity of Renin–Angiotensin system [27,28,32] .Ras include Angiotensinogen (AGT) , Renin, Angiotensinogen I (Ang I) , Angiotensinogen II (Ang II) , and Angiotensinogen 1-7(Ang-(1-7)) , they are transferred by Endopeptidase, converting enzyme (ACE) , converting enzym type-2(ACE2), Angiotensinogen 1 receptor (AT1R) , Angiotensinogen 2 receptor (AT2R) and Mas receptor (MasR) .Private evidence shows that ACE/Ang Ⅰ / AT1R axis and ACE2 / Ang -(1-7) / MasR axis play an important role in regulating RAS system.The ACE/AngII/AT1R axis and ACE2/Ang-(1-7)/MasR axis are in a state of dynamic balance, and play a variety of physiological roles such as electrolyte homeostasis, cardiovascular control, and body fluid volume regulation [33].At the ACE/AngII/AT1R axis, the renin first class cuts Angiotensinogen to Angiotensinogen I.Ang I is converted from ace to Ang II, and ACE successively simulates AT1R and AT2R [34].Angiotensinogen II has a higher affinity for AT1R than AT2R, and plays a variety of physiological roles, such as vasoconstriction, neuroinflammation, oxidative stress, apoptosis and cell proliferation [34].On the ACE2/Ang-(1-7)/MasR axis, Ang II is hydrolyzed to Ang(1-7) by ACE2 and binds to the Mas receptor.Activation of ACE2/Ang-(1-7) / MasR axis can lead to vasodilation, angiogenesis, anti-inflammatory, antioxidant and anti apoptotic reactions, and play a vascular protective role.SARS-COV-2 particle infection downregulates active ACE2 and Ang-(1-7) and increases Angiotensinogen II (AngII) , leading to inhibition of ACE2/ang-(1-7)/MasR axis and over activation of ACE/AngⅠⅠ/AT1R axis[35].Overactivation of the ACE/AngII /AT1R axis can lead to elevated blood pressure, hypertrophy, fibrosis, and ultimately increased risk of intracranial hemorrhage.Inhibition of ACE2/Ang-(1-7)/MasR axi leads to reduced vasodilation, angiogenesis, anti-inflammatory, antioxidant and anti-apoptotic responses, as well as antithrombotic, arteriosclerosis and neuroprotective effects, this increases the risk of ich [25](figure 1) .

Renin

Ang Ⅰ

6/5000

Angiotensin 1

Xiěguǎn jǐnzhāng sù 1

6/5000

Angiotensin 1

Ang ⅠⅠ ↑

Angiotensinogen

AT1 receptor

Mas receptor

AT2 receptor

Ang-(1-7) ↓

SARS-CoV-2

The axis of ACE/AngⅠⅠ/AT1R ↑

activates the RAS system

1. elevated BP
2. hypertrophy
3. fibrosis

The axis of ACE2/Ang(1-7)/MasR ↓

inhibits the RAS system

1. Lower vasdilation
2. growth inhibition
3. lowwer antifibrotic

Risk of ICH ↑

Risk of ICH ↑

Figure 1. Potential mechanisms of increased risk of hemorrhagic stroke in 2019 patients with coronavirus disease.

**2.Endothelial toxicity on the blood-brain barrier**

The blood-brain barrier (BBB) is a structure formed by endothelial cells interacting with pericytes, astrocyte, neurons and Microglia, and plays an important role in homeostasis in the brain, is essential for normal neuronal activity and brain function.We believe that BBB endothelial cytotoxicity may be related to COVID-19[36].First, SARS virus invades directly through endothelial cells on the blood-brain barrier[37].Secondly, the infection of SARS-COV-2 virus particles may lead to a combination of systemic factors including proinflammatory cytokine, chemokines, protease action, thrombogenic factors, inflammatory cytokines, and coagulation cascades[38].Thirdly, hypoxia can cause hydrostatic or chemical-related damage to the blood-brain barrier, leading to extravasation of blood[39].Subsequently, the blood-brain barrier was destroyed.The entry of the virus into the central nervous system can cause vasculitis, encephalitis, acute necrotizing encephalopathy, leukoencephalopathy and other manifestations [40-45].Fourthly, a sudden increase in intracranial pressure caused by violent coughing and sneezing can damage already damaged Endothelium and lead to intracerebral hemorrhage[46].Finally, the risk of intracranial hemorrhage is increased.Intracerebral hemorrhage can cause inflammatory response and form positive feedback effect, which ultimately aggravates cell necrosis and apoptosis, leading to neuron damage, brain edema and cell death [28].

**3.Anxity and stress**

Levels of stress, anxiety and depression increase during the initial stages of the COVID-19 outbreak [47]. study in China at the beginning of the COVID-19 epidemic showed that 16.5% of participants showed moderate to severe depressive symptoms, 28.8% had moderate to severe anxiety symptoms, 8.1% reported moderate to severe stress levels [48].Studies have shown that stress can increase the catecholamine output of normal people, and the catecholamines of the noradrenergic system of locus coeruleus are involved in mediating stress-induced anxiety [49,50].In fact, epinephrine stimulation with excessive catecholamines can lead to severe vasospasm and disturbance of microcirculation, leading to an acute hypertensive response that increases the risk of cerebral hemorrhage [51,52].

**Conclusions:**

In the presence of ICH, patients with coronavirus disease have poor critical disease, mortality and functional prognosis.My patient was susceptible to the SRAS-COV-2 infection and had serious complications due to the infection.In these cases, it is not clear whether COVID-19 infection is accidentally related to cerebral hemorrhage.Previous studies have shown that sras-cov-2 may destroy the blood-brain barrier, increase public anxiety and eventually lead to intracranial hemorrhage by down regulating the expression of ACE2.The underlying mechanisms of cerebral hemorrhage and COVID-19 need to be further studied.For patients with COVID-19 intracerebral hemorrhage, especially those with a higher degree of severity, there is an urgent need to understand the neurologic manifestations and potential neurotrophic factors of COVID-19, in order to determine the priority and individualization of the treatment programme according to the specific situation.Clinicians should consider the possibility of SARS-COV-2 infection in patients with cerebral hemorrhage, so as to avoid delay diagnosis or misdiagnosis, and to ensure the prevention of virus transmission.In addition, patients in COVID-19 can consider anticoagulation therapy. Although the risk of cerebral hemorrhage should be considered when making the treatment plan, it is best to do head CT in advance for patients who can't have a good neurological examination, so as to avoid the risk of catastrophic hemorrhage due to accidental large-scale acute infarction.

**Authors’ contributions**

Xinyue Wang and Fang Ding collected data, searched literatures and drafted the manuscirpt.

Zhaowei Wang critically revised the manuscirpt.

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**Availability of data and materials**

Not applicable.

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**Conflicts of interest**

All authors declared that there are no conflicts of interest.

**Ethical approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Reference**

[1]R.Thompson.Pandemic potential of 2019-nCoV.The Lancet. Infectious diseases.2020;20(3):280.

[2] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu.Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China.JAMA neurology.2020;77(6):683-690.

[3] J. Helms, S. Kremer, H. Merdji, R. Clere-Jehl, M. Schenck, C. Kummerlen, O. Collange, C. Boulay, S. Fafi-Kremer, M. Ohana, M. Anheim, F. Meziani.Neurologic Features in Severe SARS-CoV-2 Infection.The New England journal of medicine.2020;382(23):2268-2270.

[4] F.A. Klok, M. Kruip, N.J.M. van der Meer, M.S. Arbous, D. Gommers, K.M. Kant, F.H.J. Kaptein, J. van Paassen, M.A.M. Stals, M.V. Huisman, H. Endeman.Incidence of thrombotic complications in critically ill ICU patients with COVID-19.Thrombosis research.2020;191:145-147.

[5] J. Li, X. Long, Q. Zhang, X. Fang, F. Fang, X. Lv, D. Zhang, Y. Sun, N. Li, S. Hu, Z. Lin, N. Xiong.Emerging evidence for neuropsycho-consequences of COVID-19.Current neuropharmacology.2020.

[6] M. Morassi, D. Bagatto, M. Cobelli, S. D'Agostini, G.L. Gigli, C. Bnà, A. Vogrig.Stroke in patients with SARS-CoV-2 infection: case series.J Neurol.2020;267(8):2185-2192.

[7] D. Vu, M. Ruggiero, W.S. Choi, D. Masri, M. Flyer, I. Shyknevsky, E.G. Stein.Three unsuspected CT diagnoses of COVID-19.Emergency radiology.2020;27(3):229-232.

[8] S. Muhammad, A. Petridis, J.F. Cornelius, D. Hänggi.Letter to editor: Severe brain haemorrhage and concomitant COVID-19 Infection: A neurovascular complication of COVID-19.Brain, behavior, and immunity.2020;87:150-151.

[9] A. Sharifi-Razavi, N. Karimi, N. Rouhani.COVID-19 and intracerebral haemorrhage: causative or coincidental?New microbes and new infections.2020;35:100669.

[10] Y. Li, M. Li, M. Wang, Y. Zhou, J. Chang, Y. Xian, D. Wang, L. Mao, H. Jin, B. Hu.Acute cerebrovascular disease following COVID-19: a single center, retrospective, observational study.Stroke and vascular neurology.2020;5(3):279-284.

[11] J.E. Siegler, P. Cardona, J.F. Arenillas, B. Talavera, A.N. Guillen, A. Chavarría-Miranda, M. de Lera, P. Khandelwal, I. Bach, P. Patel, A. Singla, M. Requena, M. Ribo, D.V. Jillella, S. Rangaraju, R.G. Nogueira, D.C. Haussen, A.R. Vazquez, X. Urra, Á. Chamorro, L.S. Román, J.M. Thon, R. Then, E. Sanborn, N.P. de la Ossa, M. Millàn, I.N. Ruiz, O.Y. Mansour, M. Megahed, C. Tiu, E.O. Terecoasa, R.A. Radu, T.N. Nguyen, G. Curiale, A. Kaliaev, A.L. Czap, J. Sebaugh, A.M. Zha, D.S. Liebeskind, S. Ortega-Gutierrez, M. Farooqui, A.E. Hassan, L. Preston, M.S. Patterson, S. Bushnaq, O. Zaidat, T.G. Jovin.Cerebrovascular events and outcomes in hospitalized patients with COVID-19: The SVIN COVID-19 Multinational Registry.International journal of stroke : official journal of the International Stroke Society.2020:1747493020959216.

[12] C. D'Amore, M. Paciaroni, G. Silvestrelli, G. Agnelli, P. Santucci, A. Lanari, A. Alberti, M. Venti, M. Acciarresi, V. Caso.Severity of acute intracerebral haemorrhage, elderly age and atrial fibrillation: independent predictors of poor outcome at three months.European journal of internal medicine.2013;24(4):310-3.

[13] B.M. Hansen, O.G. Nilsson, H. Anderson, B. Norrving, H. Säveland, A. Lindgren.Long term (13 years) prognosis after primary intracerebral haemorrhage: a prospective population based study of long term mortality, prognostic factors and causes of death.Journal of neurology, neurosurgery, and psychiatry.2013;84(10):1150-5.

[14] M. Benger, O. Williams, J. Siddiqui, L. Sztriha.Intracerebral haemorrhage and COVID-19: Clinical characteristics from a case series.Brain, behavior, and immunity.2020;88:940-944.

[15] J. Li, X. Long, C. Zhu, S. Hu, Z. Lin, J. Li, N. Xiong.A case of COVID-19 pneumonia with cerebral hemorrhage.Thrombosis research.2020;193:22-24.

[16] K. Rajdev, S. Lahan, K. Klein, C.A. Piquette, M. Thi.Acute Ischemic and Hemorrhagic Stroke in COVID-19: Mounting Evidence.Cureus.2020;12(8):e10157.

[17] Y. Bao, S.Y. Lin, Z.H. Cheng, J. Xia, Y.P. Sun, Q. Zhao, G.J. Liu.Clinical Features of COVID-19 in a Young Man with Massive Cerebral Hemorrhage-Case Report.SN comprehensive clinical medicine.2020:1-7.

[18] E.H. Dillon, M. Van Leeuwen, M.A. Fernandez, B. Eikelboom, W. Mali.CT angiography: application to the evaluation of carotid artery stenosis.Radiology.1993;189(1):211-219.

[19] S. Cui, S. Chen, X. Li, S. Liu, F. Wang.Prevalence of venous thromboembolism in patients with severe novel coronavirus pneumonia.Journal of thrombosis and haemostasis : JTH.2020;18(6):1421-1424.

[20] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao.Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.Lancet.2020;395(10229):1054-1062.

[21] J.M. Connors, J.H. Levy.COVID-19 and its implications for thrombosis and anticoagulation.Blood.2020;135(23):2033-2040.

[22] S. Dogra, R. Jain, M. Cao, S. Bilaloglu, D. Zagzag, S. Hochman, A. Lewis, K. Melmed, K. Hochman, L. Horwitz, S. Galetta, J. Berger.Hemorrhagic stroke and anticoagulation in COVID-19.Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.2020;29(8):104984.

[23] Y. Chen, Q. Liu, D. Guo.Emerging coronaviruses: Genome structure, replication, and pathogenesis.Journal of medical virology.2020;92(4):418-423.

[24] A. Wu, Y. Peng, B. Huang, X. Ding, X. Wang, P. Niu, J. Meng, Z. Zhu, Z. Zhang, J. Wang, J. Sheng, L. Quan, Z. Xia, W. Tan, G. Cheng, T. Jiang.Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China.Cell host & microbe.2020;27(3):325-328.

[25] A.A. Divani, S. Andalib, M. Di Napoli, S. Lattanzi, M.S. Hussain, J. Biller, L.D. McCullough, M.R. Azarpazhooh, A. Seletska, S.A. Mayer, M. Torbey.Coronavirus Disease 2019 and Stroke: Clinical Manifestations and Pathophysiological Insights.Journal of stroke and cerebrovascular diseases : the official journal of National Stroke Association.2020;29(8):104941.

[26] S. Ludwig, A. Zarbock.Coronaviruses and SARS-CoV-2: A Brief Overview.Anesthesia and analgesia.2020;131(1):93-96.

[27] H.H. Hoffmann, W.M. Schneider, F.J. Sánchez-Rivera, J.M. Luna, A.W. Ashbrook, Y.M. Soto-Feliciano, A.A. Leal, J. Le Pen, I. Ricardo-Lax, E. Michailidis, Y. Hao, A.F. Stenzel, A. Peace, C.D. Allis, S.W. Lowe, M.R. MacDonald, J.T. Poirier, C.M. Rice.Functional interrogation of a SARS-CoV-2 host protein interactome identifies unique and shared coronavirus host factors.bioRxiv : the preprint server for biology.2020.

[28] S. Dong, P. Liu, Y. Luo, Y. Cui, L. Song, Y. Chen.Pathophysiology of SARS-CoV-2 infection in patients with intracerebral hemorrhage.Aging.2020;12(13):13791-13802.

[29] I. Hamming, W. Timens, M.L. Bulthuis, A.T. Lely, G. Navis, H. van Goor.Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis.The Journal of pathology.2004;203(2):631-7.

[30] J. Gu, E. Gong, B. Zhang, J. Zheng, Z. Gao, Y. Zhong, W. Zou, J. Zhan, S. Wang, Z. Xie, H. Zhuang, B. Wu, H. Zhong, H. Shao, W. Fang, D. Gao, F. Pei, X. Li, Z. He, D. Xu, X. Shi, V.M. Anderson, A.S. Leong.Multiple organ infection and the pathogenesis of SARS.The Journal of experimental medicine.2005;202(3):415-24.

[31] H. Wang, X. Tang, H. Fan, Y. Luo, Y. Song, Y. Xu, Y. Chen.Potential mechanisms of hemorrhagic stroke in elderly COVID-19 patients.Aging.2020;12(11):10022-10034.

[32] D. Gurwitz.Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics.Drug development research.2020;81(5):537-540.

[33] O.A. Abiodun, M.S. Ola.Role of brain renin angiotensin system in neurodegeneration: An update.Saudi journal of biological sciences.2020;27(3):905-912.

[34] M.M. Arroja, E. Reid, C. McCabe.Therapeutic potential of the renin angiotensin system in ischaemic stroke.Experimental & translational stroke medicine.2016;8:8.

[35] T. Jiang, L. Gao, J. Lu, Y.D. Zhang.ACE2-Ang-(1-7)-Mas Axis in Brain: A Potential Target for Prevention and Treatment of Ischemic Stroke.Current neuropharmacology.2013;11(2):209-17.

[36] S. Liebner, R.M. Dijkhuizen, Y. Reiss, K.H. Plate, D. Agalliu, G. Constantin.Functional morphology of the blood-brain barrier in health and disease.Acta neuropathologica.2018;135(3):311-336.

[37] J.D. Huber.Diabetes, cognitive function, and the blood-brain barrier.Current pharmaceutical design.2008;14(16):1594-600.

[38] L. Hauer, S. Pikija, E.C. Schulte, L.K. Sztriha, R. Nardone, J. Sellner.Cerebrovascular manifestations of herpes simplex virus infection of the central nervous system: a systematic review.Journal of neuroinflammation.2019;16(1):19.

[39] N.A. Gupta, C. Lien, M. Iv.Critical illness-associated cerebral microbleeds in severe COVID-19 infection.Clinical imaging.2020;68:239-241.

[40] K. Bihlmaier, R. Coras, C. Willam, S. Grampp, S. Jabari, P. Eichhorn, F. Haller, J. Kuramatsu, S. Schwab, I. Castellanos, T. Birkholz, J. Schüttler, J. Altmeppen, M. Schiffer, L. Herbst.Disseminated Multifocal Intracerebral Bleeding Events in Three Coronavirus Disease 2019 Patients on Extracorporeal Membrane Oxygenation As Rescue Therapy.Critical care explorations.2020;2(9):e0218.

[41] M.D. Soldatelli, L.F.D. Amaral, V.C. Veiga, S.S.O. Rojas, S. Omar, V.H.R. Marussi.Neurovascular and perfusion imaging findings in coronavirus disease 2019: Case report and literature review.The neuroradiology journal.2020;33(5):368-373.

[42] A. Radmanesh, A. Derman, Y.W. Lui, E. Raz, J.P. Loh, M. Hagiwara, M.J. Borja, E. Zan, G.M. Fatterpekar.COVID-19-associated Diffuse Leukoencephalopathy and Microhemorrhages.Radiology.2020;297(1):E223-e227.

[43] A. Filatov, P. Sharma, F. Hindi, P.S. Espinosa.Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy.Cureus.2020;12(3):e7352.

[44] Y. Zhang, M. Xiao, S. Zhang, P. Xia, W. Cao, W. Jiang, H. Chen, X. Ding, H. Zhao, H. Zhang, C. Wang, J. Zhao, X. Sun, R. Tian, W. Wu, D. Wu, J. Ma, Y. Chen, D. Zhang, J. Xie, X. Yan, X. Zhou, Z. Liu, J. Wang, B. Du, Y. Qin, P. Gao, X. Qin, Y. Xu, W. Zhang, T. Li, F. Zhang, Y. Zhao, Y. Li, S. Zhang.Coagulopathy and Antiphospholipid Antibodies in Patients with Covid-19.The New England journal of medicine.2020;382(17):e38.

[45] S. Bhaskar, A. Sinha, M. Banach, S. Mittoo, R. Weissert, J.S. Kass, S. Rajagopal, A.R. Pai, S. Kutty.Cytokine Storm in COVID-19-Immunopathological Mechanisms, Clinical Considerations, and Therapeutic Approaches: The REPROGRAM Consortium Position Paper.Frontiers in immunology.2020;11:1648.

[46] G. Flores, J.I. Kumar, E. Pressman, J. Sack, P. Alikhani.Spontaneous Brainstem Hemorrhagic Stroke in the Setting of Novel Coronavirus Disease 2019 - A Case Report.Cureus.2020;12(10):e10809.

[47] N. Ozamiz-Etxebarria, M. Dosil-Santamaria, M. Picaza-Gorrochategui, N. Idoiaga-Mondragon.Stress, anxiety, and depression levels in the initial stage of the COVID-19 outbreak in a population sample in the northern Spain.Cadernos de saude publica.2020;36(4):e00054020.

[48] C. Wang, R. Pan, X. Wan, Y. Tan, L. Xu, C.S. Ho, R.C. Ho.Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic among the General Population in China.International journal of environmental research and public health.2020;17(5).

[49] R.J. Mathew, B.T. Ho, D.J. Francis, D.L. Taylor, M.L. Weinman.Catecholamines and anxiety.Acta psychiatrica Scandinavica.1982;65(2):142-7.

[50] J.G. McCall, R. Al-Hasani, E.R. Siuda, D.Y. Hong, A.J. Norris, C.P. Ford, M.R. Bruchas.CRH Engagement of the Locus Coeruleus Noradrenergic System Mediates Stress-Induced Anxiety.Neuron.2015;87(3):605-20.

[51] J.R.U. Santos, A. Brofferio, B. Viana, K. Pacak.Catecholamine-Induced Cardiomyopathy in Pheochromocytoma: How to Manage a Rare Complication in a Rare Disease?Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme.2019;51(7):458-469.

[52] J. Inamasu, S. Moriya, M. Oheda, M. Hasegawa, Y. Hirose.Role of catecholamines in acute hypertensive response: subarachnoid hemorrhage versus spontaneous intracerebral hemorrhage.Blood pressure monitoring.2015;20(3):132-7.