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Review article

Immune system changes in those with hypertension when infected with SARS-CoV-2

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ABSTRACT

The coronavirus disease 2019 (COVID-19) outbreak has become an evolving global health crisis. With an increasing incidence of primary hypertension, there is greater awareness of the relationship between primary hypertension and the immune system [including CD4+, CD8+ T cells, interleukin-17 (IL-17)/T regulatory cells (Treg) balance, macrophages, natural killer (NK) cells, neutrophils, B cells, and cytokines]. Hypertension is associated with an increased risk of various infections, post-infection complications, and increased mortality from severe infections. Despite ongoing reports on the epidemiological and clinical features of COVID-19, no articles have systematically addressed the role of primary hypertension in COVID-19 or how COVID-19 affects hypertension or specific treatment in these high-risk groups. Here, we synthesize recent advances in understanding the relationship between primary hypertension and COVID-19 and its underlying mechanisms and provide specific treatment guidelines for these high-risk groups.

1. Introduction

Corona Virus Disease 2019 (COVID-19) is an acute respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a public health emergency of international concern. In the COVID-19 epidemic, researchers found that nearly half of COVID-19 inpatients had comorbidities, with hypertension being the most common comorbidity [1–5]. What's more, hypertension is more frequently observed in patients with severe COVID-19 compared to non-severe patients [6]. This suggests that there may be a causal relationship between hypertension and COVID-19 or its severity, which may be mainly related to the specific immune status of hypertension. Understanding how the immune system changes with hypertension and how the immune system interacts with COVID-19 is important, as each key link is expected to be a potential target for COVID-19, providing new approaches and ideas for treating COVID-19 in patients with hypertension. Generally, hypertension can be divided into primary hypertension and secondary hypertension. This paper mainly discusses the interaction of immune system change in primary hypertension with SARS-CoV-2 (see Table 1).

2. The invasion of SARS-CoV-2

Hypertension has a specific inflammatory immune state that may increase the risk of contracting COVID-19 and progressing to severe pneumonia [7,8]. When SARS-CoV-2 enters patients with high blood pressure, the body's immune system is more likely to trigger a cytokine storm, raising the possibility that the virus will cause serious consequences, such as severe pneumonia and death.

The angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for coronaviruses [9], including SARS-CoV and SARS-CoV-2. Studies have shown that SARS-CoV-2 uses spikes glycoprotein (S) proteins to bind to ACE2 on target cells [10]. Serum ACE2 activity is elevated in hypertensive patients [11]. In addition, with the development of hypertension, the number of ACE2 in patients will increase with the occurrence of other cardiovascular diseases, such as coronary atherosclerosis, myocardial ischemia, myocardial infarction, and heart failure [11,12]. This suggests that people with high blood

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Table 1
Effects of changes in the immune system of hypertension on COVID-19.

Cell/ Receptor/ Cytokine	Function	Changes in hypertension	Effects on hypertension	Effects on SARS-CoV-2
CD4+ T cells	Secrete pro-inflammatory cytokines; identify antigen[151]	Activated	Attenuate the vascular and renal immune-inflammation	Contribute to cytokine storms and are associated with severe SARS-CoV-2 infection
CD8+ T cells	Secrete pro-inflammatory cytokines; killing effects[151]	Activated	Promote vascular endothelial dysfunction, vascular sparsity and sodium and water retention induced by Ang II[28]	Associated with the pathogenesis of extremely severe SARS-CoV-2 infection[80]
Th17 cells	Promote inflammatory response[41]; down-regulate Treg mRNA[152]	Activated	Aggravate vascular inflammatory response Vascular dysfunction[152]	Promotes the onset and development of cytokine storms
Treg cells	Inhibit immunity responses	Decreased	Aggravate vascular dysfunction[40]	Promotes the onset and development of cytokine storms
B cells	Identify and process antigens; differentiates into plasma cells; secrete cytokines	Increased; activated	Enhance the effect of Ang II on raising blood pressure	Contribute to the formation of cytokine storms[43] and associated with a severe infection in COVID-19 [47,138]
Plasma cells	Produce antibodies and cytokine[153]	Increased	IgG produced by plasma cells deposits in the aorta[43]	Promotes the onset and development of cytokine storms
Neutrophil	Phagocytosis; antibacterial activity [154,155]; induces tissue inflammation and fibrosis	Increased	Promotes ROS - induced vascular damage and kidney damage[156]	Promotes the onset and development of cytokine storms
NK cells	Cytolytic activity; secrete cytokines and chemokines	Increased	Interact with monocytes and promote Ang II-induced vascular dysfunction [49,50]	Contribute to SARS-COV-2 invasion and promotes the formation of cytokine storms
Monocytes	Phagocytosis; antigen presentation[157]	Activated	Aggravate vascular dysfunction[49]	Promote the onset and development of cytokine storms
Dendritic cells	Present antigen and activate T cell; secrete cytokines	Activated	Oxidative injury and inflammation[59]	Promote the onset and development of cytokine storms
Macrophage	Phagocytosis; secretes cytokines and chemokines	Activated	Promotes hypertension through RAAS [57]; causes vascular endothelial disorders and renal sodium excretion disorders[158]	Promote the onset and development of cytokine storms
IFN-γ	Antiangiogenesis; promotes inflammatory response and antigen presentation[159]	Increased	Promotes vascular inflammation and vascular dysfunction and induces target organ damage	Promotes the onset and development of cytokine storms; synergistic interaction between TNF and IFN-γ specifically induces cell death, leading to multiple organ damage[160]
TNF	Promotes apoptosis and renal vasoconstriction; reduces glomerular filtration rate[161]	Increased	Promotes the development of Ang II-dependent hypertension[162] and induces target organ damage[33]	Promotes the onset and development of cytokine storms; synergistic interaction between TNF and IFN-γ specifically induces cell death, leading to multiple organ damage[160]
VEGF	Stimulates the proliferation of vascular endothelial cells and induces angiogenesis; increases vascular permeability [163]	Increased	Aggravates abnormal angiogenesis and endothelial dysfunction[164]	Cause central nervous system damage via Ang II mediation[165]
TGF-β	Promotes the fibrosis[166]; inhibits immune cell proliferation and secretion of cytokines[167]	Increased	Promotes salt-induced hypertension and leads to kidney and heart fibrosis[166]	Reduces inflammatory response and symptoms; delays virus clearance, and increases infection rates
GM-CSF	Increases monocyte and neutrophil; Initiation and perpetuation of inflammatory response[168,169]	Increased	Promotes Ang II-induced vascular dysfunction[170]	Limits virus-related injury in the early phases; inappropriate release promotes the cytokine storms in later phases[171]
IL-1	Activates T cells, B cells and other immune cells[172]	Increased	Promotes Ang II-dependent hypertension[173]	Promotes the onset and development of cytokine storms
IL-2	Activates T cell and NK cell cytotoxicity [174]	Decreased	–	Conducive to SARS-CoV-2 invasion
IL-4	Induces CD4+ T cells to differentiate into Th2 phenotype[175]; regulates cell proliferation and apoptosis[176]	Decreased	Reduces endothelial dysfunction[177]	Promotes the onset and development of cytokine storms
IL-6	Stimulates the proliferation of activated B cells and secretes antibodies; stimulates T cell proliferation and CTL activation[178]	Increased	Promotes Ang II - and cold-mediated hypertension[179]	Promotes the onset and development of cytokine storms
IL-8	Up-regulates VEGF synthesis in endothelial cells	Increased	Promotes vascular inflammation, abnormal angiogenesis, and endothelial dysfunction[164]	Promotes the onset and development of cytokine storms
IL-10	Prevents and limits tissue damage caused by excessive immune response[180]	Decreased	Aggravates vascular dysfunction[181]	Conducive to SARS-CoV-2 invasion; aggravates tissue damage
IL-13	Inhibits monocyte releasing pro-inflammatory cytokines; promotes Th cell immune response[182,183]	Decreased	–	Promotes the onset and development of cytokine storms
IL-17	Mediates tissue inflammation[184]	Increased	Resists stress urinary sodium excretion [104]; promotes Ang II-induced vascular dysfunction[185]	Promotes the onset and development of cytokine storms
IL-22	Induces pro-inflammatory cytokines production	Increased	Exacerbates Ang II-induced vascular dysfunction[64]	Promotes the onset and development of cytokine storms
IL-23	Regulates Th17 phenotypes by IL-23 receptors[186]; promotes chronic inflammatory response[187]	Increased	Exacerbates vascular inflammation; aggravates vascular dysfunction	Promotes the onset and development of cytokine storms

(*continued on next page*)

pressure are more susceptible to SARS-CoV-2 infection and more likely to suffer deterioration of the disease. After cell invasion, the virus replicates heavily and activates various immune cells, which release large amounts of cytokines.

The internalization and exfoliation of ACE2 caused by virus invasion reduced the expression of ACE2 on the cell membrane [13]. ACE2 has a lung-protective effect [14], and a decreased level of ACE2 may aggravate lung injury. Besides, angiotensin 1-7 (Ang 1-7) is the main product of angiotensin II (Ang II) degradation by ACE2, which produces vasodilation by activating bradykinin and nitric oxide (NO), releasing prostaglandin, and inhibiting the release of norepinephrine [15,16]. Ang 1-7 also has anti-inflammatory effects mediated by MAS receptors [17]. The decrease of ACE2 also leads to the decrease of Ang 1-7, which will further aggravate hypertension and make the inflammatory response more intense. Hypertension patients are with high levels of Ang II [18–20]. Ang II levels were linearly correlated with viral load and lung injury [21]. Ang II binds to angiotensin II type 1 receptor (AT1R) to stimulate the Janus Kinase (JAK)/ signal transduction and transcriptional activator (STAT) pathway and promotes the production of downstream interleukin-6 (IL-6), which in turn triggers the JAK/STAT pathway to release more cytokines through positive feedback, such as IL-6 and interferon (IFN) [22]. Ang II also interacts with nuclear factor Kappa B (NF- binding κ B) and promotes transcription and inflammatory cytokines such as interferon-γ (IFN-γ), IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor (TNF) [23]. These may facilitate cytokine storms in COVID-19 patients with hypertension and lead to further disease deterioration.

3. The interaction of SARS-CoV-2 and the immune system of hypertension

Compared with those without hypertension, patients with hypertension have a special immune state characterized by endothelial dysfunction and oxidative stress [24]. They are often affected by low-grade chronic inflammation, which may affect how people with high blood pressure respond to viral infections, and SARS-CoV-2 is no exception. This state may promote cytokine storms, with severe consequences for those infected with COVID-19, potentially leading to death. This may explain why COVID-19 patients with hypertension are more likely to develop severe pneumonia and die than those without hypertension [25] (Fig. 1).

Pathogen-related molecular patterns (PAMs) produced after SARS-CoV-2 invasion and danger-associated molecular patterns (DAMPs) released by damaged cells in vivo bind to pattern recognition receptors (PRRs), including epithelial cells, macrophages, and dendritic cells. These cells produce an intracellular cascade reaction, releasing many cytokines that activate and attract more immune cells, such as macrophages, NK cells, neutrophils, CD4+ T cells, CD8+ T cells, and B cells. These activated immune cells concentrate on the damaged site, exert corresponding immune effects, and release more cytokines, creating a cascade effect that may eventually lead to a cytokine storm [26]. Pre-existing inflammation combined with the direct assault of SARS-CoV-2 may make hypertension patients more likely to develop cytokine storms.

Ang II stimulates T cell proliferation [27,28]. T cells play a central role in the regulation of hypertension, and they are overactivated and proliferated in patients with hypertension [29,30]. The lymphocyte count was positively correlated with the values of systolic and diastolic blood pressure[31]. These T cells exhibit a senescent phenotype characterized by telomere shortening, loss of costimulatory factors CD27 and CD28, and increased surface marker CD57. Due to the lack of costimulatory receptors, senescent T cells cannot participate in classical activation through T cell receptor (TCR) [32]. They lose their ability to fight the virus. However, these cells showed a continuous state of pro-inflammatory activation. T cells produce pro-inflammatory cytokines, such as IFN-γ and TNF [CD8+ T, CD4+ T helper 1(Th1)] and IL-17A (γδ -T, CD4+ T h17), that exacerbate hypertension-related responses and induce endothelial dysfunction, as well as heart, kidney, and neurodegenerative damage [33]. Aging CD8+ T cells also produce many cytotoxic granulosa (IFN-γ perforin and granzyme) [34]. The hyperfunction of CD4+ and CD8+ T cells may be associated with the pathogenesis of severe SARS-COV-2 infection [35,36]. There is an abnormal ratio of helper T cells (Th17) to regulatory T cells (Treg) in hypertensive patients [37–41]. Treg cells inhibit innate and adaptive immune responses [40], and with the reduction of Treg cells, the anti-inflammatory effect in patients with hypertension decreases. There is a physiological shift in hypertension patients to a Th17 environment conducive to the expression of inflammatory cytokines IFN-γ, vascular endothelial growth factor (VEGF), IL −1α, and IL-1β, IL-6, IL-12, IL-17). This provides the conditions for cytokine storms to occur.

Ang II increased B cell and plasma cell activation in lymphoid tissue and induced aortic IgG deposition [42]. So in patients with hypertension, B cells are activated and release various cytokines [IL-1, IL-6, IL-8, TNF, lymphotoxin-α (LT-α), GM-CSF, granulocyte colony-stimulating factor (G-CSF), macrophage-colony stimulating factor (M-CSF), IL-7] [43] and differentiate into plasma cells to release antibodies [44,45]. Highly activated B cells may be associated with severe COVID-19 [46–48].

In Ang II-induced hypertension, NK cells and monocytes activate each other [49]. NK cells have cytolytic activity against tumor or pathogen-infected cells, and they also release cytokines including IFN-γ, TNF, and GM-CSF, as well as chemokines such as chemokine ligand (CCL) 4, CCL5, and CCL22 [50,51]. The increase of NK cells in patients with hypertension leads to a significantly enhanced inflammatory response. Circulating monocytes in hypertensive patients have a pro-inflammatory phenotype [52] and contain high concentrations of harmful cytokines in the serum (IL-1β and TNF) [53]. Increased pro-

Table 1 (*continued*)

Cell/ Receptor/ Cytokine	Function	Changes in hypertension	Effects on hypertension	Effects on SARS-CoV-2
CRP	Activates the complement pathway; promotes the release of pro-inflammatory cytokines and apoptosis[188]	Increased	Promotes vascular endothelial dysfunction and atherosclerosis[189]	Promotes the onset and development of cytokine storms
ACE2	Promotes angiotensin conversion; functional receptors for SARS-COV-2	Increased; activated	Promotes Ang II-mediated hypertension [190]	Conducive to the invasion of SARS-COV-2; exacerbates lung injury
C3	Promotes immune cells to engulf pathogens; regulates cytokine release, and promotes an inflammatory response[191]	Increased	Aggravates inflammatory response and terminal organ injury[192]	Promotes inflammation and exacerbates symptoms of SARS-COV-2 infection[191]

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Ang II, angiotensin II; Th17 cells, T helper cell 17; Th2 cell, T helper cell 2; Treg cells, regulatory cells; ROS, reactive oxygen species; NK cells, natural killer cells; RAAS, renin-angiotensin-aldosterone-system; IFN-γ, interferon gamma; TNF, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor; TGF-β, transforming growth factor-beta; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1, interleukin 1; IL-2, interleukin 2; IL-4, interleukin 4; IL-6, interleukin 6; IL-8, interleukin 8; IL-10, interleukin 10; IL-13, interleukin 13; IL-17, interleukin 17; IL-22, interleukin 22; IL-23, interleukin 23; CTL, cytotoxicity T lymphocyte; CRP, C-reactive protein; ACE2, angiotensin-converting enzyme 2; C3, complement 3.

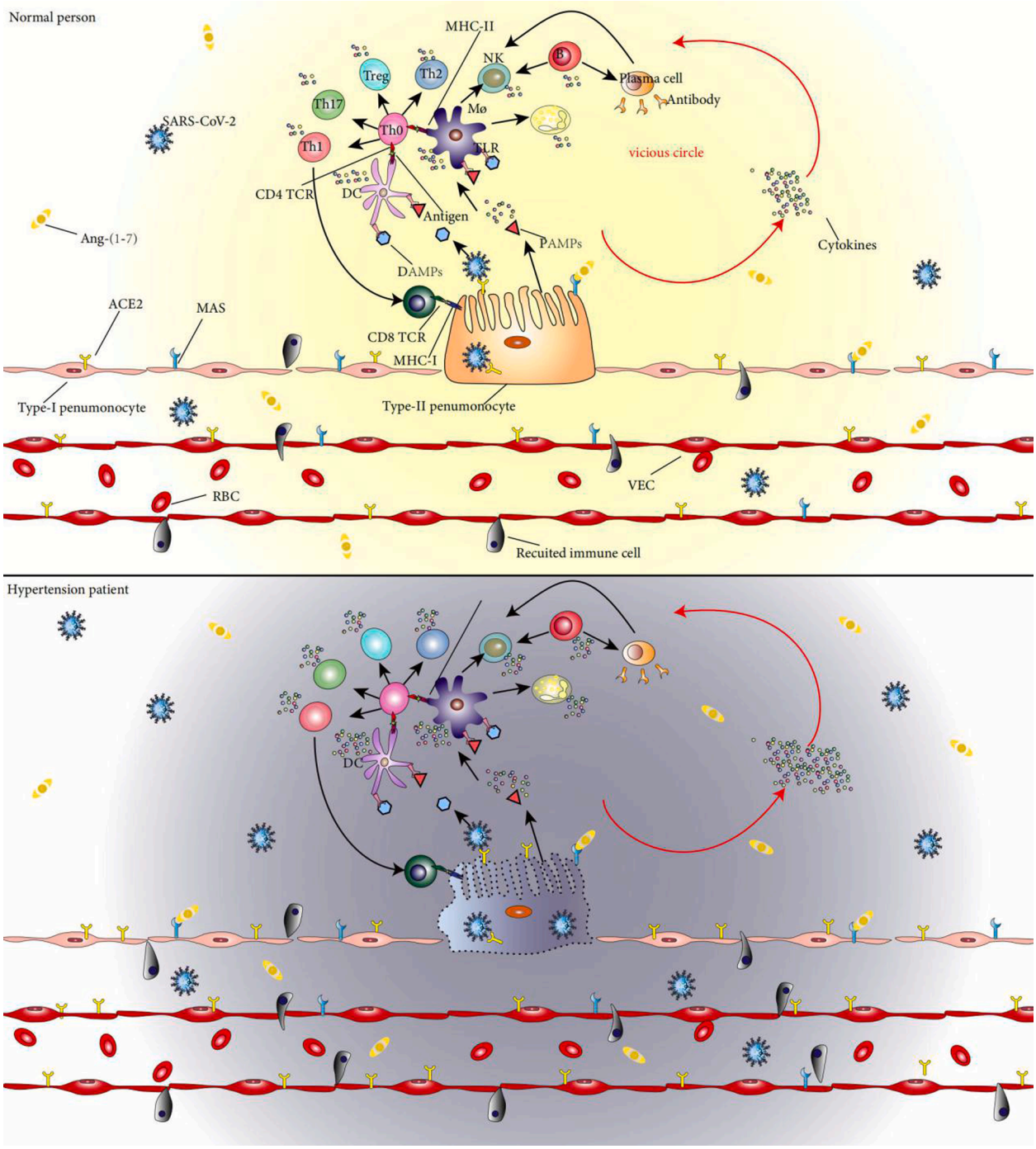

Fig. 1. SARS-CoV-2 binds to ACE2 in alveolar epithelial cells and invades cells. Dendritic cells and macrophages recognize the antigen of SARS-CoV-2, and their surface MCH-II binds to the surface CD4 TCR of Th0 cells, promoting the differentiation of Th0 cells into Th1, Th2, Th17 and Treg phenotypes. These cells secrete cytokines to promote inflammation. Dendritic cells stimulate Th1 cells to activate CTL, and CD8 TCR on the CTL surface recognizes and binds to MHC-I on SARS-COV-2-infected cells and then lyses the infected cells. Macrophages activate NK cells to release lethal substances, thereby clearing SARS-CoV-2-infected cells. When activated, B cells release cytokines to promote the killing activity of NK cells and differentiate into plasma cells, producing neutralizing antibodies to clear SARS-CoV-2. PAMS and DAMPS, generated after SARS-CoV-2 invasion, bind to PRR on the surface of dendritic cells and macrophages, which promotes the release of cytokines in these cells. And then, other immune cells are activated and release cytokines, which results in a cascade reaction, even a cytokine storm. Hypertensive patients are in a special immune state, which hints the inflammatory response is more serious and the risk of cytokine storm is higher than in normal people. Of note, ACE2 has a protective effect on the lung, and its hydrolysate Ang-(1-7) has an anti-inflammatory effect. The level of ACE2 and Ang-(1-7) in hypertension patients is relatively high, which may be with a certain protective effect on various organs. However, SARS-CoV-2 is more likely to invade cells due to a high level of ACE2.

inflammatory (M1) macrophage activity and number were observed in angiotensin II-induced salt hypertension [54–58]. M1 macrophages can produce pro-inflammatory cytokines, such as IL-1β, IL-6, IL-12, IL-23, and TNF, which aggravate the cytokine storm [58]. Dendritic cells are activated in hypertensive patients and trigger T cell activation and proliferation to produce IL-17A, TNF, and IFN-γ [59]. Patients with hypertension have elevated levels of neutrophils [60] that will further promote the occurrence and development of cytokine storms in COVID-19 patients.

The levels of IFN-γ, TGF-β, VEGF, IL -1α, TNF, IL-1β, IL-6, IL-8, IL-17,

IL-22, IL-23, C-reactive protein (CRP), complement component 3 (C3), and chemokines were increased [61–65]. On the contrary, IL-4 [66], IL-2 [67], IL-10 [68,69], and IL-13 [70] levels were decreased. These changes – during hypertension – have been associated with worsening symptoms in patients with COVID-19 and the occurrence and development of cytokine storms.

4. Immune changes in COVID-19 lead to hypertension

Studies have shown that people with COVID-19 can develop high blood pressure [71]. Ang II levels were significantly higher in patients with elevated blood pressure after COVID-19. Renin-angiotensin-aldosterone-system (RAAS) plays a key role in the cardiovascular system, including the classical RAAS axis (ACE-ANG II-AT1R pathway) and the non-classical RAAS axis (ACE2-ANG 1-7- Mas receptor pathway), balancing the roles of the two axes in regulating cardiovascular physiology and disease [72,73]. In those people with COVID-19 that develop high blood pressure, this may be related to the inhibition of Ang II degradation by the combination of SARS-COV-2 and ACE2, leading to increased blood pressure. At the same time, elevated Ang II promotes inflammatory and cytokine storms [23] that stimulate the nicotinamide adenine dinucleotide (NADH)/ nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and trigger cell contraction and vasoconstriction, exacerbating COVID-19-related organ damage [21] (Fig. 2).

Hypertension is a cause or result of endothelial dysfunction [74]. Endothelial dysfunction after SARS-CoV-2 infection is the key to the progression of COVID-19 [75], so patients infected with SARS-CoV-2 are at increased risk of developing hypertension and exacerbation of hypertension.

The number of CD4+ and CD8+ T cells was significantly reduced in peripheral blood, and their state was overactivated. And increased Th17 and high cytotoxicity of CD8 T cells were observed [76,77]. In addition, circulating levels of different pro-inflammatory cytokines dramatically

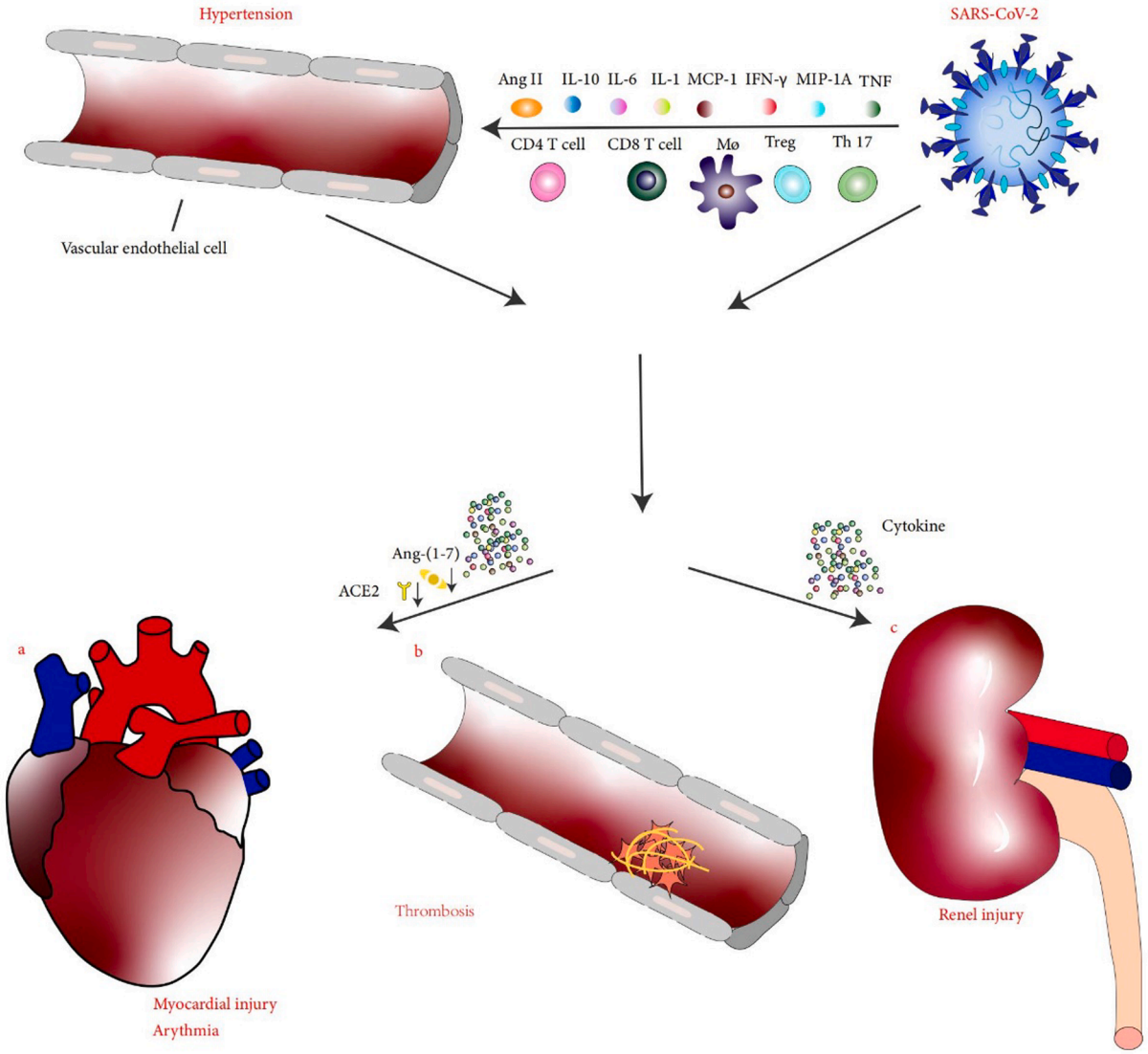

Fig. 2. In COVID-19 patients, CD4+ T cells, CD8+ T cells, and macrophages increase, and then cytokines, such as TNF, IL-1 and IL-6, produced by these cells increase, which promotes the occurrence of inflammatory reactions in vivo and leads to vascular endothelial dysfunction, thus increasing the risk of the occurrence and aggravation of hypertension. (a) Both COVID-19 and chronic hypertension can lead to arrhythmias. Cytokines such as TNF are increased in hypertensive patients with COVID-19, further damaging myocardial cells and increasing arrhythmias. (b) High plasma fibrinogen levels and impaired vascular endothelium in hypertensive patients are conducive to thrombosis. People with high blood pressure who have COVID-19 are more likely to develop blood clots because of their abnormal clotting status and endothelial dysfunction due to inflammation. (c) Many macrophages and T cells infiltrate renal microvessels in COVID-19 patients, while patients with hypertension are more likely to form cytokine storms, which leads to acute kidney injury. TNF, tumor necrosis facor; IL-1, interleukin 1; IL-6, interleukin 6.

increase, causing CD4 and CD8 to accumulate in target organs, which was related to severe acute respiratory syndrome [78]. Cytokines secreted by T cells play a key role in developing hypertension [30]. Moreover, CD4+ T cells and CD8+ T cells play a central role in hypertension. In line with this, patients with COVID-19 are more likely to develop or have worsened hypertension [79].

In COVID-19 patients, the level of Treg cells decreased [35,80], the level of Th17 cells increased, and the ratio of Treg/Th17 cells decreased [81]. There is an overall decrease in NK cell subsets in COVID-19, and the balance of NK cell subsets favors inflammation rather than cytotoxicity [82]. Inflammatory monocyte-derived macrophages increase in COVID-19 patients and infiltrate the lungs, promoting inflammatory response [78]. Meanwhile, levels of IFN-γ, TNF, IL-1, IL-6, IL-8, IL-10, monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1A (MIP-1A) were significantly elevated in COVID-19 patients [4,80,83]. This makes the immune state of the body to pro-inflammatory state change, which will be conducive to the occurrence and development of hypertension.

5. COVID-19 with hypertension leads to adverse outcomes

COVID-19 with hypertension can increase the risk and severity of cardiovascular system and kidney damage (Fig. 2).

Long-term high blood pressure can damage the heart muscle [84,85]. COVID-19 patients with cardiovascular disease have a higher prevalence of myocardial damage and are more likely to require admission to the Intensive Care Unit (ICU) [86]. SARS-COV-2 binds to ACE2, and a decrease in ACE2 leads to age-dependent cardiomyopathy, cardiac insufficiency, and heart failure [87,88]. Down-regulation of ACE2 also reduces Ang 1-7, impeding its cardioprotective effect, leading to increased production of TNF and promoting inflammatory responses [87,89]. Meanwhile, pre-existing inflammation combined with the direct assault of SARS-CoV-2 may make hypertension patients more likely to develop cytokine storms, which release large amounts of cytokines and cause damage to heart cells [26].

Changes in cardiac hemodynamics, structure, and electrophysiological characteristics caused by chronic hypertension can lead to supraventricular and ventricular arrhythmias [90]. COVID-19 can cause arrhythmias, possibly due to electrolyte and hemodynamic disturbances and high inflammatory stress [91–94]. Patients with severe COVID-19 and myocardial damage have a higher incidence of arrhythmias[1], and hypertension is a risk factor for severe COVID-19 and cardiac injury. Consequently, people with high blood pressure who have COVID-19 are more likely to develop myocardial damage and arrhythmias.

Patients with hypertension have high plasma fibrinogen levels, impaired fibrinolysis, endothelial dysfunction, and favorable thrombosis [95]. Likewise, studies have suggested that COVID-19 is an endothelial disease, which can lead to clotting disorders [96]. When endothelial dysfunction persists, coagulation cascade activation and microvascular obstruction occur [97]. Dysfunction of ACE2 leads to abnormal activation of RAAS and systemic endodermatitis, which is associated with abnormal clotting in COVID-19 patients [98]. In addition, overactivation of the inflammatory response is also involved in COVID-19-related thrombosis [99]. If hypertension patients are infected by SARS-COV-2, an existing abnormal clotting state in the body will further promote the formation of thrombosis.

Because COVID-19 patients with high blood pressure are more likely to develop cardiovascular complications that can lead to death in severe cases, therefore, we should pay more attention to the cardiovascular situation of COVID-19 patients with hypertension, timely detection of problems and appropriate treatment measures.

Patients with COVID-19 have a high incidence of renal dysfunction and are prone to acute kidney injury [100]. The main immune mechanisms of renal damage in COVID-19 patients are macrophage and *T*-cell-dominated microvascular inflammation (glomerulitis and peritubular capillaries) [101]. The innate and adaptive immune systems of hypertensive patients are active [102]. Activated immune cells (monocytes, macrophages, neutrophils, dendritic cells, NK cells, and T cells) can promote a host of pro-inflammatory cytokines, such as TNF, TGF-β, IL-1, IL-6, IL-17, and IFN-γ, which magnify elevated kidney injury [103–106]. This is similar to the overactivation of the immune system in patients with COVID-19 and the eventual formation of cytokine storms. Therefore, the co-occurrence of hypertension and COVID-19 may increase the risk of impaired renal function, and we recommend long-term renal function testing and blood pressure control in these patients [107,108].

6. Hypertension therapy under COVID-19

In the COVID-19 pandemic, medication options for patients with hypertension will be different (Table 2).

RAAS inhibitors, especially ACE inhibitors (ACEI) or angiotensin receptor blockers (ARB), are widely used in patients with hypertension because of their good antihypertensive effect [73]. RAAS inhibitors, particularly ACE inhibitors or angiotensin receptor blockers, may lead to increased expression of ACE2 in the respiratory tract, thereby increasing the risk of infection and serious life-threatening complications due to COVID-19 [109]. However, numerous studies have shown that RAAS inhibitors are safe. The use of RAAS inhibitors did not increase the risk of hospitalization for COVID-19 or the occurrence of critical illness [110,111]. Meanwhile, there was no significant difference in clinical outcomes between ACEI alone and ARB alone [112]. However, ACEI therapy is associated with suppressing excessive inflammation associated with COVID-19 and an increased intracellular antiviral response, whereas ARB is not [113].

Furthermore, RAAS inhibitors have been shown to reduce complications and mortality in patients with COVID-19 compared to other antihypertensive drugs [114]. COVID-19 patients who have previously used RAAS inhibitors have a better prognosis than those who have not previously used them [115]. This may be related to the lung-protective effect of ACE2 and the vasodilatory anti-inflammatory effect of its degradation product Ang 1-7. The clinical benefits of ARB and ACEI therapy for COVID-19 patients with hypertension deserve further investigation.

Calcium channel antagonists, another common treatment for hypertension, also reduce mortality from COVID-19. Amlodipine can resist the infection of novel coronavirus and inhibit replication of novel coronavirus [116]. But hypertension patients with COVID-19 who used

Table 2
Treatment of hypertension in COVID-19.

Therapeutic function	Drug	Mechanism of action	Effect in COVID-19
Antihypertensive	ACEI	Inhibits angiotensin II biosynthesis[193]	Dampens COVID-19-related hyperinflammation and increases cell-intrinsic antiviral response[113]
	ARB	Blocks angiotensin II receptor[193]	Enhances epithelial-immune cell interactions[113]
	CCB	Blocks Ca2+ via voltage-dependent calcium channels [194]	Suppresses the activation of immune reactions[195]
	β-blockers	Against catecholamines, adrenergic transmitters[196]; decreases ACE2 receptors expression and CD147[197]	Decreases the SARS-CoV-2 cellular entry; decreases the morbidity and mortality in COVID-19 patients[197]

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CCB, calcium channel blockers; COVID-19, Coronavirus Disease 2019.

ACEI and ARB for a long period had lower hospitalization and mortality rates than patients who used this channel antagonist [117,118]. It is worth noting that calcium channel blockers (CCBs) offered protective effects in hypertensive patients with COVID-19 [119]. However, it has also been reported that CCBs may increase mortality in patients with severe COVID-19, which may be related to how CCBs inhibit pulmonary vasoconstriction during hypoxia [120]. Therefore, CCBs should be used according to the actual clinical situation.

Beta-blockers, another class of blood pressure drug, do not increase the rate of COVID-19 infection [121]. Studies have shown that beta-blockers may also benefit patients with high blood pressure due to COVID-19 [122]. However, other studies have shown that stopping beta-blockers at admission has no impact on the clinical outcome of COVID-19 patients [123]. Therefore, the specific effects of beta-blockers need to be further studied.

There have been few reports on the effects of diuretic use, with only studies suggesting that discontinuing the drug does not affect the prognosis of COVID-19 patients [123].

7. COVID-19 therapy under hypertension

The treatment of COVID-19 in patients with hypertension will differ from those without hypertension, and more attention should be paid to cardiovascular side effects when taking medication. We have summarized several drugs suitable for treating COVID-19 in patients with hypertension (Table 3).

Remdesivir is a novel broad-spectrum antiviral nucleotide prodrug that inhibits viral replication by interrupting viral RNA transcription. In vitro and in vivo experiments have shown that it can resist the replication of SARS-CoV [124,125]. Studies have shown that remdesivir may reduce clinical recovery time for COVID-19 patients [126]. There have been no reports of cardiovascular side effects and toxicity associated with remdesivir, which is a very promising treatment [127].

Bamlanivima and etesevimab are recombinant human immunoglobulin G1 antibodies that rapidly protect against SARS-COV-2 infection and COVID-19 by binding to the Spike protein. Studies have shown that bamlanivima can reduce infection rates in people at high risk of COVID-19 and reduce the risk of hospitalization in patients with mild cases [128,129]. Treatment with bamlanivimab and etesevimab significantly reduced SARS-COV-2 load compared with placebo in out-of-hospital patients with mild-to-moderate COVID-19 and reduced hospitalizations and deaths [128,130]. Patients with other chronic conditions, such as cardiovascular disease and high blood pressure, could benefit [130].

Tocilizumab is an IL-6 antagonist. Studies have shown that tocilizumab reduces all-cause mortality in patients with COVID-19, which may be related to the fact that IL-6 antagonists reduce inflammation in patients and help the immune system fight COVID-19 [131]. Other IL-6 antagonists have been shown to have similar effects [131,132]. Notably, IL-6 antagonists improved outcomes in patients with severe cardiovascular complications [132].

Interferon is a cytokine that regulates the immune response to viral infection. Studies have shown that IFN β-1a improves antiviral response and lung function, contributing to improvement or recovery in patients with SARS-CoV-2 infection, and is also safe and effective in patients with hypertension [133,134]. Similarly, other interferons, such as interferon -α and interferon α-2b, are equally effective against COVID-19 [135].

Baricitinib is a selective inhibitor of Janus kinase (JAK) 1 and 2 [136]. Baricitinib can decrease the cytokines, including IL-2, IL-6, IL-10, INF-γ, and GM-CSF, and improves lymphocyte counts in patients with COVID-19 [137]. Despite concerns about immunosuppressive secondary infections and thrombosis with JAK inhibitors, the addition of baritinib was not associated with a significantly increased incidence of adverse events or thromboembolic events [138]. It is a relatively safe drug, but further studies are needed for COVID-19 patients with hypertension.

Corticosteroids are steroid hormones and are used as immunosuppressants in clinical work. Systemic corticosteroids are used to treat people with COVID-19 because they counter hyper-inflammation, such

Table 3
Treatment of COVID-19 with hypertension.

Therapeutic function	Drug	Mechanism of action	Effect in COVID-19	Adverse effects
Anti-virus				
	Remdesivir	Inhibits viral replication by interrupting viral RNA transcription[198]	Inhibits the replication of COVID-19 coronavirus [125,126]	Hypotension, nausea, acute respiratory failure, hypokalemia[199] …
	Bamlanivimab Etesevimab	Binds to Spike protein and protects against SARS-COV-2 infection[200]	Accelerates the decline in the SARS-CoV-2 viral load[129,138]	Nausea, rash, dizziness, diarrhea, hypertension[138]…
Cytokine antagonists				
	Tocilizumab	Binds soluble IL-6 receptor and inhibits IL-6 signalling[201,202]	Reduces inflammatory response and reduces symptoms after SARS-CoV-2 infection[132]	Infection, rash, headache, dizziness, hypertension, cough[202]…
	IFN β −1a	Supplies IFN[203]	Prevents cytokine storm, improves antiviral response and lung function	Injection-related, neuropsychiatric problems, hypersensitivity reactions [204]…
Others				
	Baricitinib	Binds to AAK1 and GAK; suppresses JAK1/JAK2[205]	Interrupts SARS-COV-2 access to target cells and intracellular assembly; moderates cytokine storm	Malignancy, thrombosis, neutropenia, lymphopenia, anemia, thrombocytosis
	Vitamin D	Regulates the imbalance of Treg/Th17 and prevents excessive inflammatory response[206]	Against respiratory viral infections and prevents excessive inflammatory response	–
	Convalescent plasma	Supplies virus-associated antibodies	Reduces the progression of COVID-19	–
	Steroids	Suppress innate and adaptive immunity	Reduce the catastrophic effects generated by the overactivation of the immune system	Hyperglycemia, infection, water sodium retention[207,208]…
Vaccination				
	Messenger RNA vaccines Viral vector vaccines Inactivated and protein subunit vaccines	Induces an immune response	Reduce the risk of contracting COVID-19 and progressing to severe pneumonia; slow the further spread of COVID-19	Anaphylaxis, myocarditis, thrombosis, capillary leak syndrome [209]

COVID-19, Coronavirus Disease 2019; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; JAK1, Janus kinase 1; JAK2, Janus kinase 2; AAK1, AP2-associated protein kinase-1; GAK, cyclin G-associated kinase; IL-6, interleukin-6; IFN, interferon; Treg/Th17, T regulatory cells/ T helper cell 17.

as suppressing pro-inflammatory cytokines and increasing anti-inflammatory cytokine mediators. The benefits and risks of glucocorticoid use in patients with mild COVID-19 are uncertain [139–141]. For patients of critical severity, glucocorticoid treatment reduced mortality [142]. However, corticosteroids may increase the risk of hyperglycemia, infection, and water sodium retention. Therefore, glucocorticoids should be used with caution in COVID-19 patients with hypertension.

Vitamin D is an immunomodulatory hormone that can prevent excessive inflammatory response and speeds up the healing process in affected areas, primarily lung tissue [143]. Vitamin D supplementation protects against acute respiratory infections [144]. In the meantime, vitamin D has a protective effect against the development of hypertension [145,146]. Vitamin D is, therefore, a promising complementary therapy.

Convalescent plasma therapy is one of the promising treatments for COVID-19 disease. It should be most effective in the early stages of infection before organ damage becomes apparent. Hospitalized adult patients with severe COVID-19 pneumonia received no improvement in convalescent plasma clinical status or overall mortality [147]. Early administration of high titer convalescent plasma resistant to SARS-CoV-2 to mildly infected older adults can reduce the progression of COVID-19, and it has been shown to be safe and effective in patients with hypertension [148].

Vaccination is one of the most promising preventive measures against COVID-19. It provides immune protection and reduces the risk of contracting COVID-19 and progressing to severe pneumonia if infected [149]. Vaccination can also slow the further spread of COVID-19. Vaccination is safe and effective for people with high blood pressure. Up to now, few cardiovascular side effects have been reported with the vaccine [149,150]. More extensive research is required regarding vaccinating hypertension patients.

8. Conclusion

COVID-19-related immune system changes in hypertension patients involve multiple cytokines, cells, and receptors. The special immune system status of hypertension patients makes them more susceptible to SARS-CoV-2 invasion. After SARS-CoV-2 invades hypertension patients, the body's immune response may be more serious, along with a higher risk of cytokine storms, which increases post-infection complications and mortality from severe infections. Therefore, it is important to accurately identify COVID-19 inflammatory pathways and therapeutic targets in hypertension patients.

Author contributions

HS and JL conceived and designed the study. SS, RC, and SZ performed the literature search and drafted the manuscript. All authors contributed to the article and approved the submitted version.

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