


# Association Between COVID-19 and Hypertension

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## Abstract

Chinese authorities reported the first human-to-animal SARS-CoV-2 transmission in late 2019. The virus then quickly spread from person to person throughout the world and increased the mortality rate of those with underlying illnesses, particularly hypertension. After attaching the virus to a special receptor, that is, angiotensin-converting enzyme-2 (ACE2), ACE2 degrades angiotensin 2 (Ang2). Ang2 as a modulator of blood pressure and a vasoconstrictor plays an adverse regulatory role in the renin-angiotensin system (RAS). Additionally, it changes Ang2 into Ang1-7, which functions as an antioxidant and an anti-inflammatory factor. Infection with SARS-CoV-2 lowers ACE2 levels in hypertensive patients because the virus binds to the blood vessel, preventing Ang II degradation. As a result, complications related to hypertension increase, and the pumping of blood from the lungs to the left atrium decreases. Additionally, there is a decrease in the final product, Ang1-7, and the concomitant anti-inflammatory action is lost. The virus grows, multiplies, damages lung cells, causing inflammation in immune cells and cytokines and expanding lung tissue. This ultimately leads to lung injury, a decline in the oxygen supply, and death. The management of hypertensive patients can prevent infection in this population and reduce mortality with proper oxygen therapy and probably exogenous ACE2 supplementation.

**Keywords:** SARS-CoV-2, COVID-19, Transmission, Hypertension, Risk factor

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## Introduction

Human health is seriously threatened by infectious diseases, of which the coronavirus outbreak is thought to be the most recent. Previous studies reported a big family of various enveloped viruses with the largest genome among RNA viruses, positive-sense RNA, and single-stranded RNA. At the end of 5', there are overlapping open reading frames (ORF1a and ORF1b) that make up about two-thirds of the coronavirus genome. They are progressively translated into polyprotein 1a (pp1a) and also pp1ab, which are then broken down by viral proteases to produce the virus's non-structural proteins.<sup>1</sup> Different structural proteins of the virus such as the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins are encoded by the remaining portion of the genome.<sup>2</sup> Similar to the flu virus, coronaviruses spread naturally among various animal species. It encompasses the four genera: alpha,

beta, gamma, and delta. Mammal infections can be caused by alpha and beta, while bird infections can be triggered by delta and gamma. The beta coronavirus is one of the viruses that can cause serious, sometimes fatal illnesses.<sup>3</sup> The six coronaviruses that caused human infections were the Middle East respiratory syndrome coronavirus (MERS-CoV), human coronavirus 229E (HCoV-229E), HCoV-NL63, HCoV-OC43, HCoV-HKU1, and severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1). The seventh coronavirus that infects humans is SARS-CoV-2.<sup>4</sup> The acute respiratory tract infection virus, SARS-CoV-2, has spread quickly throughout the world and is now a major concern.<sup>5-7</sup> The first case of the COVID-19, also known as SARS-CoV-2 infection, was reported in the province of Wuhan, China, in December 2019.<sup>8-11</sup> Based on preliminary investigations, it appears that the virus was initially passed from an animal to a human at a wet market,



and it could also spread between people.<sup>12</sup> Approximately 80% homology exists between SARS-CoV-2 and subtype SARS-CoV-1,<sup>13</sup> and the receptor binding domain (RBD) of the two viruses was highly similar, indicating a shared host cell receptor.<sup>14</sup> Both viruses are capable of entering the host cell through the cellular receptor identified as angiotensin-converting enzyme 2 (ACE2).<sup>2,15</sup> Transmembrane serine protease 2 is linked to the proteolytic degradation of ACE2 following attaching the SARS-CoV-2 spike protein to ACE2.<sup>16</sup> An enzyme called ACE2 is connected to the renin-angiotensin system (RAS) and functions as a SARS-CoV-2 virus receptor. This link may make those with underlying medical conditions more susceptible to COVID-19. Diabetes, high blood pressure, and cardiovascular disease are the most prevalent underlying illnesses.<sup>17</sup> RAS blockers such as ACE inhibitors (ACEIs) and Ang2 receptor blockers (ARBs) are used by people with such disorders.<sup>18</sup> Increased COVID-19 mortality has been linked to hypertension as an underlying cause.<sup>19</sup> We hypothesize that hypertension may aggravate COVID-19 and lead to a complication in the course of SARS-CoV-2 infection because of the elevated prevalence of the condition and the use of RAS blockers. Thus, one of the current topics of discussion is the use of RAS blockers in patients who have COVID-19 or in individuals who have been exposed to COVID-19. In this review, we examined the association between elevated blood pressure and higher death rates in COVID-19 patients.

## Methods

We systematically searched both PubMed and Google Scholar databases to find related publications from all peer-reviewed journals. To conduct comprehensive search, Medical Subject Heading terms were used, including 'Hypertension', 'SARS-CoV-2', 'COVID-19', 'Risk Factor', and 'Transmission'. The search was done and completed on May 1, 2020, without any search filters on the type of publications, literature language type, or other related fields during the expected periods. Then, to locate advanced and qualified studies, reference lists of all pertinent publications were chosen manually.

## Clinical Characteristics of SARS-CoV-2

It is critical to comprehend the clinical indicators of COVID-19. Fatigue, fever, myalgia, and cough are among the common symptoms that patients with COVID-19 experience despite the fact that the diagnosis was initially difficult because of the wide range of clinical symptoms and chest computed tomography (CT) imaging findings.<sup>20</sup> Adults with robust immune systems who contracted COVID-19 experienced fever, dyspnea, and hazy lungs. Moreover, severe cases of the disease have been reported to exhibit symptoms such as diarrhea, a disorder in renal and hepatic function, dizziness, lymphopenia, some level of thrombocytopenia, and a high degree of inflammation, particularly in older adults and those with underlying

diseases other than pulmonary insufficiency.<sup>19</sup> The ocular, nasal, and oral secretions of a SARS-CoV-2-infected individual have demonstrated individual transmission and surface dissemination of the virus. Given that SARS-CoV-2 has a serious incubation period of about 2–14 days and its high transmission power and symptoms resemble the common cold, these factors have contributed to an increase in the disease's prevalence and transmission among humans.<sup>21</sup>

## Hypertension

As a chronic illness with multiple cardiovascular risk factors, hypertension raises the chance of major events such as heart attacks, strokes, Alzheimer's, and kidney and heart failures. The two categories are primary and secondary hypertension, while 90 to 95% of cases are primary cases, with no specific medical reason.<sup>22</sup> Through the negative regulation of RAS, ACE2 plays a crucial role in hypertension, regulating blood pressure, and most importantly, preserving homeostasis.<sup>23,24</sup> Through converting angiotensin 2 (Ang2) to Ang1-7, ACE2 provides protection against acute lung damage and also acute respiratory distress syndrome (ARDS), which are conditions where Ang2 is overproduced.<sup>25,26</sup> Consequently, the development of heart, kidney, and lung injuries can be caused by ACE2 deficiency or dysfunction.<sup>27</sup> Reduced ACE2 levels result in hypertension and associated complications. A decrease in ACE2 and an elevation in the blood pressure can lead to shortness of breath, pulmonary edema, and cough. The two main causes of pulmonary edema are lung tissue inflammation and the left ventricle's incapacity to effectively pump the high amount of blood from the lungs into the arterial system.<sup>28</sup> Blood pressure is linked to both acquired and innate immune responses.<sup>29</sup> Activated immune cells migrate with blood pressure to target organs such as blood vessels and kidneys organ, and their mediator factors such as cytokines, reactive oxygen species, and metalloproteinases, ultimately impair target organ function.<sup>30</sup> Hypertension identified as a chronic disease is related to a pre-inflammatory state. This state is manifested by an increase in several mediators' expression, including chemokines, leukocyte adhesion molecules, some particular growth factors, angiotensin, and endothelin-1.<sup>31</sup> There is considerable evidence for altering the immune system following hypertension which is related to elevated secretion of immunoglobulins and declined T-lymphocyte (T-cell) number and also function. Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (IFN- $\gamma$ ), and interleukin 17A (IL-17A) are among the inflammatory cytokines released by T cells when they invade the kidneys, lungs, and tissues surrounding the arteries. These factors can alter organ and vascular function and ultimately lead to end-organ damage.<sup>32</sup> As a result, individuals with high blood pressure are more vulnerable to several illnesses such as chronic lower respiratory diseases and acute respiratory disorders.<sup>33</sup>

### Renin Angiotensin System

ACE/Ang2/angiotensin receptor 1 (AT1R) and also ACE2/Ang1-7/Mas receptor are the two pathways via which the RAS regulates blood pressure and hydro electrolyte balance.<sup>34</sup> Furthermore, ACE1 and ACE2, two RAS enzymes that are members of the dipeptidyl carboxypeptidases family, have distinct physiological roles.<sup>18</sup> Since these two enzymes are primarily located in the heart, kidneys, lungs, and blood vessels, they are widely dispersed throughout the human body. The gastrointestinal system also contains ACE2.<sup>35</sup> In particular, ACE2 is a homologous enzyme rather than an isoenzyme of ACE1.<sup>36</sup> They play a role in the process of synthesizing the RAS active components.<sup>37</sup> Following a decrease in blood pressure, juxtaglomerular cells produce prorenin in the kidneys, convert it to renin, and release it into the bloodstream; afterward, the liver secretes angiotensinogen that converts to Ang1. Then, Ang 1 changes into Ang2 by using ACE1. Ang2 is a peptide that has a pro-inflammatory effect and raises blood pressure by constricting blood vessels. Additionally, it increases aldosterone secretion from the cortical of the adrenal gland. Aldosterone enhances the absorption of both sodium and water from the renal tubules, thus leading to an elevation in the blood volume and pressure. Ang1 and 2 are converted by ACE2 into the Ang1-9 and Ang1-7 peptides, respectively. Afterward, Ang1-9 is processed to Ang1-7, which has antioxidant and anti-inflammatory properties.<sup>38,39</sup> The excessive elevation of blood pressure occurs when the renin-angiotensin-aldosterone system is abnormally activated.

### SARS-CoV-1 and Angiotensin-converting Enzyme 2

The coronavirus SARS-CoV-1 was the cause of the SARS outbreak in 2002–2003. All viruses, including SARS-CoV-1 and SARS-CoV-2, have a crown-like appearance due to the highly glycosylated viral spike protein that spreads on their surface. This protein is crucial to the virus's ability to bind to target cells and infiltrate them.<sup>2,40</sup> The spike protein attaches to the ACE2 receptor during SARS-CoV-1 infection, which results in the down-regulation of their expression.<sup>41</sup> Therefore, the cytopathic influence of the virus or excess cytokines may be the direct cause of clinical amplification of SARS-CoV-1. Patients infected with SARS-CoV-1 who experience a severe multiple clinical disorder have been found to have higher levels of proinflammatory cytokines (e.g., IL-1, IL-6, IL-8, IL-12, transforming growth factor  $\beta$ , and IFN- $\gamma$ ) and various chemokines (e.g., CCL2, CXCL9, CXCL10) compared to asymptomatic patients.<sup>42,43</sup>

### SARS-CoV-2 and Angiotensin-converting Enzyme-2

SARS-CoV-2 is 10 to 20 times more probable to attach to the ACE2 receptor than SARS-CoV-1. This could indicate its appropriate entrance, replication ability, and high transmissibility.<sup>16</sup> The expression degrees of these receptors are different and include all organs. The virus

may target the lungs due to a higher expression degree of receptors through the respiratory system, specifically in alveolar type 2 epithelial cells compared to the epithelial cells of the nose, nasopharynx, or oral mucosa.<sup>44,45</sup> Reduced ACE2 expression and function result from SARS-CoV-2 infection, which causes an imbalance among the ACE/Ang2/AT1R and the ACE2/Ang1-7/Mas receptor.<sup>41</sup> Due to the similarities between SARS-CoV-1 and SARS-CoV-2, infection with SARS-CoV-2 may also lead to the downregulation of ACE2 on the cell surface, consequently reducing ACE2 activity and the Ang1-7 end product, which would decrease the anti-inflammatory activity in the respiratory tract and other infected organs.<sup>46</sup> Viruses increase Ang2 expression levels and stimulate cell growth and fibroblast proliferation.<sup>47</sup> Like a double-edged sword, elevated ACE2 expression can both enhance the risk of COVID-19 severity and mortality and facilitate COVID-19 infection.<sup>48,49</sup> Indeed, the decline in ACE2 expression can induce pulmonary edema and also decrease lung normal function.<sup>25</sup> The attachment of ACE2 to SARS-CoV-1 and potentially SARS-CoV-2 leads to the activation of TNF- $\alpha$  convertase, which is recognized as disintegrin and metalloproteinase domain-containing protein 17. This enzyme can decrease the cellular ACE2 level and lessen the likelihood of the cell being infected by the virus, in addition to inducing ACE2 ectodomain shedding and producing soluble receptors.<sup>50,51</sup> Theoretically, the soluble form of ACE2 has two mechanisms of action that could help treat COVID-19: neutralizing the virus by attaching the spike protein to the soluble form of ACE2 and reducing organ damage such as kidney, heart, and lung damage. Following the injection of human recombinant soluble ACE2, a test was conducted, and the results showed a significant decline in Ang2 and a remarkable increase in ACE2 products (Ang1-7 and Ang1-9).<sup>52</sup>

### Relationship Between Blood Pressure and the Coronavirus Disease 2019

A more severe case of COVID-19 has been linked to individuals with immune system disorders-related high blood pressure. As a result, levels of IL-2, IL-6, IL-7, chemokine (CC motif) ligand 2, TNF- $\alpha$ , granulocyte colony-stimulating factor, and CXC motif chemokine 10 (CXCL10) increased. The severity level of COVID-19 is related to elevated cytokines.<sup>53</sup> Additionally, these cytokines contribute to hypertension.<sup>54</sup> Thus, it can be concluded that COVID-19 patients with hypertension may experience a worsening of their condition due to the elevated levels of these types of cytokines in patients with hypertension and also with SARS-CoV-2. One of the characteristics of COVID-19 is lymphopenia; however, the research indicates that hypertension is also linked to lymphocytes, resulting in a decrease in CD4+ and CD8+ T cells in hypertensive patients.<sup>55</sup> The elevated synthesis of proinflammatory cytokines in these patients is another problem that may exacerbate patients' clinical state.<sup>32</sup>  $\beta$ -blockers, RAS blockers, various diuretics, and calcium

channel blockers are the most common medications used by hypertension patients. RAS blockers are mostly used as ACEIs (e.g., enalapril) and ARBs (e.g., losartan) to treat high blood pressure and other heart diseases.<sup>56</sup> ACEI treatment significantly increases Ang1, and ARB treatment increases Ang2 levels. This may stimulate the expression level of ACE2 and increase the production activity of Ang1-7, ultimately affecting cardiac function.<sup>35</sup> Furthermore, patients receiving ACEIs and ARBs may be more susceptible to infection with SARS-CoV-2 and experience more severe symptoms because they have higher ACE2 expression levels in their cell membranes.<sup>57</sup> On the other hand, reducing this type of enzyme in cells may help fight infections. However, due to its dual function, ACE2 protects lung cells from viral injury via enhancing Ang1-7.<sup>52</sup> Thus, using the supplements of soluble exogenous ACE2 may be advantageous therapeutically to protect against COVID-19 since it may inhibit the communication between SARS-CoV-2 and endogenous ACE2.<sup>46</sup>

### Conclusion

It can be concluded that individuals with high blood pressure are more vulnerable to the serious effects of COVID-19. Following the attachment of the virus to ACE2, the levels of the virus reduced in the body, most significantly in the lungs, and resulted in an increase in Ang2 as an artery-narrowing agent and a decrease in Ang1-7 as an anti-inflammatory agent. As lung damage and increased inflammation are the eventual results of this condition, mortality can be decreased by giving these patients enough oxygen and lowering their inflammation.

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### Conflict of Interests Declaration

None.

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