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

Sheng Su a,b,1, Ruirong Chen a,c,1, Shaofen Zhang d,1, Haihua Shu a,c,*, Jianfang Luo a,b,*

a The Second School of Clinical Medicine, Southern Medical University, Guangzhou, China
b Department of Cardiology, Guangdong Cardiovascular Institute, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
c Department of Anesthesiology, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China
d Department of Gynaecology and Obstetrics, Guangdong Provincial People’s Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China

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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+ T cells, 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...
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           | Secreto 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           | Secreto 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]                                                                                                          |                         |                                                                                          | Promotes the onset and development of cytokine storms                                    |
| Neutrophils            | 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                  | Antiangiogenic; 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[166] |
| TNF                    | Promotes apoptosis and renal vasconstriction; 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 mediated[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               | Conduce 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 - 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]                                                    | Conduce 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               | Exacerbate 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 exocytosis 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 at 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 promote inflammation and chronic inflammatory activation of endothelial cells. This state may promote cytokine storms, with severe consequences for those infected with COVID-19, potentially leading to death.

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 induces 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+ Th17), 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 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.

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 | Promotes Ang II-mediated hypertension [190] | Conductive 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, cytotoxic T lymphocyte; CRP, C-reactive protein; ACE2, angiotensin-converting enzyme 2; C3, complement 3.
inflammatory (M1) macrophage activity and number were observed in angiotensin II-induced salt hypertension \cite{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 \cite{58}. Dendritic cells are activated in hypertensive patients and trigger T cell activation and proliferation to produce IL-17A, TNF, and IFN-γ \cite{59}. Patients with hypertension have elevated levels of neutrophils \cite{60} that will further promote the occurrence and development of cytokine storms in COVID-19 patients.

The levels of IFN-γ, TGF-β1, 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 factor; 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 Th17/Treg 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 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 fibroblinolysis, 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, over-activation 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).

| Antihypertensive | Drug | Mechanism of action | Effect in COVID-19 |
|------------------|------|---------------------|-------------------|
| 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 interaction[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.
in vitro and in vivo experiments have shown that it can resist the replication associated protein kinase-1; GAK, cyclin G-associated kinase; IL-6, interleukin-6; IFN, interferon; Treg/Th17, T regulatory cells/ T helper cell 17.

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].

Bamlanivimab 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 bamlanivimab 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 baricitinib 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 as anaphylaxis, myocarditis, thrombosis, capillary leak syndrome, hyperglycemia, infection, water retention, sodium retention, …

Table 3

| 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 | 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 retention [207,208] |
| **Vaccination**      | Messenger RNA 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] |
|                      | Viral vector vaccines | Inactivated and protein subunit vaccines | – | – |

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 stable 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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