

REVIEW

Hypertension and Covid-19 -related Cerebrovascular Disease

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Citation: Tsenkina Y. (2020) Hypertension and Covid-19 – related Cerebrovascular Disease. Open Science Journal 5(4)

Received: 28th July 2020

Accepted: 19th October 2020

Published: 18th November 2020

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Funding: The author(s) received no specific funding for this work

Competing Interests: The author has declared that no competing interests exist.

Abstract:

Cerebrovascular disorders such as stroke and intracerebral hemorrhage (ICH) occur in COVID-19 patients with pre-existing hypertension. Elevated blood pressure (ie systolic blood values >130 mmHg and diastolic blood pressure >60 mmHg) increases the risk of COVID-19-related morbidity and mortality. Although, the exact mechanisms of action are not well understood, pre-existing imbalance in the renin-angiotensin-aldosterone system (RAAS), and hypertension-induced cerebrovascular abnormalities can facilitate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infiltration into the central nervous system (CNS) leading to severe tissue damage and cerebrovascular insults. Alternatively, SARS-CoV-2 can independently affect blood flow regulation and induce cerebrovascular disease (CeVD) via binding to its receptor angiotensin converting enzyme 2 (ACE2) and modulation of RAAS. The present article systematically reviews published retrospective clinical studies reporting neurological symptoms, cerebral and cerebrovascular abnormalities in patients with pre-existing hypertension and clinically confirmed COVID-19. The examined publications were collected via a PUBMED search based on key terminology and encompassing the period January-July 2020. The curated clinical data was analyzed in order to evaluate plausible associations between pre-existing hypertension, SARS-CoV-2, and COVID-19-related CeVD. Early identification of high-risk patients is crucial for better point of care and prevention of COVID-19-related CeVD, morbidity and mortality.

Keywords: COVID-19, SARS-CoV-2, hypertension, cerebrovascular disease, angiotensin-converting enzyme 2 (ACE2), renin-angiotensin-aldosterone system (RAAS)

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 originated in Wuhan, Hubei, China in December 2019 (1) and has since become a worldwide pandemic. The SARS-CoV-2 receptor, angiotensin-converting enzyme 2 (ACE2), is expressed in multiple tissue organs including the central nervous system (CNS) and the cerebrovasculature (2-6). Viral binding to ACE2 triggers widespread infection within the human body inducing multi-organ response associated with serious clinical manifestations such as sepsis, acute respiratory distress syndrome (ARDS), cerebrovascular disease (ie stroke, intracerebral hemorrhage (ICH)), encephalitis, encephalopathy, seizures, coma and even death (2, 7, 8, 17-25). The most common COVID-19 symptoms are difficulty breathing, fever, cough, fatigue, and loss of smell and taste (7). In patients with severe COVID-19, the disease can cause ARDS, multi-organ failure, sepsis, increased inflammation, hypercoagulation, coma, and death (8). In 2003, a coronavirus called severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) that started in Asia and spread all over the world, resulted into an epidemic which was also associated with ARSD and a range of neurological disorders including cerebrovascular disease (CeVD) (ie stroke, ICH), encephalopathy, seizures, cranial nerve palsies, peripheral neuropathy, and myopathy (9). In 2012, another coronavirus called Middle East respiratory virus (MERS) was also associated with multiple organ infection and neurological complications (10-12). Sharing a high homology to SARS-CoV-1 and MERS, not surprisingly, SARS-CoV-2 appears to injure the CNS via direct and indirect pathways (13, 14). SARS-CoV-2 can directly injure the brain through binding to its ACE2 receptor which is widely expressed within the CNS (15). Viral particles have been detected in the cerebrospinal fluid (CSF), neuronal, glial, and endothelial cells of the cerebral blood vessels (3-6). Alternatively, increased inflammation also known as cytokine storm, impaired blood-brain barrier (BBB) integrity, coagulation, multiple-organ failure, and sepsis can all contribute to the development of neuropathology, cerebrovascular abnormalities and neurological complications in COVID-19 patients.

Since the outbreak of the pandemic, cerebrovascular disorders such as stroke and ICH have been clinically diagnosed in confirmed COVID-19 cases (16-24). Focal and multifocal encephalopathy, encephalitis, and seizures are other common neurological manifestations related to SARS-CoV-2 infection (25-29). COVID-19 patients with severe neurological impairment require intensive care unit (ICU) admission and they have an increased risk of long-term morbidity and mortality (14, 30).

Little is known about the effects of underlying medical conditions such as hypertension on the development of CeVD in COVID-19 patients. A large clinical study from Wuhan, China reported that 34% of severe COVID-19 patients had underlying hypertension and these patients presented more severe neurological symptoms such as acute CeVD (5.7%) (21).

The present review discusses the potential effects of comorbid hypertension on the development of CeVD in COVID-19 patients. Retrospective case studies reporting the medical history of COVID-19 patients with CeVD as well as other neurological manifestations are systematically discussed. Hypertension is one of the major health problems in the Western world afflicting about 25% of the general population (31). Hypertension is usually defined as blood pressure above 140 mmHg systolic or 90 mmHg diastolic (140/90) (32-34) and is considered severe if the pressure is above 180/120 (35, 36). Elevated blood pressure is the major modifiable risk factor for CeVD (31, 34). Emerging clinical evidence suggests that pre-existing hypertension can impact on the severity and outcome of COVID-19 (16-24). Specifically, patients with underlying hypertension present more severe COVID-19 and are at higher risk of cerebrovascular complications, morbidity, and mortality (16-24). Hypertension is more prevalent in elderly people and it is commonly observed in patients with diabetes and kidney disease (37-39)- all of which have been associated with severe COVID-19 and an increased risk of mortality (16-29).

Early identification of high-risk patients is crucial for better point of care and prevention of COVID-19-related CeVD, morbidity and mortality.

Structure and function of SARS-Cov-2

The coronavirus (CoV) is a positive sense 30-kb single-stranded polyadenylated RNA comprising genes coding for structural and non-structural proteins (Fig. 1). The structural proteins consist of the spike (S), envelope (E), membrane (M), nucleocapsid (N), and haemagglutinin esterase (HE). Each of these proteins fulfills a different function. The S contributes to the corona shape of the virus and mediates receptor recognition and binding. The E protein encapsulates the virus in an optimal oval shape. The M protein also contributes to the formation of the corona shape and maintains the CoV structure via its interactions with the other structural proteins. The N protein encapsulates the viral genome in a helical nucleocapsid inside the viral particle, whereas the HE protein mediates the release of the viral particles from the infected cell occurring during the end of the viral replication cycle (40). CoVs are capable of rapid mutation and recombination (41, 42).

Members of the coronavirus family include the pathogenic human CoV (HCoV) and the more commonly known SARS-CoV and MERS (43).

SARS-CoV-2 is a newly discovered highly pathogenic CoV that resembles the SARS-CoV-1 in that it binds with 10- to 20-fold higher affinity to the same receptor, ACE2 and induces similar symptoms (44-46).

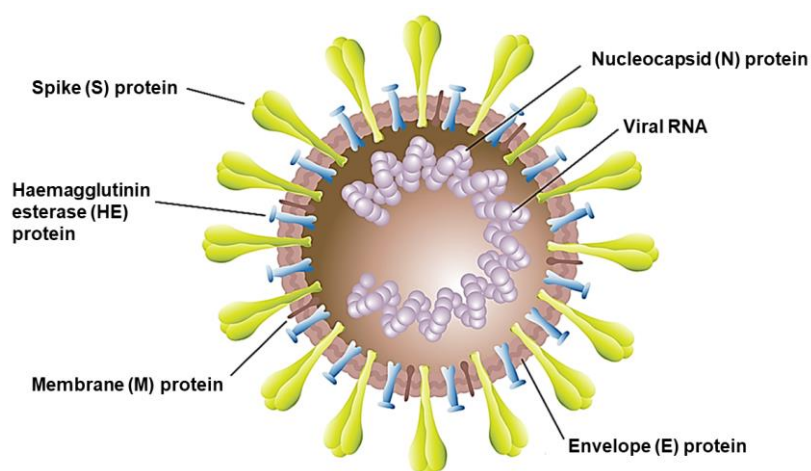


Figure 1: Schematic representation of the structural composition of SARS-CoV-2. Viral RNA and structural proteins supporting the corona shape of SARS-CoV-2 and its functions. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; S, spike protein; M, membrane protein; E, envelope protein; N, nucleocapsid; and HE, haemagglutinin esterase.

Pre-existing hypertension, SARS-CoV-2 and the renin-angiotensin-aldosterone system (RAAS) signaling pathway: major pathophysiological determinants of COVID-19-related CeVD?

Hypertension is generally considered a leading cause for the development of CeVD such as stroke and ICH (31, 34). Elevated blood pressure (ie systolic blood values >150 mmHg and diastolic blood pressure >60 mmHg) can alter the structure of the cerebral blood vessels by inducing endothelial dysfunction, vascular hypertrophy and stiffness (Fig. 2) (47). These structural abnormalities can significantly affect the normal functioning of the cerebrovasculature leading to impaired vasoconstriction, cerebral blood flow regulation, and increased BBB permeability- all of which can cause serious cerebrovascular events. Hypertension has also been associated with elevated levels of inflammatory agents (ie C-reactive protein (CRP), interleukin-6 (IL-6), interleukin-1 (IL-1), and tumour necrosis factor alpha (TNF- α)) and oxidative stress (ie nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase) which can damage the cerebral blood vessels, induce cell death, and lead to functional deficits (Fig. 2) (48). Therefore, underlying hypertension can facilitate SARS-CoV-2 infiltration into the CNS and viral-mediated injury to cells and blood vessels leading to the occurrence of stroke and ICH in COVID-19 patients.

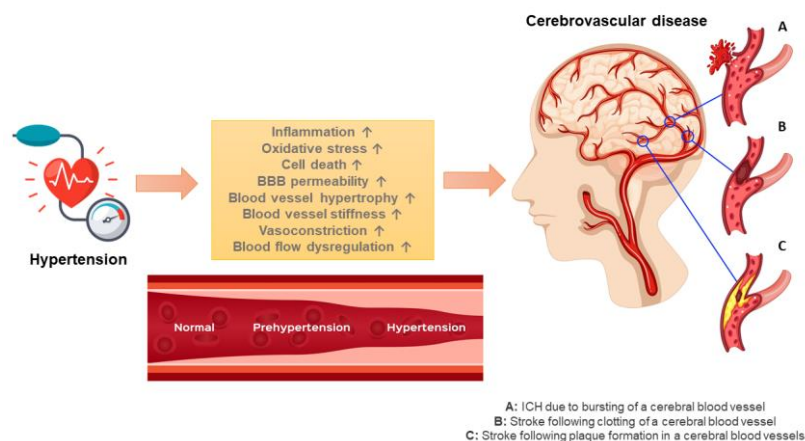


Figure 2: Cellular and molecular mechanisms underlying hypertension-induced cerebrovascular disease. Hypertension can promote the development of cerebrovascular disease such as ICH (A) and stroke (B, C) via different cellular and molecular pathways. Inflammation and oxidative stress occur under hypertensive conditions, leading to pathophysiological changes in the cerebrovasculature such as vessel stiffness, hypertrophy, vasoconstriction, impaired cerebral blood flow regulation and increased BBB permeability. ICH, intracerebral hemorrhage; BBB, blood-brain barrier.

Activation of the renin-angiotensin-aldosterone system (RAAS) is an important regulator of blood pressure and imbalance in RAAS can lead to hypertension in disease conditions as well as during aging (Fig. 3 A-C) (31). ACE2, the SARS-CoV-2 receptor, counter-regulates the RAAS signaling pathway which controls blood pressure, inflammation, and fibrosis. Specifically, ACE2 converts angiotensin II (Ang II) into angiotensin-(1-7) Ang-(1-7), which acts at the Mas receptor to lower blood pressure, reduce inflammation and fibrosis (Fig. 3 A) (49, 50). Activation of Ang-(1-7) promotes vasodilation, sodium and water excretion, reduces sympathetic nervous system activation, and increases nitric oxide production (51-54). This counteracts the main effects of the ACE/Ang II/Ang II type 1 receptor (AT1R) pathway, namely vasoconstriction, sodium and water reabsorption, increased sympathetic nervous system tone, and increased oxidative stress leading to the occurrence of pathology (e.g. inflammation and fibrosis) (50, 55, 56). Both members of the RAAS pathway are expressed in a large number of tissues, including the lungs, heart, kidney, vasculature, intestines, and CNS.

An imbalance in the RAAS signaling pathway resulting from a shift towards ACE/Ang II and inhibition of ACE2/Ang-(1-7), may be an important mediator of COVID-19-related CeVD (49). With advancing age as well as in various disease states, including hypertension there is a shift towards the ACE/Ang II pathway (Fig. 3B). Binding of SARS-CoV-2 to ACE2 can downregulate the expression of the receptor and induce a shift towards the ACE/Ang II pathway to mediate acute organ injury leading to CeVD and neurological impairment in COVID-19 patients (Fig. 3C). Pre-existing hypertension and the use of anti-hypertensive medications such as ACE inhibitors and Ang II receptor blockers (ARBs) may further enhance the severity of SARS-CoV-2 infection and the risk of mortality (57). Pharmacological inhibition of ACE and ARBs in hypertensive COVID-19 patients can block the ACE/Ang II pathway and shift the RAAS towards ACE2/Ang-(1-7) (49).

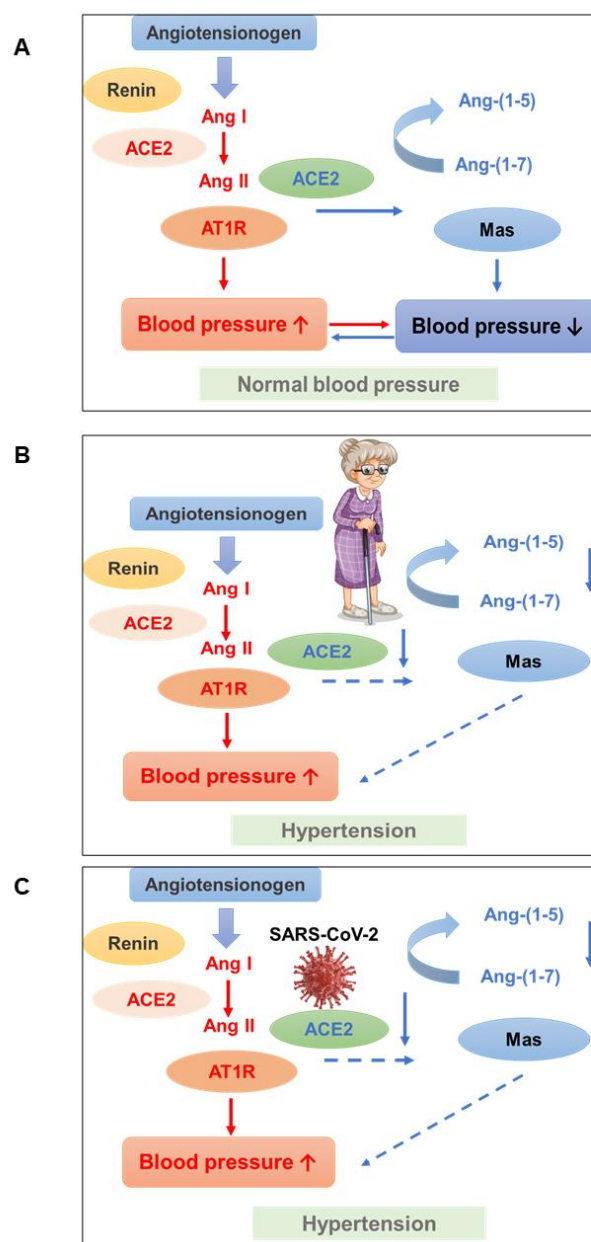


Figure 3: Schematic representation of the RAAS signaling pathway and its effects on blood pressure (A) under homeostatic conditions (e.g. in health and in young adults), RAAS is maintained in balance via the counteracting signaling of the ACE/Ang II/AT1R pathway that increases blood pressure and the ACE2/Ang-(1-7)/Mas pathways that exerts the opposite effect. B) in various disease conditions (e.g. diabetes, chronic kidney disease) and in elderly people, an increase in ACE/Ang II signaling is observed leading to hypertension. C) SARS-CoV-2 binding to ACE2 induces decreased expression of the receptor shifting the RAAS signaling towards the ACE/Ang II pathway and the occurrence of hypertension. RAAS, renin-angiotensin-aldosterone system; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE, angiotensin-converting enzyme; ACE2, angiotensin-converting enzyme 2; Ang II, angiotensin II, Ang-(1-7): angiotensin-(1-7); AT1R, Ang II type 1 receptor.

Alternatively, underlying high blood pressure (ie systolic blood pressure >200 mmHg) can increase BBB permeability allowing entry of peripheral inflammatory agents and viral particles into the CNS (47). Once present in the brain milieu, these highly pathogenic factors may trigger pathophysiological mechanisms promoting the development of CeVD in COVID-19 patients with pre-existing hypertension. However, these potential associations have not been confirmed by animal or clinical studies, therefore it remains unclear whether there is a direct association between hypertension, anti-hypertensive medication, and COVID-19-related CeVD.

In summary, there are two possible and not mutually exclusive pathways via which pre-existing hypertension can induce the development of COVID-19-related CeVD (Fig. 4):

1) enhanced viral infiltration into the CNS due to pre-existing hypertension-induced cerebrovascular abnormalities such as increased BBB permeability, vasoconstriction, blood vessel hypertrophy and stiffening,

2) SARS-CoV-2 binding to ACE2 can induce imbalance in the RAAS signaling system leading to hypertension and cerebrovascular events in COVID-19 patients.

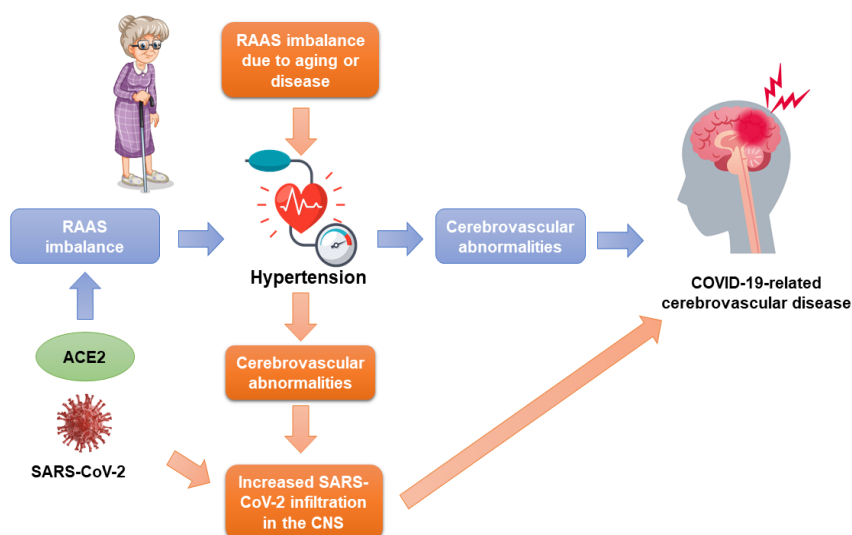


Figure 4: Overview of the potential, not mutually exclusive pathways mediating hypertension-induced cerebrovascular disease in COVID-19 patients.

In orange: an imbalance in RAAS leading to hypertension is commonly observed in elderly people and in various disease conditions. Hypertension-induced cerebrovascular abnormalities such as increased BBB permeability can facilitate SARS-CoV-2 infiltration into the CNS. Viral binding to ACE2 can further damage the cerebrovasculature leading to COVID-19-related cerebrovascular disease.

In blue: an imbalance in RAAS signaling leading to hypertension can occur following SARS-CoV-2 binding to ACE2. Hypertension-induced pathological changes in the cerebral blood vessels and the BBB integrity can result into deleterious cerebrovascular events in COVID-19 patients.

Alternative pathways via which SARS-Cov-2 can directly infect the CNS and promote the development of CeVD in COVID-19 patients with pre-existing hypertension.

SARS-CoV-2 may infect the CNS directly through the cribriform plate situated in close proximity to the olfactory bulb. The virus initially enters the body through the nose spreading to the olfactory bulb (58). Anosmia (ie the loss of sense of smell) and hyposmia (ie the loss of sense of taste) are common symptoms in COVID-19 patients thus supporting the idea of direct SARS-CoV-2 infiltration into the CNS through the olfactory bulb (21). SARS-CoV-2 can also enter the CNS through the peripheral circulation and bind to the ACE2 receptor expressed on neuronal, glial, and endothelial cells making them a target for a SARS-CoV-2 attack (3-5). A recent study demonstrated that SARS-CoV-2 directly infects the brain tissue inducing metabolic changes in infected cells (59). Furthermore, SARS-CoV-2-mediated destruction of the cerebrovasculature can have deleterious consequences for COVID-19 patients such as stroke and ICH (16-24). SARS-CoV-2 can also infiltrate the CNS via anterograde and retrograde neurotrophic pathways. Sensory and motor nerve endings such as the afferent connections of the vagus nerve can uptake SARS-CoV-2 from the lung and transport it to the CNS with help from motor proteins such as kinesin & dynein (60, 61).

SARS-CoV-2 can also cause gastrointestinal tract infection and can spread to the CNS via enteric nerve and sympathetic afferent pathways (62-64). SARS-CoV-2 can infect leukocytes and migrate with them into the brain. The viral particles can also invade the peripheral lymphatic vessels connecting with the lymphatic system of the brain. Although the exact mechanism is not known, different strains of CoV, such as SARS-CoV-1, have the ability to infect cells regulating the intrinsic immunity that supports the spread of CoV to several tissues, including the CNS (65). This is consistent with findings in mice where the murine counterpart of HCoV, the neurotropic mouse hepatitis virus (MHV) has been shown to enter into the CNS through the lymphatic systems (66). Lower lymphocyte levels and platelet counts have been reported in COVID-19 patients presenting with CNS symptoms compared to those without CNS involvement (21). Exosomal cellular transport is another pathway of possible SARS-CoV-2 systemic spread facilitating viral entry into the CNS (67).

Binding of SARS-CoV-2 to ACE2 receptors situated on lung and capillary epithelial cells triggers the formation of a cytokine storm characterized by an increased expression of inflammatory cytokines such as IL-1, IL-6, and TNF- α (16, 23). Peripheral inflammation can lead to increased BBB permeability and the rupture of blood vessels causing brain edema and ICH (68). Cerebral SARS-CoV-2 infection activates CD4+ immune cells that in turn induce cytokine release from resident microglia and macrophages. The predominant player in the cytokine storm syndrome, IL-6 can cause multi-organ failure leading to increased risk of morbidity and mortality in COVID-19 patients (69). Treatment with Tocilizumab, an IL-6 receptor blocker promoted recovery of severe COVID-19 cases (70). These data support the idea that the cytokine storm syndrome is one of the many indirect pathways via which SARS-CoV-2 can induce cerebral damage.

Increased blood coagulation leading to clot formation in the blood vessels of COVID-19 patients (71) can lead to large artery occlusion, ischemic stroke, and ICH (16-24, 72). This alternative pathway may be particularly relevant for the

development of CeVD in COVID-19 patients with pre-existing comorbidities such as hypertension. Additionally, hypercapnia caused by prolonged mechanical pulmonary ventilation can also increase the levels of carbon dioxide and inflammatory cytokines in the bloodstream leading to CNS injury, cerebrovascular abnormalities, long-term functional impairment, and mortality in COVID-19 patients (73).

In summary, regardless of the exact pathway via which SARS-CoV-2 invades the CNS (ie direct or indirect routes), the neuro-invasive potential of this virus has been related to the above discussed mechanisms, namely:

- 1) the SARS-CoV-2 direct binding to the ACE2 receptor expressed on neuronal, glial and endothelial cells.
- 2) the SARS-CoV-2 neurotropism which allows its transport to the CNS via anterograde and retrograde neurotrophic pathways.
- 3) the SARS-CoV-2-induced peripheral inflammation (ie cytokine storm syndrome) which can increase the BBB permeability and promote viral infiltration into the brain.
- 4) the SARS-CoV-2 ability to infect leukocytes and migrate with them into the brain. The viral particles can also invade the peripheral lymphatic vessels connecting with the lymphatic system of the brain.
- 5) the potential exosomal cellular transport of SARS-CoV-2 to the CNS.

Clinical data discussion of pre-existing hypertension and COVID-19

Shortly after the outbreak of the COVID-19 pandemic in Wuhan, China, initial studies reported that a large proportion of severe COVID-19 cases had previous medical history of hypertension, raising concerns as to the effects of elevated blood pressure on disease progression and clinical outcome (21). Subsequent reports from other affected countries, namely Italy, the United Kingdom, the United States, Turkey, Belgium, and France support the early studies suggesting that pre-existing hypertension may be a major risk factor in determining the occurrence of deleterious cerebrovascular events in COVID-19 patients (16-24). However, one of the major drawbacks of the current literature is that the data is predominantly obtained from a relatively old patient population (age 65 years and older), making it difficult to differentiate between the impact of age itself and other underlying conditions such as hypertension on the progression and clinical manifestations of COVID-19. Furthermore, in the majority of these reports, the data analysis is descriptive in nature presenting one-way associations based on individual case studies without employing appropriate epidemiological or statistical methods to properly determine the independent impact of hypertension on the COVID-19 outcome, including the risk of CeVD. It is well known that the risk of hypertension increases with advancing age and the use of anti-hypertensive medication is more frequent in elderly people (74). Appropriate statistical and epidemiological data analysis is urgently needed to account for the isolated effects of age, comorbid conditions (e.g. hypertension diabetes, cardiovascular abnormalities), baseline medication use, and other potential confounding factors that may affect the course and severity of COVID-19. Based on the initial descriptive data, it is difficult to make any conclusions as to the independent effects of hypertension on the risk of SARS-CoV-2 infection and/or COVID-19 outcome. There have been additional speculations based on the original SARS-CoV-1 epidemic spread suggesting that commonly prescribed anti-hypertensive drugs such as ACE inhibitors and Ang II

receptor blockers (ARBs) may also increase the risk of SARS-CoV-2 infection (57). However, to-date there have been no animal or clinical studies to support this idea, making it difficult to determine the exact role of elevated blood pressure in the progression and the clinical outcome of COVID-19.

Pre-existing hypertension and COVID-19-related CeVD

The present review aimed at examining the published medical history of COVID-19 patients with clinically diagnosed cerebrovascular disorders such as stroke and ICH in order to identify major risk factors. Systematic review of the published reports identified hypertension as the most common underlying condition observed in 37% of COVID-19 confirmed cases presenting with stroke, ICH, and other neurological manifestations (Fig. 5). These results are supported by an earlier meta-analysis including 46,248 patients with confirmed COVID-19 diagnosis where hypertension (17%), diabetes (8%), and cardiovascular disease (5%) were reported in their medical history (Fig. 5; Table 1) (75). Moreover, hypertension is also more prevalent in severe COVID-19 patients as compared to non-severe cases (odds ratio of 3.42 and 2.36, respectively) and is also associated with a higher mortality rate (76). The present review also revealed that in addition to hypertension, diabetes (22%), cardiovascular disease (15%), CeVD (5%), and chronic kidney disease (4%) are also common pre-existing comorbidities in patients suffering from COVID-19-related cerebrovascular events and other neurological manifestations (Fig. 5) (16-22, 24-29). Other contributing factors (17%) include hyperlipidemia, asthma, chronic obstructive pulmonary disease, obesity, multiple sclerosis, HIV, Behcet's disease, Addison's disease, urinary tract infection, and autism (Fig. 5) (16-18, 25-29).

Comorbidities in COVID-19 patients with cerebrovascular disease

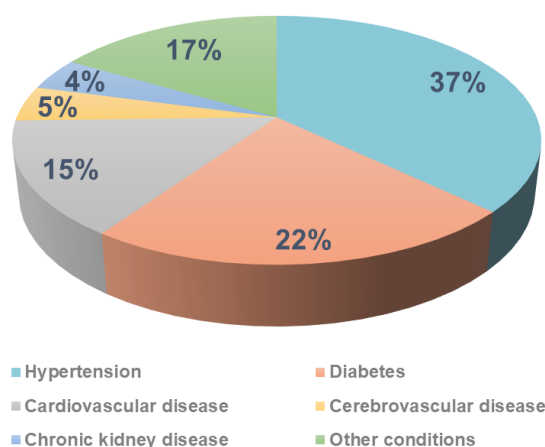


Figure 5: Relative proportion of pre-existing hypertension and other comorbidities in COVID-19 patients with cerebrovascular complications. The data is based on previously published case studies (see table 1)

Table 1: Clinical studies reporting cerebrovascular disease and other neurological complications in COVID-19 patients with hypertension

Reference	Country	Total COVID-19 patients (n)	Age (mean/ median)	COVID-19 patients with hypertension (n)	Clinical findings
Avula et al, 2020	United States	4	mean=81±5.43	4	stroke (n=4)
Benger et al, 2020	United Kingdom	5	mean=52.2±8.26	3	intracerebral hemorrhage (n=5)
Beyrouti et al, 2020	United Kingdom	6	mean=69.83±12.72	4	stroke (n=6)
Escalard et al, 2020	France	10	median=59.5	5	stroke (n=10)
Mahammedi et al, 2020	Italy	108	median=71	55	stroke (n=34)
Mao et al, 2020	China	214	mean=53.8 ± 15.0	51	stroke (n=5) intracerebral hemorrhage (n=1)
Morrassi et al, 2020	Italy	6	median=69	4	stroke (n=6)
Oxley et al, 2020	United States	5	mean=40.4±6.23	1	stroke (n=5)
Swaid et al, 2020	United States	22	mean=59.5 ± 16.0	10	stroke (n=22)
Dogan et al, 2020	Turkey	6	mean=49.2 ± 13.9	4	meningoencephalitis (n=6)
Kandemirli et al, 2020	Turkey	12	median=62	6	encephalopathy (n=12)
Pinna et al, 2020	United States	50	mean=59.6±14.3	30	encephalopathy (n=30) stroke (n=10) intracerebral hemorrhage (n=8) seizures (n=13) hypoxic brain injury (n=7) cognitive impairment (n=13) extraocular movement abnormalities (n=5)
Coolen et al, 2020	Belgium	19	mean=77±32	16	confusion & desorientation (n=6) seizure (n=1) intracerebral hemorrhage (n=3) encephalopathy (n=4) asymmetrical olfactory bulbs (n=4) white matter changes (n=1)
Hepburn et al, 2020	United States	2	mean=79±3	1	seizures (n=2) coma (n=1) encephalopathy (n=1)

Although respiratory deficiency and fever are the most common symptoms of COVID-19, an increasing number of reports suggest that the disease can also present itself with a series of neurological complications such as stroke (47%), ICH (16%), encephalopathy (23%), seizures (7%), and other CNS disorders (7%) including confusion, disorientation, and even coma (Fig. 6; Table 1).

COVID-19-related CNS disorders in patients with hypertension

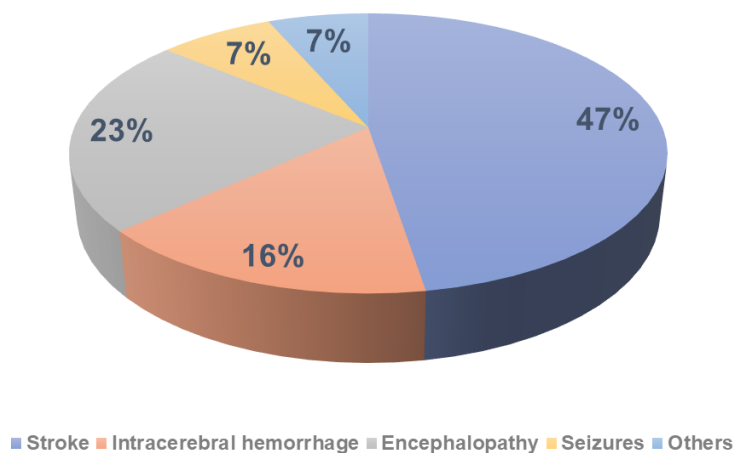


Figure 6: Relative proportion of CNS manifestations in COVID-19 patients with pre-existing hypertension. The data is based on previously published case studies (see table 1)

In an early study, 36.4% of COVID-19 patients showed neurological impairment with a different degree of severity. Neurological dysfunction was more pronounced in severe COVID-19 cases (45.5%) compared with non-severe cases (30.2%) (21). It was found that patients with severe SARS-CoV-2 infection had more underlying medical conditions compared with non-severe cases (47.7% vs 32.5%) especially hypertension (36.4% vs 15.1%). The most common COVID-19-related neurological manifestations in severe vs non-severe cases are: acute CeVDs (5.7% vs 0.8%) and impaired consciousness (14.8% vs 2.4%) (21). Beyrouti et al., 2020 described the occurrence of ischemic stroke related to large vessel occlusion with significantly elevated D-dimer and C-reactive protein levels in six COVID-19 patients- five of which had past medical history of hypertension and cardiovascular disease (18). Only one patient had no hypertension or any other condition prior to SARS-CoV-2 infection. At the neuropathological level, widespread infarcts, venous thrombosis, large vessel occlusion, white matter abnormalities, and ischemic injury have been demonstrated in COVID-19 patients with underlying high blood pressure (19, 20, 23, 24). Additionally, small cerebral ischemic infarcts, basal ganglia ischemia, and cardioembolic acute ischemic infarcts were also observed (20). Ischemic stroke (4.67%) seems to be more prevalent in COVID-19 patients than hemorrhagic stroke (2.33%) as reported by Morassi et al., 2020 in a small (n=6) study group. Stroke was found to occur primarily in patients with severe pneumonia, multi-organ failure, significantly increased liver enzyme levels, and inflammation (22). The majority of COVID-19 patients experiencing neurological deficits also had a medical history of hypertension, diabetes, cardiovascular disease, and other comorbidities (16-22, 24-29). Interestingly, Avula et al., 2020 observed that acute ischemic stroke can also appear as the first COVID-19 symptom prior to pulmonary insufficiency (16). This case study based on four patients with pre-existing hypertension suggests that high blood pressure may precipitate the development of cerebrovascular pathology in COVID-19 patients. The outcome for COVID-19 patients with stroke is usually poor with a mortality rate close to 85% and the

surviving individuals remain severely impaired (17%) (22). Advanced age and hypertension are considered the most powerful modifiable risk factors for stroke (77), independent of geographic location and ethnicity. Approximately 54% of strokes worldwide can be attributed to hypertension (78). The majority of ischemic stroke cases (72.7%) are observed in patients with pre-existing hypertension (79). High blood pressure, especially when left untreated, increases the risk of stroke 3 to 4 times (80).

Although it is believed that severe COVID-19 primarily affects the elderly (81), a study by Bengner et al., 2020 reported the presence of ICH in a relatively young patient population with confirmed SARS-CoV-2 infection (mean age of 52.2 (range 41-64)) (17). This age range is much lower than the conventional age group for ICH (82, 83). Moreover, similar to the Bengner et al., 2020 study, a meta-analysis of pooled data from six studies that examined COVID-19-related cerebrovascular events identified the mean age range of patients to be 45 – 67 years (84). The majority of patients with ICH experienced prolonged inflammation and multi-organ failure. In general, ICH is positively associated with age, race, and hypertension (85). Aged and young adults, especially African-Americans with elevated blood pressure, are more likely to suffer ICH than non-hypertensive individuals (85-88).

COVID-19-related ICH mainly affects lobar territories including the frontal and median temporal lobe (17, 89). The affected areas are situated within the anterior circulation irrigated by large cerebral arteries. Lobar ICH occurs in 15 – 30% of conventional cases and is predominantly associated with an underlying vascular abnormality (90). Interestingly, all COVID-19-related lobar hemorrhages were primarily observed in patients with pre-existing hypertension, classically associated with deep structure bleeds. The hemorrhagic complications were more frequently associated with ICU admission and ARDS (89). The delay between the onset of COVID-19 symptoms and the time of MRI diagnosis of ICH has a median of 32 days (range 14 – 38 days) (17) or a mean of 33 days (89).

The exact pathophysiological mechanisms leading to the occurrence of CeVD in COVID-19 patients are unclear. Bilateral occlusion of the middle cerebral artery accompanied by hypoperfusion and the occurrence of bilateral subacute infarcts may be the leading cause of COVID-19-related stroke (91). Increased formation of blood clots is commonly observed in SARS-CoV-2 cases (71), which can contribute to vessel occlusion and cerebral ischemia. There is increasing evidence that the SARS-CoV-2 infection triggers a series of thrombotic events (92, 93) that can compromise the BBB and increase the risk of cerebrovascular events such as stroke and ICH (94). SARS-COV-2-mediated injury to the cerebral endothelium may also play a role in the pathogenesis of stroke and ICH. ACE2 receptors are found in the vascular endothelium and SARS-CoV-2 particles have been found in blood vessels and endothelial cells suggesting a direct viral damage to the cerebrovasculature (5). In addition, myocardial injury has been reported in 22% of COVID-19 patients admitted into the ICU, and cardiac embolization may also have a contributory role in the pathogenesis of COVID-19-related cerebral ischemia and intracerebral bleeding (95). Other cardiovascular abnormalities such as atherosclerotic disease and hypertension have also been observed in COVID-19 patients and can contribute to the occurrence of CeVD (96). Systemic infection associated with activation of immune and inflammatory pathways leading to plaque disruption can serve as a source of thrombosis (97). Increased inflammation in COVID-19 patients known as cytokine storm (16, 23) can enhance the pathogenesis of CeVD in SARS-CoV-2-infected individuals. Increased D-dimer levels and increased inflammation in the CSF have been

reported in patients with underlying hypertension and COVID-19-related CeVD (18, 21, 22, 89, 91). The RAAS pathway may also play a role in COVID-19-mediated CeVD. Specifically, SARS-CoV-2 may decrease endothelial ACE2 expression thus compromising cerebral blood flow regulation (98, 99). Perfusion abnormalities, such as bilateral frontotemporal hypoperfusion, have been reported in patients with severe COVID-19 (100).

Pre-existing hypertension and other neurological manifestations in COVID-19 patients

Encephalopathy, a syndrome of overall brain dysfunction, is one of the most common neurological complications observed in severe COVID-19 cases (100). Cortical abnormalities and subcortical white matter lesions involving frontal, parietal, temporal, occipital lobe, insulate cortex, and cingulate gyrus are commonly observed in COVID-19 patients with previous history of hypertension, diabetes, cardiovascular, cerebrovascular, and chronic kidney disease (26). Other acute intracranial findings in the absence of cortical signal abnormalities include acute transverse sinus thrombosis and acute cerebral infarction in the middle cerebral artery territory. A post-mortem study on COVID-19 patients with hypertension and other pre-existing comorbidities such as cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and malignancies revealed parenchymal brain abnormalities indicative of encephalopathy (28). Additionally, asymmetrical olfactory bulbs, deep white matter abnormalities, micro/macrobleeds in subcortical areas were also reported in the same patient population. Six critically ill COVID-19 patients, four of which had clinically diagnosed hypertension developed autoimmune meningoencephalitis (25). The patients had persistently elevated peripheral levels of inflammatory markers such as ferritin, fibrinogen, IL-6 in sera, and bilateral cerebral inflammation compatible with meningoencephalitis on MRI; interestingly, there was no evidence of an active CNS infection, including SARS-CoV-2. Similar results were reported by Kandemirli et al., 2020 where the PCR analysis for SARS-CoV-2 performed on CSF samples from severe COVID-19 cases was negative (26). However, a study from Japan showed SARS-CoV-2 RNA in the CSF of a patient with clinically diagnosed meningoencephalitis (6). This controversial data suggests that direct viral infection may not be a key factor for the development of encephalopathy and autoimmune meningoencephalitis in COVID-19 cases. The exact pathophysiological mechanisms remain unclear; however, pre-existing medical conditions such as hypertension may play a role in COVID-19-related cerebrovascular accidents. Future research is needed to better understand the cellular and molecular mechanisms mediating SARS-CoV-2-related neurological impairment.

Seizures are another CNS disorder reported to occur in COVID-19 patients which often co-appears with encephalopathy (27-29). Hepburn et al., 2020 reported the occurrence of seizures in COVID-19 patients with acute encephalopathy. One of the patients had hypertension (29). Another study performed primarily on African-American (48%) and Hispanic (28%) patients with pre-existing hypertension (60%) and confirmed COVID-19 reported the occurrence of seizures, encephalopathy, CeVD, cognitive impairment, hypoxic brain injury, dysgeusia, and extraocular movement abnormalities (27). The COVID-19-related seizures are most likely a multifactorial phenomenon resulting

from viral infection, increased BBB permeability, increased cell death, and other contributing factors such as underlying hypertension.

In general, encephalopathy and seizures have been observed in hypertensive patients (101, 102). If left untreated, hypertensive encephalopathy can progress to cerebral hemorrhage, coma, and death. Other underlying conditions associated with elevated blood pressure such as kidney disease and diabetes are common comorbidities in severe COVID-19 cases and can also contribute to the occurrence of encephalopathy and seizures(103, 104).

Conclusion

Hypertension is commonly diagnosed in COVID-19 patients experiencing cerebrovascular insults such as stroke and ICH. Elevated blood pressure is associated with increased mortality and morbidity following SARS-CoV-2 infection. Hypertension may affect COVID-19 progression and the clinical outcome either independently or concomitantly with SARS-CoV-2. Future pre-clinical and clinical investigations of the pathophysiological mechanisms mediating the deleterious effects of hypertension in COVID-19 patients will be crucial for adequate patient diagnosis and treatment. Early identification of patients with underlying hypertension can minimize the risk of COVID-19-related CeVD, morbidity, and mortality.

Acknowledgements

I would like to thank Christopher Goss for thoughtful revision and diligent editing of the manuscript.

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Abbreviations:

ACE: angiotensin-converting enzyme
ACE2: angiotensin-converting enzyme 2
Ang II: angiotensin II
Ang-(1-7): angiotensin-(1-7)
ARBs: angiotensin II receptor blockers
ARDS: acute respiratory distress syndrome
AT1R: AT1R, Ang II type 1 receptor
BBB: blood-brain barrier
CeVD: cerebrovascular disease
CNS: central nervous system
CoV: coronavirus
COVID-19: Coronavirus disease 2019
CRP: C-reactive protein
CSF: cerebrospinal fluid
E: envelope protein
HE: haemagglutinin esterase
HCoV: human coronavirus
ICH: intracerebral hemorrhage
ICU: intensive care unit
IL-1: interleukin-1
IL-6: interleukin-6
M: membrane protein
MERS: Middle East respiratory virus

MHV: mouse hepatitis virus

N: nucleocapsid protein

RAAS: renin-angiotensin-aldosterone system

S: spike protein

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SARS-CoV-1: severe acute respiratory syndrome coronavirus 1

TNF- α : tumor necrosis factor-alpha