

# Different Dimensions of the Effects of SARS-CoV-2 in Causing Fluctuations in the Blood Pressure of Patients

Mahdi Asghari Ozma <sup>1,2</sup> , Edris Nabizadeh <sup>2</sup> , Mir Reza Valiollahzadeh <sup>3</sup> , Jalil Rashedi <sup>3</sup> , Behroz Mahdavi Poor <sup>3</sup> , Vahid Asgharzadeh <sup>1</sup>, Hossein Samadi Kafil <sup>4</sup> , Ehsaneh Khodadadi <sup>5</sup> , Zahra Taghinejad <sup>6</sup> , Amin Abbasi <sup>7</sup> , Ali Esmaeili <sup>8</sup>, Mohammad Asgharzadeh <sup>9,\*</sup> 

<sup>1</sup> Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>2</sup> Department of Microbiology and Virology, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>3</sup> Department of Laboratory Sciences, Faculty of Paramedicine, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>4</sup> Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>5</sup> Material Science and Engineering, Department of Chemistry and Biochemistry, University of Arkansas-Fayetteville, Fayetteville, AR, USA

<sup>6</sup> Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

<sup>7</sup> Department of Food Science and Technology, National Nutrition and Food Technology, Research Institute, Faculty of Nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>8</sup> Department of Tissue Engineering and Applied Cell Science, School of Advanced Technologies in Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

<sup>9</sup> Biotechnology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

\* Correspondence: [asgharzadehmo@yahoo.com](mailto:asgharzadehmo@yahoo.com) (M.A.);

Scopus Author ID 16232520900

Received: 17.08.2022; Accepted: 20.09.2022; Published: 31.10.2022

**Abstract:** In late 2019, SARS-CoV-2 was transmitted from animal to human in China. Subsequently, the virus spread rapidly throughout the world by human-to-human transmission and caused high mortality the people with underlying diseases, especially hypertension. This virus binds to its receptor, angiotensin-converting enzyme-2 (ACE2), via the S protein. ACE2 has a negative regulatory function in the renin-angiotensin system (RAS) and degrades angiotensin 2 (Ang II) as a vasoconstrictor which causes blood pressure regulation. It also converts Ang II to Ang1-7, which has anti-inflammatory and anti-oxidative effects. SARS-CoV-2 infection in patients with hypertension reduces ACE2 levels due to virus binding, which decreases Ang II degradation. Consequently, the complications associated with hypertension are raised, and blood pumping from the lungs into the left atrium lowers. On the other hand, the final product, Ang1-7, is reduced, and its related anti-inflammatory activity is also eliminated. The virus multiplies and damages lung cells, causing inflammation and edema of the lung tissue through the function of immune cells and cytokines, which eventually leads to lung damage, reduced oxygen delivery, and death. Careful care of patients with hypertension can prevent their infection and reduce their death with appropriate oxygen therapy and possibly using exogenous ACE2 supplements.

**Keywords:** COVID-19; host risk factors; hypertension; SARS-CoV-2; transmission.

© 2022 by the authors. This article is an open-access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

## 1. Introduction

Infectious diseases are a significant threat to human health, and the coronavirus outbreak is the latest [1]. These are a large family of enveloped viruses with single-stranded RNA and positive sense and the largest genome among RNA viruses [2, 3]. At the end of 5' is about two-thirds of the coronavirus genome with overlapping open reading frames (ORF1a and ORF1b). They are translated to polyprotein 1a (pp1a) and pp1ab and cleaved by viral proteases,

eventually producing non-structural proteins of the virus [4, 5]. The rest of the genome encodes the structural proteins of the virus, such as spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins [6]. Like the flu virus, coronavirus circulates in nature among different species of animals. It includes the four significant genera alpha, beta, gamma, and delta, in which alpha and beta can infect mammals, and gamma and delta can infect birds. Among the coronaviruses that infect humans, beta can cause severe and even fatal diseases [7]. The six coronaviruses that infected humans were HCoV- 229E, HCoV- NL63, HCoV- OC43, HCoV- HKU1, SARS-CoV-1, and MERS-CoV. SARS-CoV-2 is the seventh coronavirus that causes disease in humans [8]. Acute respiratory tract infection caused by SARS-CoV-2 is spreading rapidly worldwide and has become a global concern [9]. SARS-CoV-2 infection, called COVID-19, was first observed in December 2019 in Wuhan Province, China [10]. Preliminary studies showed that this virus was first transmitted from animal to human in a wet store where seafood was sold; also, it can be transmitted from human to human [11]. SARS-CoV-2 has many similarities to SARS-CoV-1 so that it is about 80% homologous [12], and the SARS-CoV-2 receptor binding domain (RBD) is very similar to SARS-CoV-1 RBD, which represents a common host cell receptor [13]. Both viruses can use angiotensin-converting enzyme 2 (ACE2) as a cellular receptor to enter the host cell [6, 14]. The attachment of SARS-CoV-2 spike protein to ACE2 is associated with proteolytic degradation of ACE2 by transmembrane serine protease 2 (TMPRSS2) [15]. Since ACE2 is an enzyme in the renin-angiotensin system (RAS) and also acts as a receptor for SARS-CoV-2, maybe there is a link between that system and COVID-19. On the other hand, people with underlying diseases are more at risk for COVID-19. The most common underlying diseases include cardiovascular disease, high blood pressure, and diabetes [16]. People with such diseases typically use RAS blockers such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) [17]. Hypertension as an underlying condition is associated with increased COVID-19 mortality [18]. Given the high prevalence of hypertension and the use of RAS blockers, it is speculated that hypertension may complicate the course of SARS-CoV-2 infection and exacerbate COVID-19. Therefore, the use of RAS blockers in patients with COVID-19 or people exposed to COVID-19 is currently one of the topics of discussion. Thus, this article investigated the relationship between high blood pressure and increased mortality in patients with COVID-19.

## 2. Clinical Characteristics of SARS-CoV-2

Understanding the clinical signs of COVID-19 is essential. Although the diagnosis of COVID-19 was complicated in the first stage due to the variety of clinical symptoms and imaging findings, symptoms such as fever, cough, chest pain, sore throat, misophonia, anorexia, myalgia, and fatigue are more common among COVID-19 patients [19]. Most immunocompetent adult patients with COVID-19 have symptoms such as fever, respiratory problems, and ground-glass lesions in the lungs. In severe cases of the disease, especially among aged people and those with underlying disorders, in addition to pulmonary insufficiency, symptoms such as diarrhea, dizziness, renal and hepatic dysfunction, lymphopenia, thrombocytopenia, and high inflammation have been reported [18]. Individual transmission and spread of SARS-CoV-2 on surfaces have been demonstrated by the nasal, oral, and ocular secretions of an infected person in the case of SARS-CoV-2. Since the incubation period of the disease caused by SARS-CoV-2 is 2-14 days, moreover, due to the

high transmission power of this virus and the similarity of its symptoms to the common cold, the transmission and the prevalence of the disease increases among people [20].

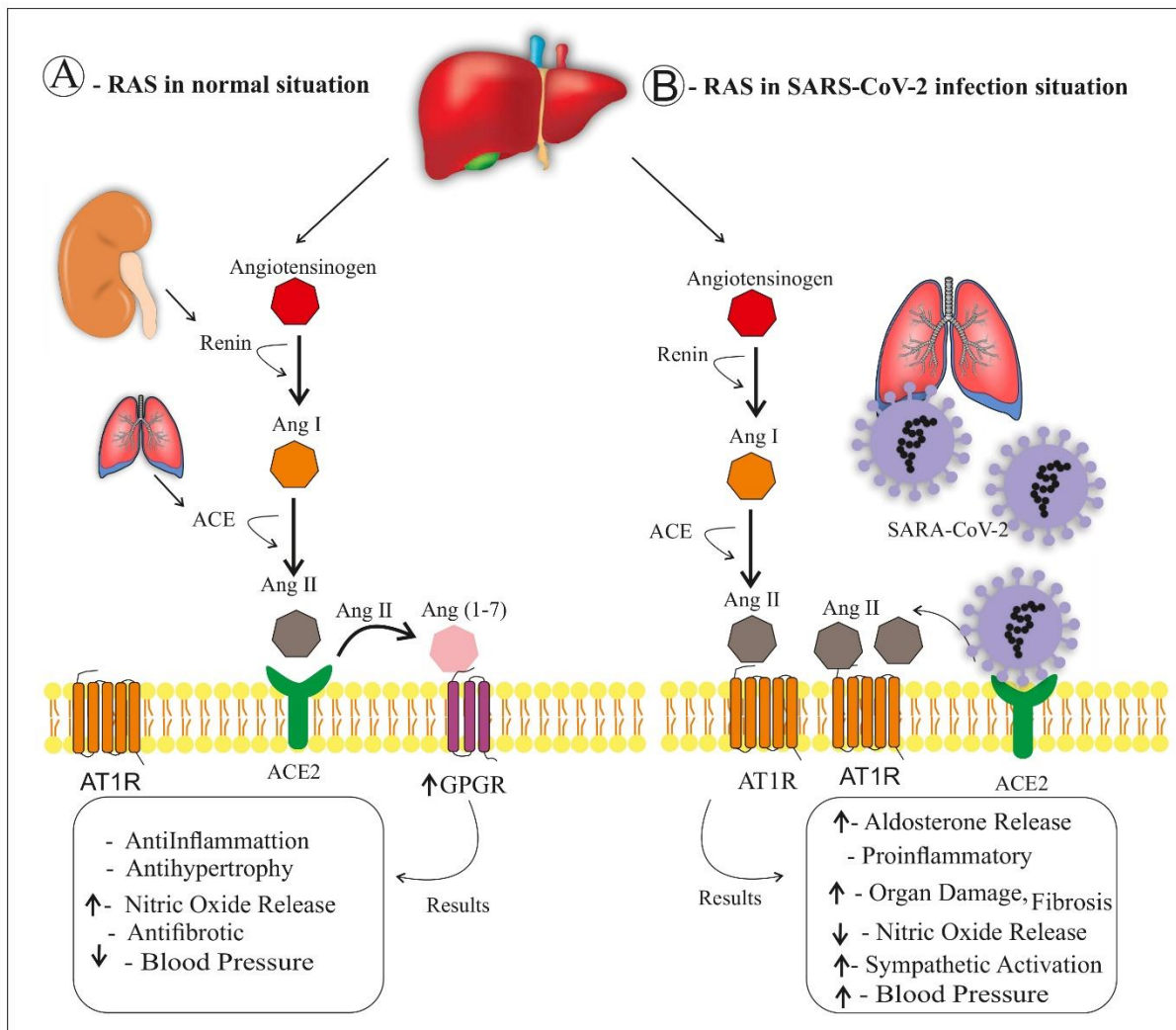
### 3. Hypertension

Hypertension is a chronic disease that is one of the most decisive cardiovascular risk factors, which significantly increases the incidence of important events such as stroke, Alzheimer's, heart attack, and heart and kidney failures. It is divided into primary and secondary hypertension [21, 22]. About 90-95% of cases are of the type of primary one, without any specific medical reason [23]. ACE2 plays an essential role in hypertension, modulating blood pressure and maintaining homeostasis by negatively regulating RAS [24, 25]. ACE2 also protects against acute respiratory distress syndrome (ARDS) and acute lung injury, in which Ang II is overproduced by converting Ang I to Ang II [26, 27]. Therefore, ACE2 deficiency and dysfunction can develop heart, kidney, and lung injuries [28]. In this regard, it can be said that a decrease in ACE2 levels leads to high blood pressure and related complications. Reducing ACE2 and subsequent increases in blood pressure can cause shortness of breath, cough, and pulmonary edema. Pulmonary edema is due to inflammation of the lung tissue and also due to left ventricular failure to adequately pump blood from the lungs into the arterial system [29, 30]. The body's first line of defense against germs is innate and acquired. The process starts when a person's immune system faces foreign agents, and immune responses are associated with blood pressure [31]. Activated immune cells are entered target organs by blood pressure, such as blood vessels and kidneys, and the mediators released by these cells, including reactive oxygen species, metalloproteinases, and cytokines, finally impair the function of the target organs [32, 33]. Hypertension as a chronic disease indicates a pro-inflammatory condition. This condition is exerted by increasing the expression of multiple mediators, such as leukocyte adhesive molecules, chemokines, specific growth factors, endothelin-1, and angiotensin [34]. There is ample evidence of changes in the immune system in hypertension, which are associated with increased levels of immunoglobulin secretion and decreased T-lymphocyte (T cell) count and function. T cells invade the lungs, kidneys, and tissues around the arteries, where they release inflammatory cytokines, including interleukin 17A (IL-17A), interferon- $\gamma$  (IFN- $\gamma$ ), and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). These factors could alter the function of the organs and blood vessels and cause damage to the final organs [35, 36]. Therefore, it can be claimed that patients with high blood pressure are prone to various diseases, including acute and chronic lower respiratory illnesses [37-39].

### 4. Renin Angiotensin System (RAS)

The RAS plays a role in controlling blood pressure and hydroelectrolyte balance through the two pathways ACE/ Ang II/ angiotensin receptor 1 (AT1R) and ACE2/ Ang I-7/ Mas receptor (Fig. 1) [40, 41]. ACE1 and ACE2 are RAS enzymes belonging to dipeptidyl-carboxy dipeptidases and exhibit different physiological functions [17]. These two enzymes are broadly spread in the human body, mainly found in the lungs, kidneys, heart, and blood vessels. ACE2 is also present in the gastrointestinal tract [42]. Specifically, ACE2 is not an ACE1 isozyme but a homologous enzyme [43]. Both of them are involved in the synthesis of active components of RAS [44, 45]. When blood pressure drops, the prorenin produced by juxtaglomerular cells in the kidney is converted to renin and enters the bloodstream, converting angiotensinogen secreted by the liver to angiotensin I. Angiotensin I is converted to angiotensin

II by ACE1. Angiotensin II is a peptide that increases blood pressure by narrowing blood vessels (vasoconstriction) and has a pro-inflammatory role. It also stimulates the aldosterone secretion from the adrenal cortical part. Aldosterone increases sodium and water absorption from the renal tubules, thereby increasing blood volume and blood pressure. ACE2 exerts its function by converting angiotensin 1 and 2 to the peptides Ang1-9 and Ang1-7, respectively, which Ang1-9 is also metabolized to Ang1-7, with anti-inflammatory and antioxidant roles [46-48]. If the renin-angiotensin system is abnormally activated, blood pressure will rise excessively. Because the function of this system is different under normal and pathologic situations, including when the cell is infected with the SARS-CoV-2 (Figure 1).

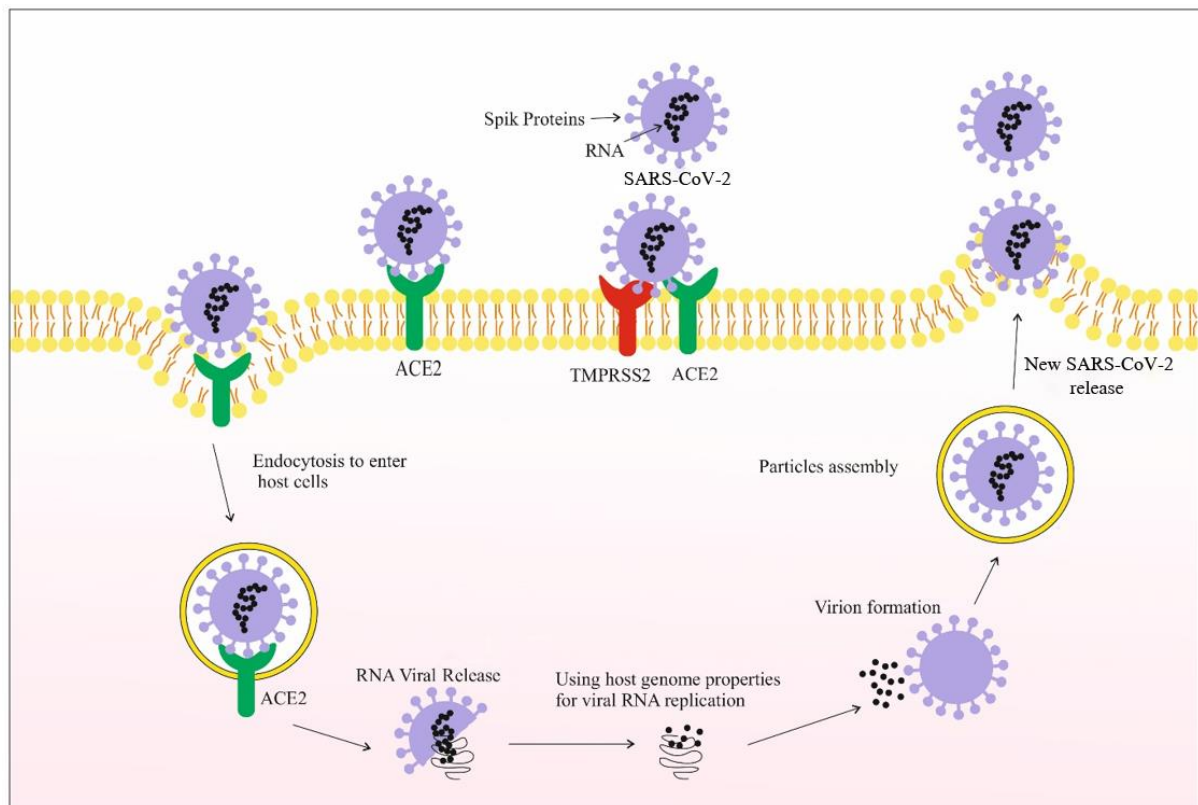


**Figure 1.** The Renin-angiotensin system (RAS) is illustrated under normal and pathologic situations. In normal situations (the left side), Ang II is converted to Ang (1e7) by ACE2, which produces protection conditions. But, in pathologic situations (the right side), Ang (1e7) is not synthesized enough, and Ang II increases and binds to AT1R, which causes the production of pro-inflammatory signals and other consequences, including increased blood pressure.

## 5. SARS-CoV-1 and ACE2

SARS-CoV-1, a member of the coronavirus family, caused the SARS epidemic in 2002-2003. These viruses use ACE2 and TMPRSS2 receptors to enter the host cell (Fig. 2). The viral spike protein is highly glycosylated and spreads on the surface of the virus, giving the appearance of a crown-like to all of them, including SARS-CoV-1 and SARS-CoV-2, and

is a significant factor in the virus binding and entering to the target cells (Figure 2) [6, 49]. In SARS-CoV-1 infection, the attachment of spike protein to the ACE2 receptor causes down-regulation of their expression. This action reduces Ang1-7 and, consequently, lung damage [50]. Thus, the clinical worsening of SARS-CoV-1 may be directly due to the cytopathic effects of the virus or an excessive increase of cytokines. Compared with asymptomatic patients, high levels of pro-inflammatory cytokines (IL-1, IL-6, IL-12, IFN- $\gamma$ , and transforming growth factor  $\beta$ ) and cellular mechanics regulator chemokines (CCL2, CXCL9, CXCL10) and IL-8 in patients with SARS-CoV-1, with a severe clinical condition, has been observed [51, 52].



**Figure 2.** SARS-CoV-2 life cycle and the importance of ACE2 and TMPRSS2 receptors in entering this virus into the cell.

## 6. SARS-CoV-2 and ACE2

The attachment tendency of SARS-CoV-2 to ACE2 is 10-20 times higher than the tendency of SARS-CoV-1 to this receptor. This can signify proper entry and replication and its high transmissibility [15]. These receptors are expressed in almost all body parts to varying degrees. The expression of the receptors in the respiratory system, mainly in alveolar type 2 epithelial cells, is more than the epithelial cells of the oral mucosa, nose, and nasopharynx. This may be why the virus targets the lungs [53, 54]. SARS-CoV-2 infection reduces ACE2 expression and its function, leading to an imbalance between ACE/Ang II/angiotensin II type 1 receptor (AT1R) and ACE2/Ang (1-7)/Mas receptor [50]. Due to the similarity of SARS-CoV-1 and SARS-CoV-2 with each other, SARS-CoV-2 infection may also cause ACE2 downregulation at cell surface area, leading to decreased ACE2 activity and decreased Ang1-7 end product, causing loss of anti-inflammatory activity in infected organs such as the respiratory tract [55]. The virus increases the expression of Ang II, which stimulates cell growth and proliferation of lung fibroblasts [56-58]. ACE2 level acts like a double-edged sword, so increasing its expression may facilitate the COVID-19 probability of infection and

increase the danger of COVID-19 severity and mortality [59, 60]. On the other hand, decreased ACE2 expression causes pulmonary edema and disturbs lung function [26]. Binding of SARS-CoV-1 and possibly SARS-CoV-2 to ACE2 increases the activity of disintegrin and metalloproteinase domain-containing protein 17 (ADAM17), which is also called TNF- $\alpha$  convertase. This enzyme can induce ectodomain shedding of ACE2, produce the soluble receptors, on the one hand, reduce the cellular level of ACE2, and decrease the chance of the virus invading the cell on the other hand [61-63]. The soluble form of ACE2 can theoretically be effective in treating COVID-19 through two mechanisms of action: I) neutralization of the virus by binding the spike protein to the soluble ACE2, II) minimizes damage to various organs such as the lungs, kidneys, and heart. In a test performed after the injection of human recombinant soluble ACE2, it was observed that the amount of Ang II was significantly reduced, and the amount of ACE2 products (Ang1-7 and Ang1-9) was also increased [64-66].

## 7. Relationship between Blood Pressure and COVID-19

COVID-19 in people with high blood pressure due to immune system disorders can be associated with a more severe disease condition. The severity of COVID-19 is related to an increase in cytokines; accordingly, an increase in IL-2, IL-6, and IL-7, granulocyte colony-stimulating factor, CXC motif chemokine 10 (CXCL10), chemokine (CC motif) ligand 2 (CCL2), and TNF- $\alpha$  have been observed in these patients [67, 68]. These cytokines also play a role in causing high blood pressure (Figure 2) [69]. Therefore, it can be claimed that the increase of these cytokines in both hypertension and SARS-CoV-2 infection can make the condition more difficult for COVID-19 patients with hypertension. Lymphopenia is one of the hallmarks of COVID-19. On the other hand, the study shows that high blood pressure is also associated with lymphocytes, so CD4<sup>+</sup> and CD8<sup>+</sup> T cells are reduced in patients with hypertension [70, 71]. Increased generation of pro-inflammatory cytokines in this disease is also an issue that can worsen the clinical condition of patients (Figure 2) [35]. Patients with hypertension mainly use drugs such as renin-angiotensin system (RAS) blockers,  $\beta$ -blocker, calcium channel blockers (CCBs), and diuretics. RAS blockers are primarily utilized as ACE inhibitors (ACEIs) (such as enalapril) and Ang II receptor blockers (ARBs) (such as losartan) for the treatment of hypertension and other heart diseases [72]. With ACEIs, Ang I is increased, and therapy with ARB significantly increases Ang II levels, which can induce ACE2 expression levels and increase its activity in Ang1-7 production, which can affect heart function [42, 73]. Patients treated with ACEIs and ARBs have increased levels of ACE-II expression in their cell membranes, which may increase the rate or susceptibility to SARS-CoV-2 infection and the severity of the disease [68, 74]. On one side, reducing the level of this enzyme in the cell can help to fight infection, but on the other hand, due to the bilateral role of ACE2, the presence of this enzyme protects lung cells from damage caused by the virus by increasing Ang1-7[64]. Therefore, therapeutically, soluble exogenous ACE2 supplements could theoretically be desirable for protection against COVID-19 because they could prevent the interaction of SARS-CoV-2 with endogenous ACE2 [55].

## 8. Conclusions

It can be concluded that COVID-19 has more severe consequences in people with high blood pressure, which due to the binding of the virus to ACE2, reduces its level in the body, especially in the lungs, and increases Ang II as a substance that narrows the arteries, and

reduces Ang1-7, as an anti-inflammatory. This condition results in increased inflammation and lung damage, so by providing adequate oxygen to these patients and reducing inflammation, mortality can be reduced.

## Funding

This research received no external funding.

## Acknowledgments

This study was supported by Tabriz University of Medical Sciences (project numbers 61930 and 65136).

## Conflicts of Interest

The authors declare no conflict of interest.

## References

1. Sabahi, S.; Homayouni Rad, A.; Aghebati-Maleki, L.; Sangtarash, N.; Ozma, M.A.; Karimi, A.; Hosseini, H.; Abbasi, A. Postbiotics as the new frontier in food and pharmaceutical research. *Critical Reviews in Food Science and Nutrition* **2022**, 1-28, <https://doi.org/10.1080/10408398.2022.2056727>.
2. Li, G.; Fan, Y.; Lai, Y.; Han, T.; Li, Z.; Zhou, P.; Pan, P.; Wang, W.; Hu, D.; Liu, X.; Zhang, Q.; Wu, J. Coronavirus infections and immune responses. *Journal of medical virology* **2020**, 92, 424-432, <https://doi.org/10.1002/jmv.25685>.
3. Agirbasli, M. The effects of antihypertensive medications on severity and outcomes of COVID19. *Journal of Human Hypertension* **2022**, 36, 875-879, <https://doi.org/10.1038/s41371-022-00722-9>.
4. Durai, P.; Batool, M.; Shah, M.; Choi, S. Middle East respiratory syndrome coronavirus: transmission, virology and therapeutic targeting to aid in outbreak control. *Experimental & molecular medicine* **2015**, 47, e181, <https://doi.org/10.1038/emm.2015.76>.
5. Ozma, M.A.; Maroufi, P.; Khodadadi, E. et al. Clinical manifestation, diagnosis, prevention and control of SARS-CoV-2 (COVID-19) during the outbreak period. *Infez Med* **2020**, 28, 153-165.
6. Najafi, K.; Maroufi, P.; Khodadadi, E.; Zeinalzadeh, E.; Ganbarov, K.; Asgharzadeh, M.; Kafil, H.S. SARS-CoV-2 receptor ACE2 and molecular pathway to enter target cells during infection. *Reviews & Research Medical Microbiology* **2022**, 33, e105-e113, <https://doi.org/10.1097/MRM.0000000000000237>.
7. Velavan, T.P.; Meyer, C.G. The COVID-19 epidemic. *Tropical Medicine & International Health* **2020**, 25, 278-280, <https://doi.org/10.1111/tmi.13383>.
8. Tang, Q.; Song, Y.; Shi, M.; Cheng, Y.; Zhang, W.; Xia, X. Inferring the hosts of coronavirus using dual statistical models based on nucleotide composition. *Sci. Rep.* **2015**, 5, 17155, <https://doi.org/10.1038/srep17155>.
9. Li, Q.; Guan, X.; Wu, P. et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *New England Journal of Medicine* **2020**, 382, 1199-1207, <https://doi.org/10.1056/nejmoa2001316>.
10. Zhou, P.; Yang, X.-L.; Wang, X.-G. et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **2020**, 579, 270-273, <https://doi.org/10.1038/s41586-020-2012-7>.
11. Riou, J.; Althaus, C.L. Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. *Eurosurveillance* **2020**, 25, 2000058, <https://doi.org/10.2807/1560-7917.es.2020.25.4.2000058>.
12. Lu, R.; Zhao, X.; Li, J. et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet* **2020**, 395, 565-574, [https://doi.org/10.1016/s0140-6736\(20\)30251-8](https://doi.org/10.1016/s0140-6736(20)30251-8).
13. Monteil, V.; Kwon, H.; Prado, P. et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* **2020**, 181, P905-913, <https://doi.org/10.1016/j.cell.2020.04.004>.

14. Battistoni, A.; Volpe, M. Might renin–angiotensin system blockers play a role in the COVID-19 pandemic? *European Heart Journal-Cardiovascular Pharmacotherapy* **2020**, *6*, 248-251, <https://doi.org/10.1093/ehjcvp/pvaa030>.
15. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S. et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* **2020**, *181*, P271-280, <https://doi.org/10.1016/j.cell.2020.02.052>.
16. Rashedi, J.; Poor, B.M.; Asgharzadeh, V.; Pourostadi, M.; Kafil, H.S.; Vegari, A.; Tayebi-Khosroshahi, H.; Asgharzadeh, M. Risk Factors for COVID-19. *Le infezioni in medicina* **2020**, *28*, 469-474.
17. Bavishi, C.; Maddox, T.M.; Messerli, F.H. Coronavirus disease 2019 (COVID-19) infection and renin angiotensin system blockers. *JAMA Cardiology* **2020**, *5*, 745-747, <http://jamanetwork.com/article.aspx?doi=10.1001/jamacardio.2020.1282>.
18. Guan, W.-j.; Ni, Z.-y.; Hu, Y. et al. Clinical characteristics of coronavirus disease 2019 in China. *New England Journal of Medicine* **2020**, *382*, 1708-1720, <https://doi.org/10.1056/nejmoa2002032>.
19. Zu, Z.Y.; Jiang, M.D.; Xu, P.P.; Chen, W.; Ni, Q.Q.; Lu, G.M.; Zhang, L.J. Coronavirus disease 2019 (COVID-19): a perspective from China. *Radiology* **2020**, *296*, 200490, <https://doi.org/10.1148/radiol.2020200490>.
20. Tang, B.; Wang, X.; Li, Q.; Bragazzi, N.L.; Tang, S.; Xiao, Y.; Wu, J. Estimation of the transmission risk of the 2019-nCoV and its implication for public health interventions. *Journal of Clinical Medicine* **2020**, *9*, 462, <https://doi.org/10.3390/jcm9020462>.
21. Ozma, M.A.; Khodadadi, E.; Pakdel, F.; Kamounah, F.S.; Yousefi, M.; Yousefi, B.; Asgharzadeh, M.; Ganbarov, K.; Kafil, H.S. Baicalin, a natural antimicrobial and anti-biofilm agent. *Journal of Herbal Medicine* **2021**, *27*, 100432, <https://doi.org/10.1016/j.hermed.2021.100432>.
22. Abbasi, A.; Rad, A.H.; Ghasempour, Z.; Sabahi, S.; Kafil, H.S.; Hasannezhad, P.; Rahbar Saadat, Y.; Shahbazi, N. The biological activities of postbiotics in gastrointestinal disorders. *Critical Reviews in Food Science and Nutrition* **2022**, *62*, 5983-6004, <https://doi.org/10.1080/10408398.2021.1895061>.
23. Carretero, O.A.; Oparil, S. Essential hypertension: part I: definition and etiology. *Circulation* **2000**, *101*, 329-335, <https://doi.org/10.1161/01.CIR.101.3.329>.
24. Li, J.; Wang, X.; Chen, J.; Zhang, H.; Deng, A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiology* **2020**, *5*, 825-830, <https://doi.org/10.1001/jamacardio.2020.1624>.
25. Reynolds, H.R.; Adhikari, S.; Pulgarin, C. et al. Renin–angiotensin–aldosterone system inhibitors and risk of Covid-19. *New England Journal of Medicine* **2020**, *382*, 2441-2448, <https://doi.org/10.1056/nejmoa2008975>.
26. Imai, Y.; Kuba, K.; Rao, S. et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* **2005**, *436*, 112-116, <https://doi.org/10.1038/nature03712>.
27. Oudit, G.Y.; Liu, G.C.; Zhong, J. et al. Human recombinant ACE2 reduces the progression of diabetic nephropathy. *Diabetes* **2010**, *59*, 529-538, <https://doi.org/10.2337/db09-1218>.
28. Oudit, G.Y.; Herzenberg, A.M.; Kassiri, Z.; Wong, D.; Reich, H.; Khokha, R.; Crackower, M.A.; Backx, P.H.; Penninger, J.M.; Scholey, J.W. Loss of angiotensin-converting enzyme-2 leads to the late development of angiotensin II-dependent glomerulosclerosis. *The American Journal of Pathology* **2006**, *168*, 1808-1820, <https://doi.org/10.2353/ajpath.2006.051091>.
29. Marik, P.E.; Varon, J. Hypertensive crises: challenges and management. *Chest* **2007**, *131*, 1949-1962, <https://doi.org/10.1378/chest.06-2490>.
30. Ozma, M.A.; Abbasi, A.; Ahangarzadeh Rezaee, M.; Hosseini, H.; Hosseinzadeh, N.; Sabahi, S.; Noori, S.M.A.; Sepor deh, S.; Khodadadi, E.; Lahouty, M.; Kafil, H.S. A Critical Review on the Nutritional and Medicinal Profiles of Garlic's (*Allium sativum* L.) Bioactive Compounds. *Food Reviews International* **2022**, *1*-38, <https://doi.org/10.1080/87559129.2022.2100417>.
31. Mian, M.O.R.; Paradis, P.; Schiffrin, E.L. Innate immunity in hypertension. *Current Hypertension Reports* **2014**, *16*, 413, <https://doi.org/10.1007/s11906-013-0413-9>.
32. Norlander, A.E.; Madhur, M.S.; Harrison, D.G. The immunology of hypertension. *Journal of Experimental Medicine* **2018**, *215*, 21-33, <https://doi.org/10.1084/jem.20171773>.
33. Ozma, M.A.; Khodadadi, E.; Rezaee, M.A.; Asgharzadeh, M.; Aghazadeh, M.; Zeinalzadeh, E.; Ganbarov, K.; Kafil, H.S. Bacterial Proteomics and its Application in Pathogenesis Studies. *Current Pharmaceutical Biotechnology* **2022**, *23*, 1245-1256, <https://doi.org/10.2174/1389201022666210908153234>.

34. LI, J.-j. Inflammation in hypertension: primary evidence. *Chinese Medical Journal* **2006**, *119*, 1215-1221, <https://doi.org/10.5555/cmj.0366-6999.119.14.p1215.01>.
35. Itani, H.A.; McMaster Jr, W.G.; Saleh, M.A. et al. Activation of human T cells in hypertension: studies of humanized mice and hypertensive humans. *Hypertension* **2016**, *68*, 123-132, <https://doi.org/10.1161/hypertensionaha.116.07237>.
36. Asgharzadeh, M.; Ozma, M.A.; Rashedi, J.; Poor, B.M.; Agharzadeh, V.; Vegari, A.; Shokouhi, B.; Ganbarov, K.; Ghalehlou, N.N.; Leylabadlo, H.E.; Kafil, H.S. False-positive Mycobacterium tuberculosis detection: Ways to prevent cross-contamination. *Tuberculosis and Respiratory Diseases* **2020**, *83*, 211-217, <https://doi.org/10.4046/trd.2019.0087>.
37. Zaki, N.; Alashwal, H.; Ibrahim, S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review. *Diabetes & Metabolic Syndrome: Clinical Research & Reviews* **2020**, *14*, 1133-1142, <https://doi.org/10.1016%2Fj.dsx.2020.07.005>.
38. Ozma, M.A.; Lahouty, M.; Abbasi, A.; Rezaee, M.A.; Kafil, H.S.; Asgharzadeh, M. Effective Bacterial Factors Involved in the Dissemination of Tuberculosis. *BRIAC* **2022**, *13*, 234, <https://doi.org/10.33263/BRIAC133.234>.
39. Ozma, M.A.; Rashedi, J.; Poor, B.M.; Vegari, A.; Asgharzadeh, V.; Kafil, H.S.; Kazemi, A.; Sahebi, L.; Asgharzadeh, M. Tuberculosis and diabetes mellitus in Northwest of Iran. *Infectious Disorders-Drug Targets* **2020**, *20*, 667-671, <https://doi.org/10.2174/1871526519666190715142100>.
40. Hampl, V.; Herget, J.; Bíbová, J.; Baňasová, A.; Husková, Z.; Vaňourková, Z.; Jíchová, Š.; Kujal, P.; Vernerová, Z.; Sadowski, J.; Cervenka, L. Intrapulmonary activation of the angiotensin-converting enzyme type 2/angiotensin 1-7/G-protein-coupled Mas receptor axis attenuates pulmonary hypertension in Ren-2 transgenic rats exposed to chronic hypoxia. *Physiol. Res.* **2015**, *64*, 25-38, <https://doi.org/10.33549/physiolres.932861>.
41. Ozma, M.A.; Abbasi, A.; Akrami, S. et al. Postbiotics as the key mediators of the gut microbiota-host interactions. *Le Infezioni in Medicina* **2022**, *30*, 180-193, <https://doi.org/10.53854/liim-3002-3>.
42. Li, G.; Hu, R.; Zhang, X. Antihypertensive treatment with ACEI/ARB of patients with COVID-19 complicated by hypertension. *Hypertension Research* **2020**, *43*, 588-590, <https://doi.org/10.1038/s41440-020-0433-1>.
43. Soler, M.J.; Barrios, C.; Oliva, R.; Batlle, D. Pharmacologic modulation of ACE2 expression. *Current Hypertension Reports* **2008**, *10*, 410-414, <https://doi.org/10.1007/s11906-008-0076-0>.
44. Reddy Gaddam, R.; Chambers, S.; Bhatia, M. ACE and ACE2 in inflammation: a tale of two enzymes. *Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy)* **2014**, *13*, 224-234, <https://doi.org/10.2174/1871528113666140713164506>.
45. Matsuzawa, Y.; Kimura, K.; Ogawa, H.; Tamura, K. Impact of renin–angiotensin–aldosterone system inhibitors on COVID-19. *Hypertension Research* **2022**, *45*, 1147-1153, <https://doi.org/10.1038/s41440-022-00922-3>.
46. Bosso, M.; Thanaraj, T.A.; Abu-Farha, M.; Alanbaei, M.; Abubaker, J.; Al-Mulla, F. The two faces of ACE2: the role of ACE2 receptor and its polymorphisms in hypertension and COVID-19. *Molecular Therapy-Methods & Clinical Development* **2020**, *18*, P321-327, <https://doi.org/10.1016%2Fj.omtm.2020.06.017>.
47. Tikellis, C.; Bernardi, S.; Burns, W.C. Angiotensin-converting enzyme 2 is a key modulator of the renin–angiotensin system in cardiovascular and renal disease. *Current Opinion in Nephrology and Hypertension* **2011**, *20*, 62-68, <https://doi.org/10.1097/mnh.0b013e328341164a>.
48. Rocheleau, G.L.; Lee, T.; Mohammed, Y. et al. Renin-Angiotensin System Pathway Therapeutics Associated With Improved Outcomes in Males Hospitalized With COVID-19. *Critical Care Medicine* **2022**, *50*, 1306-1317, <https://doi.org/10.1097/ccm.0000000000005589>.
49. Chung, M.K.; Karnik, S.; Saef, J. et al. SARS-CoV-2 and ACE2: The biology and clinical data settling the ARB and ACEI controversy. *eBioMedicine* **2020**, *58*, 102907, <https://doi.org/10.1016/j.ebiom.2020.102907>.
50. Kuba, K.; Imai, Y.; Rao, S. et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus–induced lung injury. *Nature Medicine* **2005**, *11*, 875-879, <https://doi.org/10.1038/nm1267>.
51. Wong, C.; Lam, C.; Wu, A.; Ip, W.; Lee, N.; Chan, I.; Lit, L.; Hui, D.; Chan, M.; Chung, S. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. *Clin. & Exp. Immunol.* **2004**, *136*, 95–103, <https://doi.org/10.1111/j.1365-2249.2004.02415.x>.
52. Huang, K.J.; Su, I.J.; Theron, M.; Wu, Y.C.; Lai, S.K.; Liu, C.C.; Lei, H.Y. An interferon-γ-related cytokine storm in SARS patients. *Journal of Medical Virology* **2005**, *75*, 185-194, <https://doi.org/10.1002/jmv.20255>.

53. Hamming, I.; Timens, W.; Bulthuis, M.; Lely, A.; Navis, G.v.; van Goor, H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. *The Journal of Pathology* **2004**, *203*, 631-637, <https://doi.org/10.1002/path.1570>.
54. Zou, X.; Chen, K.; Zou, J.; Han, P.; Hao, J.; Han, Z. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. *Frontiers of Medicine* **2020**, *14*, 185-192, <https://doi.org/10.1007/s11684-020-0754-0>.
55. Shibata, S.; Arima, H.; Asayama, K. et al. Hypertension and related diseases in the era of COVID-19: a report from the Japanese Society of Hypertension Task Force on COVID-19. *Hypertension Research* **2020**, *43*, 1028-1046, <https://doi.org/10.1038/s41440-020-0515-0>.
56. Marshall, R.P.; McAnulty, R.J.; Laurent, G.J. Angiotensin II is mitogenic for human lung fibroblasts via activation of the type 1 receptor. *American Journal of Respiratory and Critical Care Medicine* **2000**, *161*, 1999-2004, <https://doi.org/10.1164/ajrccm.161.6.9907004>.
57. Wang, Z.; Xiang, L.; Lin, F.; Cai, Z.; Ruan, H.; Wang, J.; Liang, J.; Wang, F.; Lu, M.; Cui, W. Inhaled ACE2-engineered microfluidic microsphere for intratracheal neutralization of COVID-19 and calming of the cytokine storm. *Matter* **2022**, *5*, 336-362, <https://doi.org/10.1016/j.matt.2021.09.022>.
58. Bakhshandeh, B.; Sorboni, S.G.; Javanmard, A.-R.; Mottaghi, S.S.; Mehrabi, M.-R.; Sorouri, F.; Abbasi, A.; Jahanafrooz, Z. Variants in ACE2; potential influences on virus infection and COVID-19 severity. *Infection, Genetics and Evolution* **2021**, *90*, 104773, <https://doi.org/10.1016/j.meegid.2021.104773>.
59. Fang, L.; Karakiulakis, G.; Roth, M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet. Respiratory Medicine* **2020**, *8*, E21, [https://doi.org/10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8).
60. Rashedi, J.; Poor, M.B.; Asgharzadeh, M. Sodium Bicarbonate Nebulized Therapy in Patients with Confirmed COVID-19. *Advanced Pharmaceutical Bulletin* **2021**, *11*, 397-398, <https://doi.org/10.34172/apb.2021.047>.
61. Haga, S.; Yamamoto, N.; Nakai-Murakami, C.; Osawa, Y.; Tokunaga, K.; Sata, T.; Yamamoto, N.; Sasazuki, T.; Ishizaka, Y. Modulation of TNF- $\alpha$ -converting enzyme by the spike protein of SARS-CoV and ACE2 induces TNF- $\alpha$  production and facilitates viral entry. *Proceedings of the National Academy of Sciences* **2008**, *105*, 7809-7814, <https://doi.org/10.1073/pnas.0711241105>.
62. Patel, V.B.; Clarke, N.; Wang, Z.; Fan, D.; Parajuli, N.; Basu, R.; Putko, B.; Kassiri, Z.; Turner, A.J.; Oudit, G.Y. Angiotensin II induced proteolytic cleavage of myocardial ACE2 is mediated by TACE/ADAM-17: a positive feedback mechanism in the RAS. *Journal of Molecular and Cellular Cardiology* **2014**, *66*, 167-176, <https://doi.org/10.1016/j.yjmcc.2013.11.017>.
63. Gheware, A.; Ray, A.; Rana, D. et al. ACE2 protein expression in lung tissues of severe COVID-19 infection. *Scientific Reports* **2022**, *12*, 4058, <https://doi.org/10.1038/s41598-022-07918-6>.
64. Zoufaly, A.; Poglitsch, M.; Aberle, J.H. et al. Human recombinant soluble ACE2 in severe COVID-19. *The Lancet Respiratory Medicine* **2020**, *8*, 1154-1158, [https://doi.org/10.1016/s2213-2600\(20\)30418-5](https://doi.org/10.1016/s2213-2600(20)30418-5).
65. Saengsiwaritt, W.; Jittikoon, J.; Chaikledkaew, U.; Udomsinprasert, W. Genetic polymorphisms of ACE1, ACE2, and TMPRSS2 associated with COVID-19 severity: A systematic review with meta-analysis. *Reviews in Medical Virology* **2022**, *32*, e2323, <https://doi.org/10.1002/rmv.2323>.
66. Fagyas, M.; Fejes, Z.; Sütő, R. et al. Circulating ACE2 activity predicts mortality and disease severity in hospitalized COVID-19 patients. *International Journal of Infectious Diseases* **2022**, *115*, 8-16, <https://doi.org/10.1016/j.ijid.2021.11.028>.
67. Huang, C.; Wang, Y.; Li, X. et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* **2020**, *395*, P497-506, [https://doi.org/10.1016/s0140-6736\(20\)30183-5](https://doi.org/10.1016/s0140-6736(20)30183-5).
68. Abbasi, A.; Kafil, H.S.; Ozma, M.A.; Sangtarash, N.; Sabahi, S. Can food matrices be considered as a potential carrier for COVID-19? *Le Infezioni in Medicina* **2022**, *30*, 59-72, <https://doi.org/10.53854/2Fliim-3001-7>.
69. Carnevale, D.; Wenzel, P. Mechanical stretch on endothelial cells interconnects innate and adaptive immune response in hypertension. *Cardiovasc. Res.* **2018**, *114*, 1432-1434, <https://doi.org/10.1093/cvr/cvy148>.
70. Sereti, E.; Stamatelopoulos, K.S.; Zakopoulos, N.A.; Evangelopoulou, A.; Mavragani, C.P.; Evangelopoulos, M.E. Hypertension: An immune related disorder? *Clinical Immunology* **2020**, *212*, 108247, <https://doi.org/10.1016/j.clim.2019.108247>.
71. Oosthuizen, D.; Sturrock, E.D. Exploring the Impact of ACE Inhibition in Immunity and Disease. *Journal of the Renin-Angiotensin-Aldosterone System* **2022**, *2022*, 9028969, <https://doi.org/10.1155/2022/9028969>.

72. Huang, Z.; Cao, J.; Yao, Y. et al. The effect of RAS blockers on the clinical characteristics of COVID-19 patients with hypertension. *Annals of Translational Medicine* **2020**, *8*, 430, <https://doi.org/10.21037/atm.2020.03.229>.
73. Sultan, R.H.; Abdallah, M.; Ali, T.M.; Ahmed, A.E.; Assal, H.H.; Elesawy, B.H.; Ahmed, O.M. The Associations between Cytokine Levels, Kidney and Heart Function Biomarkers, and Expression Levels of Angiotensin-Converting Enzyme-2 and Neuropilin-1 in COVID-19 Patients. *Vaccines* **2022**, *10*, 1045, <https://doi.org/10.3390/vaccines10071045>.
74. Speth, R.C. Response to recent commentaries regarding the involvement of angiotensin-converting enzyme 2 (ACE2) and renin-angiotensin system blockers in SARS-CoV-2 infections. *Drug Development Research* **2020**, *81*, 643-646, <https://doi.org/10.1002/ddr.21672>.