**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 coronavirus disease (COVID-19) has confirmed 261329867 infections and 5209278 deaths worldwide, resulting in a 2.0 percent mortality rate (according to the real-time big data report, as of November 28). While general medical consequences gained the majority of attention during the COVID-19 pandemic, only a few research have examined SARS-potential COV-2's direct effects and neurotrophic potential on cerebral hemorrhage. Our objective in the study of COVID-19 is to integrate a preliminary case series and a series of clinical observations in order to accurately explain the involvement of intracerebral hemorrhage and the performance of COVID-19 patients.

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

**Introduction**

COVID-19 was initially detected in Wuhan, China, in mid-December 2019 and quickly spread around the world[1]. Coronavirus is a disease caused by acute respiratory syndrome coronavirus type 2 (sars-cov-2) and is highly contagious. There have been a total of 261329867 confirmed cases of illness and 5209278 deaths, giving a mortality rate of 2.0 percent (as of November 28, according to Real time big data reports). As a respiratory pathogen, it mostly manifests itself through respiratory symptoms such as coughing, expectoration, tiredness, and shortness of breath. Other neurological signs have been observed, including headache, loss of consciousness, seizures, hypotaste, hyposmell, and dysphagia [2,3].

Although an increasing number of studies have demonstrated an association between COVID-19 and ischemic stroke [4]. Intracerebral hemorrhage had less clinical features in individuals with COVID-19. We suspect that cerebral bleeding, in addition to ischemic stroke, may be a significant neurological symptom in COVID-19 individuals. Thorough treatment of intracerebral hemorrhage in patients with COVID-19 is a comprehensive therapy of intracerebral hemorrhage in the emergency room. We will examine the clinical findings and probable pathophysiology of individuals with cerebral hemorrhage and COVID-19 in this section.

**Clinical observation**

Coronavirus is increasingly being shown to be capable of infecting the central nervous system and causing nervous system disorders [5]. There are three types of nervous system symptoms associated with COVID-19 infection: central nervous system (CNS) symptoms or disorders, peripheral nervous system (PNS) symptoms, and muscle symptoms [5]. Cerebrovascular disease (CVD) is the most prevalent consequence in people with COVID-19, particularly in severe instances. Cerebrovascular disorders are mostly hemorrhagic stroke and ischemic stroke. At the moment, a considerable body of literature indicates that ischemic stroke is associated with cerebral COVID-19, however there is less evidence that COVID-19 is associated with intracranial bleeding. Until yet, only isolated cases have been recorded [6-9].

The purpose of this review is to highlight clinical facts that strongly show a link between SARS-COV-2 infection and intracerebral hemorrhage.

A retrospective analysis of 219 hospitalized COVID-19 patients discovered that around 5% experienced cerebrovascular disease sequelae, including 4.6 percent with acute ischemic stroke, 0.5 percent with cerebral venous sinus thrombosis, and 0.5 percent with cerebral hemorrhage. Cerebrovascular disease is more likely to develop in patients infected with coronavirus who are older and have more underlying disorders. Intracerebral hemorrhage is associated with high blood pressure (130/80mmhg) and more severe COVID-19 symptoms, which can terminate 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 placed a greater emphasis on short-term functional outcomes and survival in patients with COVID-19 and related cerebrovascular disease than the previous study did. The primary outcome of this retrospective cohort study involving multiple centers is the incidence of cerebrovascular events, including acute ischemic stroke, intracranial hemorrhage, and cortical venous sinus thrombosis (CVST). 172 (1.13 percent) of the 14483 individuals with COVID-19 experienced an acute cerebrovascular episode (CVE). Acute ischemic stroke was the most common type of CVE, with 156 patients (1.08 percent;1080/100000, 95 percent CI 920-1260/100000) observed, of whom 28 patients (0.19 percent;190/100000, 95 percent CI 130-280/100,000) had imaging-confirmed primary intracerebral hemorrhage and three had CVST (0.02 percent; 20/100000, 95 percent CI 4–60/100000). The median period from commencement of ICH to death was 3.5 days (IQR 1-7), and 11 of these patients (39.3 percent) died within 7 days. Stroke associated with SARS-COV-2 was associated with a 38.1 percent in-hospital mortality rate, while ICH was associated with a 58.3 percent in-hospital mortality rate. Although there is a small but significant risk of intracranial hemorrhage in association with COVID-19, active surveillance and early intervention are recommended to minimize adverse outcomes [11].

Five patients were diagnosed with cerebral bleeding by brain CT between 14 to 38 days following the beginning of COVID-19, according to Matthew's case series [12-13]. We learned from this case report that the patient was younger than expected for traditional ICH and that the majority of the intracerebral hemorrhage occurred in the frontal lobe, which is supplied by the anterior circulation vessels. We also learned that the median delay between the onset of COVID-19 symptoms and the diagnosis of ICH was 32 days (14-38 days) [14].

Another example recounts a patient with COVID-19 who experienced abrupt cerebral bleeding on the 23rd day following fever, cough, and exhaustion. This is the first report of a patient with COVID-19 who developed intracerebral hemorrhage. The patient developed atrial fibrillation after taking warfarin for an extended period of time and was switched to low molecular weight heparin upon admission. The patient presented with altered consciousness, increased blood pressure, creatinine, d-dimer, and PT on the 12th day following admission. Hemorrhage was seen in the right temporal occipital lobe and left frontal occipital parietal lobe, which spread to the bilateral lateral ventricles on head CT imaging. Despite therapy with concomitant dehydration to lower intracranial pressure and antiviral and antibiotic infections, the patient continued to suffer progressive multiple organ failure with deteriorating respiratory and renal failure. Finally, the patient succumbed to his injuries. According to this case report, the cytokine storm generated by SARS-COV-2 encouraged progressive multiple organ dysfunction syndrome and may have led to the patient's intracerebral hemorrhage [15].

There is a case report reporting a COVID-19 positive patient who was diagnosed with ischemic stroke and afterwards suffered from severe cerebral hemorrhage while in the hospital. A 62-year-old gentleman with a history of hypertension and smoking was brought to the hospital with lung infection clinical symptoms. The nasopharyngeal swab was positive for cCOVID-19 PCR. He was diagnosed with cerebral infarction and given aspirin and atorvastatin on the tenth day of stay. His mental condition, however, continued to deteriorate until both pupils dilated and a CT scan of his brain revealed a fresh intracerebral hematoma measuring 6.0cm in diameter. After 27 days in the hospital, the patient died. We know from this instance that hemorrhagic stroke is related with COVID-19 infection and a significantly increased risk of mortality [16].

Intriguingly, intracerebral hemorrhage is a common clinical symptom of COVID-19 individuals with coronavirus illness.A 38-year-old male patient with no known history of COVID-19 infection was identified with intracerebral hemorrhage by brain CT and underwent left intracerebral hematoma excision via left flap decompression dural resection.Although the patient experienced trouble breathing and low oxygen saturation upon admission, and the chest CT reexamination revealed patches and strips of high-density shadows on the backs of both lungs, the patient's first new coronavirus antibody tests - IgG and IgM - were negative.Unfortunately, despite the administration of anti-infective medications during hospitalization, the patient's blood oxygen saturation could not be maintained, and later sputum testing revealed a positive result for SARS-COV-2 nucleic acid.

According to the findings, novel coronavirus is extremely infectious and the initial symptom in novel coronavirus patients may be cerebral haemorrhage[17].

A comparable case described in Gabriel Baudouin's report demonstrates how a patient with a big region of intraparenchymal hemorrhage may suffer difficulties during a pandemic; even patients without risk factors for bleeding should be aware of this COVID-19.A 40-year-old man with a history of obesity, hypertension, and type 2 diabetes was hospitalized for mental illness, sleepiness, and respiratory distress.Cranial CT revealed significant bleeding in the pons and midbrain, intraventricular extension affecting the third and fourth ventricles, and early hydrocephalus. The patient tested positive for SARS-COV-2 quick polymerase chain reaction (PCR).

Respiratory distress, multiple organ failure, deterioration of consciousness, and other symptoms happened sequentially upon admission.Finally, the family sought counseling and opted for simply the most convenient solutions.The report indicates that intracranial hemorrhage is possible in patients with COVID-19, despite the absence of obvious bleeding characteristics, such as hypertension in the emergency department, anticoagulant or antiplatelet drug use.In comparison, a retrospective investigation of 33 patients with COVID-19 positive cerebral hemorrhage identified the usage of anticoagulants in this cohort [18].

Patients with coronavirus disease (COVID-19) were more likely to experience thrombotic events and higher coagulation markers, which were linked with an increased risk of death [4,19,20].For these individuals, a variety of anticoagulant therapy alternatives are being considered[21].

The primary worry with increasing anticoagulant usage is the increased risk of bleeding in general, and particularly cerebral hemorrhage.The retrospective study of 33 patients with COVID-19 positive neuroimaging ICH explored the use of anticoagulant treatment in this cohort [22].

The average age of these patients with cerebral hemorrhage was 61.6 years (range: 37 to 83 years), with 78.8 percent being male. Five patients (15.2%) had mass effect and herniated parenchymal hemorrhage, with a 100 percent mortality rate. All five patients received therapeutic anticoagulation, three received high d-dimer therapy (60 percent), and two received known thrombus therapy (40 percent). All of these hemorrhages are regarded to be secondary to ischemic stroke rather than hemorrhagic transformation. Seven (25 percent) of the remaining 28 patients had punctured bleeding, primarily involving the cortex, and seventeen (17 percent) had punctured bleeding. 7 percent) experienced minor hemorrhage, 4 cases (14.3 percent) experienced significant single-site bleeding without signs of hernia, and 26 (80 percent) experienced hemorrhagic transformation of ischemic infarction. The case report demonstrates that patients diagnosed with COVID-19 may benefit from anticoagulation therapy. Although the risk of cerebral hemorrhage should be considered when developing a treatment plan, it is best to perform head CT in advance for patients who are unable to undergo a thorough neurological examination in order to avoid catastrophic hemorrhage due to an accidental large-scale acute infarction [22].

**Potential mechanisms of cerebral hemorrhage caused by SARS-COV-2**

The pathophysiology of SARS-COV-2 and other human coronaviruses provides insight into possible nerve damage mechanisms.The SARS-COV-2 virus genome is composed 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]. our structural proteins play a key role in infection, including nucleocapsid protein (N) surrounding 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 induce infection [27].ACE2 exists in arterial and venous endothelial cells and arterial smooth muscle cells of many 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]. Patients with ICH are sensitive to SRAS-COV-2 infection and frequently experience major consequences as a result of infection [28]. The available data clearly shows that infection with SARS-COV-2 increases the risk of hemorrhagic stroke considerably, particularly in high-risk individuals [31]. We propose three probable reasons for cerebral bleeding in COVID-19 -19 individuals in our review (Fig. 1).

1. **Reduce ACE2 expression**

SARS-COV-2, like SARS-COV-1, employs S Glycoprotein as its primary receptor, impairing the Renin–Angiotensin system's function [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 transported by endopeptidase, converting enzyme (ACE), converting enzyme type-2 (ACE2), Angiotensinogen 1 receptor (AT1R),Angiotensinogen 2 receptor

Private data indicates that the ACE/Ang I/AT1R axis and the ACE2/Ang -(1-7)/MasR axis are critical regulators of the RAS system.The ACE/AngII/AT1R and ACE2/Ang-(1-7)/MasR axes are dynamically balanced and are involved in a range of physiological functions, including electrolyte homeostasis, cardiovascular control, and body fluid volume regulation [33].

The renin first class reduces Angiotensinogen to Angiotensinogen I via the ACE/AngII/AT1R axis.

Ang I is transformed to Ang II, and ACE mimics AT1R and AT2R sequentially [34].Angiotensinogen II binds to the AT1R more strongly than the AT2R and is involved in a range of physiological processes, including vasoconstriction, neuroinflammation, oxidative stress, apoptosis, and cell proliferation [34].Ang II is hydrolyzed to Ang(1-7) by ACE2 and then binds to the Mas receptor via the ACE2/Ang-(1-7)/MasR axis.Activation of the ACE2/Ang-(1-7)/MasR axis can result in vasodilation, angiogenesis, anti-inflammatory, antioxidant, and antiapoptotic responses, as well as play a protective role for the vascular system.SARS-COV-2 particle infection decreases active ACE2 and Ang-(1-7) and increases Angiotensinogen II (AngII), inhibiting the ACE2/Ang-(1-7)/MasR axis and activating the ACE/AngII/AT1R axis[35].Excessive activation of the ACE/AngII/AT1R axis can result in elevated blood pressure, hypertrophy, fibrosis, and eventually an increased risk of intracranial hemorrhage.Inhibiting the ACE2/Ang-(1-7)/MasR axis results in decreased vasodilation, angiogenesis, anti-inflammatory, antioxidant, and anti-apoptotic responses, as well as antithrombotic, arteriosclerosis, and neuroprotective effects, thereby increasing 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

AEC

AT1 receptor

ACE2↓

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 underlying the higher risk of hemorrhagic stroke in 2019 coronavirus illness patients.

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

The blood-brain barrier (BBB) is a structure created by endothelial cells interacting with pericytes, astrocytes, neurons, and microglia. It is critical for normal neuronal activity and brain function and plays a critical role in homeostasis in the brain. We hypothesize that the cytotoxicity of BBB endothelial cells may be connected to COVID-19[36]. To begin, the SARS virus enters the brain directly through endothelial cells on the blood-brain barrier[37]. Second, infection with SARS-COV-2 virus particles may result in the production of a variety of systemic factors, including proinflammatory cytokines, chemokines, protease activity, thrombogenic factors, inflammatory cytokines, and coagulation cascades[38]. Thirdly, hypoxia can disrupt the blood-brain barrier due to hydrostatic or chemical forces, resulting in blood extravasation[39]. The blood-brain barrier was then dissolved. The virus can induce vasculitis, encephalitis, acute necrotizing encephalopathy, leukoencephalopathy, and other symptoms when it enters the central nervous system [40-45]. Fourthly, an abrupt increase in intracranial pressure induced by forceful coughing and sneezing might cause further injury to the Endothelium, resulting in intracerebral hemorrhage[46]. Finally, there is an increased risk of cerebral bleeding. Intracerebral bleeding can trigger an inflammatory response and create a positive feedback loop, aggravating cell necrosis and apoptosis and eventually resulting in neuronal injury, brain edema, and cell death [28].

1. **Anxity and stress**

During the early phases of the COVID-19 epidemic, levels of tension, anxiety, and depression increased [47]. At the start of the COVID-19 outbreak in China, a research found that 16.5 percent of individuals experienced moderate to severe depression symptoms, 28.8 percent experienced moderate to severe anxiety symptoms, and 8.1 percent experienced moderate to severe stress levels [48]. Stress has been found to raise normal people's catecholamine production, and catecholamines produced by the noradrenergic system of the locus coeruleus are implicated in mediating stress-induced anxiety [49,50]. Indeed, excessive catecholamine stimulation with epinephrine can result in severe vasospasm and microcirculation disruption, resulting in an acute hypertensive response that raises 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.

**Declarations**

**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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