ACE2 and SARS-CoV-2

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Angiotensin-Converting Enzyme 2 (ACE2) is an essential enzyme in the renin-angiotensin system (RAS), effectively maintaining RAS equilibrium. Recently, scientists have also found that through the mediation of the S protein, SARS-CoV-2 can invade host cells using ACE2 as the target.

Keywords: SARS-CoV-2 ; ACE2

1. Introduction

In December 2019, pneumonia outbreaks with unexpected results occurred throughout the world. Scientists subsequently identified a novel coronavirus, which lifted the veil of this infectious viral pneumonia [1][2]. This novel coronavirus pneumonia caused widespread concern throughout the world. In February 2020, the International Committee on Taxonomy of Viruses gave this coronavirus an official name, “SARS-CoV-2.” At the same time, the World Health Organization (WHO) named it “coronavirus disease 2019 (COVID-19)” [3][4]. This epidemic has now spread to all parts of the world. As of 18 January 2021, the confirmed total number of COVID-19 cases reached 93,805,612 globally, and the total number of deaths was 2,026,093 [5]. These figures continue to rise each day and bring a serious threat to human health, social and economic development, and the global medical and public health system. Scientists around the world are actively developing effective treatment strategies, focusing on vaccines and antiviral agents. The most frequently used antiviral agents include chloroquine, hydroxychloroquine, and remdesivir. Among them, the more in-depth studies are focusing on remdesivir.

Remdesivir belongs to inhibitors of viral RNA polymerase/RNA synthesis; it has a broad spectrum antiviral activity against several viruses [6][7][8]. Replication of SARS-CoV-2 requires the viral RNA-dependent RNA polymerase (RdRp) enzyme, a target of remdesivir. It has shown in vitro activity against SARS-CoV-2. Remdesivir appears to have a favorable clinical safety profile [9]. SARS-CoV-2 can enter the body through glycoprotein recognition, and this process can be blocked by vaccines. When the vaccines act on the body, they can induce the body to produce neutralizing antibodies targeting glycoprotein and block the virus from entering the host cells. Previously, a variety of vaccines had been designed based on SARS-CoV and MERS-CoV, among which the vaccines entering clinical trials included inactivated virus vaccine, nucleic acid vaccine, and vector vaccine [10][11][12][13]. Recently, some SARS-CoV-2 vaccines have been developed, and their efficacy and safety have been preliminarily proved. These vaccines mainly include nucleic acid vaccines BNT162b2 mRNA and mRNA-1273 [14][15]. Collectively, safe and effective vaccines and antiviral drugs are the most effective measure to curb the spread of the virus. Therefore, further exploration of the molecular mechanism of SARS-CoV-2 infection can better deal with its infection risk.

SARS-CoV-2, SARS-CoV, and Middle East respiratory syndrome coronavirus (MERS-CoV) belong to the Betacoronavirus genus, which are positive single-stranded RNA viruses that can infect a large number of mammals, including humans [16]. Research is currently ongoing concerning SARS-CoV-2 pathogenic mechanisms. More specifically, studies on angiotensin-converting enzyme 2 (ACE2) as an invasion target have received widespread attention. Considering the degree of high homology in gene sequences of SARS-CoV and SARS-CoV-2 [17], researchers have used computer-guided homology modeling to confirm further that the spike (S) protein amino acid sequences are 76.5% homologous between the two viruses, which also share an almost identical three-dimensional structure in their receptor-binding domain (RBD) and maintain similar van der Waals forces and electrostatic relationships in their interactions [18]. Previous investigations illustrate that the spike protein has a high binding affinity for ACE2 [19]. Recently, scientists have also found that through the mediation of the S protein, SARS-CoV-2 can invade host cells using ACE2 as the target [2][20]. ACE2 is an essential enzyme in the renin-angiotensin system (RAS), effectively maintaining RAS equilibrium [21]. RAS balance is widely recognized as critical to maintaining normal heart function. Researchers have recently employed single-cell RNA sequencing technology to analyze ACE2 expression in various human organs and cells. They found that ACE2 is not only highly expressed in type II alveolar epithelial cells and lower respiratory tract mucosal epithelial cells but also in the myocardium, vascular endothelial cells, ileal and esophageal epithelium, proximal renal tubules, and bladder epithelial

cells, suggesting that the heart is also a high-risk target for SARS-CoV-2 infection [22]. From clinical practice, 29.3–45.7% of COVID-19 patients have associated cardiac injury, which is closely related to the case fatality rate [23][24][25]. The underlying mechanism for cardiac injury may be related to ACE2 depletion caused by direct SARS-CoV-2 binding with ACE2, thus leading to RAS imbalance. It might also be related to the indirect triggering of cytokine storm, yet the specific underlying mechanisms are currently unknown [26][27].

2. Therapeutic Strategies Using ACE2 as a Potential Target

There are currently no effective and specific therapeutic strategies for SARS-CoV-2 treatment. Many treatment options may be derived by summarizing the treatment experiences for SARS and MERS. The primary research and development (R&D) strategy is the screening of existing broad-spectrum antiviral drugs and further developing drugs that can simultaneously target the virus and the host [28][29][30][31][32]. Previous studies have found that SARS-CoV-2 may invade host cells via ACE2 receptors, which has provided many targets for the R&D of treatments and SARS-CoV-2 vaccines, including the blockade of the SARS-CoV-2 S protein binding with ACE2 receptors via the application of ACE inhibitors, among other strategies [33][34][35].

Several glycosylation sites can be found in the extracellular structure of ACE2 expressed in mammalian cells. The glycosylation of these sites may affect SARS-CoV-2 S protein binding with the ACE2 receptor, providing us with new strategies to block SARS-CoV-2 S protein binding with the ACE2 receptor [36]. Additionally, recent studies have discovered that chloroquine can block viral infection through the improvement of endosomal pH required for virus/cell fusion and interfere with ACE2 terminal glycosylation [31][37]. Furthermore, China has listed chloroquine phosphate as a therapeutic drug for COVID-19 patients in the “Diagnosis and Treatment Protocol for Coronavirus Disease 2019 (Trial Version 7)” and has included this drug in large-scale clinical trials [38]. Several medical teams in China and abroad have developed ACE2 antibodies, S protein antibodies, and others based on the blockade of binding between the ACE2 receptor and the SARS-CoV-2 S protein [33][34][35][39]. At present, there is still much controversy surrounding the use of ACE inhibitor-like drugs in patients with cardiac injury after SARS-CoV-2 infection. There are two main types of ACE inhibitor-like drugs that have received significant attention: angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB). SARS-CoV-2 infection can lead to decreased ACE2, an imbalance between the ratio of ACE and ACE2, an absolute or relative increase in Ang II, and an over-activation of AT1R, which can result in impaired cardiac function. ACEI and ARB may inhibit the above pathophysiological changes and improve cardiac injury after SARS-CoV-2 infection [40][41][42].

Meanwhile, some reports revealed that the use of common classes of antihypertensive medications did not increase the risk of positive or severe COVID-19 [43][44][45]. These data support the continuation of existing treatment for patients with hypertension during the COVID-19 pandemic. There are also some contrary views: some studies revealed that although administering hypertensive rats with ACEI/ARB can reduce their blood pressure, their ACE2 levels were elevated by 4.7- and 2.8-fold, respectively. This means the application of ACEI/ARB may increase ACE2 negative feedback and increase infection risk [46]. Liu et al. argued that the application of ACE inhibitor-like drugs might increase cells’ susceptibility to viral invasion or worsen the disease [47]. This supposition is because ACE inhibitors can lead to an increase in bradykinin levels, which can lead to vasodilation and lower blood pressure, as well as causing edema and exacerbating the inflammatory response.

In summary, the application of ACE inhibitor-like drugs after SARS-CoV-2 infection, especially in patients with cardiac injury, still requires support from a large amount of clinical data to validate these conclusions.

3. Outlook

The epidemic caused by SARS-CoV-2 infection has achieved global focus. The WHO has also designated this viral epidemic as a significant global public health emergency. However, thus far, our understanding of SARS-CoV-2 is only the “tip of the iceberg.” Many researchers have reported that the SARS-CoV-2 sequence identity is at most 88% homologous with bat-derived coronaviruses, suggesting that bats may be a natural host [1][48]. Subsequently, researchers from the South China University of Technology found through the analysis of more than 1000 metagenomic samples that pangolins may also be a candidate intermediate SARS-CoV-2 host [49]. The primary sources of SARS-CoV-2 infection are persons infected with this virus. The main transmission routes are via respiratory droplets and contact transmission, with high population susceptibility [50][51]. Concerning SARS-CoV-2 infection pathogenesis, current studies were combined with the existing literature to conclude that SARS-CoV-2 invades host cells via the mediation of the S protein targeting ACE2. Many experimental studies and reports of clinical symptoms in patients with COVID-19 suggest that the heart is a potential target organ for SARS-CoV-2 infection. Moreover, the mechanism of cardiac injury may be caused directly by

ACE2 depletion resulting from SARS-CoV-2 binding with ACE2 and indirectly by a cytokine storm. It is hoped that the findings of the above studies will provide new directions for the future development of ACE2 as a therapeutic target for cardiac injury after SARS-CoV-2 infection, as well as for related vaccines.

Based on a large number of reported clinical cases of SARS-CoV-2, we found that in addition to cardiac and pulmonary injury, SARS-CoV-2 infection might also lead to kidney, liver, gastrointestinal tract, testicular, and even ocular injury. This damage may be due to the organ and cell specificity of ACE2 distribution, such that SARS-CoV-2 can attack multiple organs using ACE2 as a target [22][52]. It may also be related to the immune defense mechanisms, whereby the intensity of the immune response varies from individual to individual, and some studies have shown that autoimmune attack may also cause multiple organ injuries. This response will be a key focus in future research [53]. The mechanism of cardiac injury after SARS-CoV-2 infection remains unclear. Apart from the mechanism involving ACE2 as the target of invasion, which is highlighted in this review, there may be many other mechanisms involved, such as the series of pathophysiological changes induced by hypoxemia, leading to cardiac injury. Disorders of pulmonary gas exchange in patients with COVID-19 may lead to hypoxemia, while acidosis, oxidative stress, and induced inflammatory reactions during hypoxia and reperfusion can exacerbate cardiac injury [54]. Finally, among patients infected with SARS-CoV-2, 50% have chronic underlying diseases, such as hypertension, heart disease, and diabetes. These patients are more prone to develop severe diseases. During the treatment of these patients, SARS-CoV-2 infection was only the initial illness, and the final causes of death are often heart failure and multiple organ dysfunction [25][55][56]. Therefore, we should be more vigilant when it comes to the cardiac condition of COVID-19 patients in clinical practice, complying with the principles of individualization in the application and selection of ACE inhibitor-like drugs for these patients.

Of course, safe and effective vaccines are also urgently needed. As we know, it is not feasible for COVID-19 to obtain group immunity through human infection. In the development process of new crown vaccines, researchers are facing a variety of problems and challenges, such as the weak immunogenicity of a single dose vaccine, incomplete virus inactivation, disease risk, and safe mass production. However, we believe that with the development of effective vaccines and antiviral drugs we will eventually defeat SARS-CoV-2 infection.

References

1. Zhu, N.; Zhang, D.; Wang, W.; Li, X.; Yang, B.; Song, J.; Zhao, X.; Huang, B.; Shi, W.; Lu, R.; et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N. Engl. J. Med. 2020, 382, 727–733.
2. Wu, F.; Zhao, S.; Yu, B.; Chen, Y.-M.; Wang, W.; Song, Z.-G.; Hu, Y.; Tao, Z.-W.; Tian, J.-H.; Pei, Y.-Y.; et al. A new coronavirus associated with human respiratory disease in China. Nature 2020, 579, 265–269.
3. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acutrespiratory syndrome-related coronavirus: Classifying 2019-nCoV and naming it SARS-CoV-2. Nat. Microbiol. 2020, 5, 536–544.
4. Jiang, S.; Shi, Z.; Shu, Y.; Song, J.; Gao, G.F.; Tan, W.; Guo, D. A distinct name is needed for the new coronavirus. Lancet 2020, 395, 949.
5. World Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. WHO Health Emergency Dashboard, 18 January 2021.
6. Agostini, M.L.; Andres, E.L.; Sims, A.C.; Graham, R.L.; Sheahan, T.P.; Lu, X.; Smith, E.C.; Case, J.B.; Feng, J.Y.; Jordan, R.; et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio 2018, 9, e00221-18.
7. Lo, M.K.; Jordan, R.; Arvey, A.; Sudhamsu, J.; Shrivastava-Ranjan, P.; Hotard, A.L.; Flint, M.; McMullan, L.K.; Siegel, D.; Clarke, M.O.; et al. GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. Sci. Rep. 2017, 7, srep43395.
8. Sheahan, T.P.; Sims, A.C.; Graham, R.L.; Menachery, V.D.; Gralinski, L.E.; Case, J.B.; Leist, S.R.; Pyrc, K.; Feng, J.Y.; Trantcheva, I.; et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci. Transl. Med. 2017, 9, eaal3653.
9. Grein, J.; Ohmagari, N.; Shin, D.; Diaz, G.; Asperges, E.; Castagna, A.; Feldt, T.; Green, G.; Green, M.L.; Lescure, F.-X.; et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N. Engl. J. Med. 2020, 382, 2327–2336.
10. Jackson, L.A.; Anderson, E.J.; Rouphael, N.G.; Roberts, P.C.; Makhene, M.; Coler, R.N.; McCullough, M.P.; Chappell, J.D.; Denison, M.R.; Stevens, L.J.; et al. An mRNA Vaccine against SARS-CoV-2—Preliminary Report. N. Engl. J. Med. 2020, 383, 1920–1931.

11. Smith, T.R.F.; Patel, A.; Ramos, S.; Elwood, D.; Zhu, X.; Yan, J.; Gary, E.N.; Walker, S.N.; Schultheis, K.; Purwar, M.; et al. Immunogenicity of a DNA vaccine candidate for COVID-19. Nat. Commun. 2020, 11, 2601.
12. Wang, H.; Zhang, Y.; Huang, B.; Deng, W.; Quan, Y.; Wang, W.; Xu, W.; Zhao, Y.; Li, N.; Zhang, J.; et al. Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2. Cell 2020, 182, 713–721.e9.
13. Zhang, N.-N.; Li, X.-F.; Deng, Y.-Q.; Zhao, H.; Huang, Y.-J.; Yang, G.; Huang, W.-J.; Gao, P.; Zhou, C.; Zhang, R.-R.; et al. A Thermostable mRNA Vaccine against COVID-19. Cell 2020, 182, 1271–1283.e16.
14. Polack, F.P.; Thomas, S.J.; Kitchin, N.; Absalon, J.; Gurtman, A.; Lockhart, S.; Perez, J.L.; Marc, G.P.; Moreira, E.D.; Zerbini, C.; et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N. Engl. J. Med. 2020, 383, 2603–2615.
15. Baden, L.R.; El Sahly, H.M.; Essink, B.; Kotloff, K.; Frey, S.; Novak, R.; Diemert, D.; Spector, S.A.; Rouphael, N.; Creech, C.B.; et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N. Engl. J. Med. 2020.
16. Chen, Y.; Liu, Q.; Guo, D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J. Med. Virol. 2020, 92, 418–423.
17. Lu, R.; Zhao, X.; Li, J.; Niu, P.; Yang, B.; Wu, H.; Wang, W.; Song, H.; Huang, B.; Zhu, N.; et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet 2020, 395, 565–574.
18. Xu, X.; Chen, P.; Wang, J.; Feng, J.; Zhou, H.; Li, X.; Zhong, W.; Hao, P. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci. China Life Sci. 2020, 63, 457–460.
19. Yin, Y.; Wunderink, R.G. MERS, SARS and other coronaviruses as causes of pneumonia. Respirology 2017, 23, 130–137.
20. Zhou, P.; Yang, X.-L.; Wang, X.-G.; Hu, B.; Zhang, L.; Zhang, W.; Si, H.-R.; Zhu, Y.; Li, B.; Huang, C.-L.; et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020, 579, 270–273.
21. Zhang, H.; Penninger, J.M.; Li, Y.; Zhong, N.; Slutsky, A.S. Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. Intensive Care Med. 2020, 46, 586–590.
22. Zou, X.; Chen, K.; Zou, J.; Han, P.; Hao, J.; Han, Z.-G. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Front. Med. 2020, 14, 185–192.
23. Lake, M.A. What we know so far: COVID-19 current clinical knowledge and research. Clin. Med. 2020, 20, 124–127.
24. Zhou, F.; Yu, T.; Du, R.; Fan, G.; Liu, Y.; Liu, Z.; Xiang, J.; Wang, Y.; Song, B.; Gu, X.; et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet 2020, 395, 1054–1062.
25. Deng, S.-Q.; Peng, H.-J. Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China. J. Clin. Med. 2020, 9, 575.
26. Hoffmann, M.; Kleine-Weber, H.; Schroeder, S.; Krüger, N.; Herrler, T.; Erichsen, S.; Schiergens, T.S.; Herrler, G.; Wu, N.H.; Nitsche, A.; et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020, 181, 271–280.
27. Shereen, M.A.; Khan, S.; Kazmi, A.; Bashir, N.; Siddique, R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J. Adv. Res. 2020, 24, 91–98.
28. Zhang, L.; Liu, Y. Potential interventions for novel coronavirus in China: A systematic review. J. Med. Virol. 2020, 92, 479–490.
29. Wang, M.; Cao, R.; Zhang, L.; Yang, X.; Liu, J.; Xu, M.; Shi, Z.; Hu, Z.; Zhong, W.; Xiao, G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020, 30, 269–271.
30. Lu, H. Drug Treatment Options for the 2019-new Coronavirus (2019-nCoV). Biosci. Trends 2020, 14, 69–71.
31. Cunningham, A.C.; Goh, H.P.; Koh, D. Treatment of COVID-19: Old tricks for new challenges. Crit. Care 2020, 24, 1–2.
32. Baden, L.R.; Rubin, E.J. Covid-19—The Search for Effective Therapy. N. Engl. J. Med. 2020, 382, 1851–1852.
33. Gurwitz, D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev. Res. 2020, 81, 537–540.
34. Ahmed, S.F.; Quadeer, A.A.; McKay, M.R. Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies. Viruses 2020, 12, 254.

35. Dhama, K.; Sharun, K.; Tiwari, R.; Dadar, M.; Malik, Y.S.; Singh, K.P.; Chaicumpa, W. COVID-19, an emerging coronavirus infection: Advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics. Hum. Vaccines Immunother. 2020, 16, 1232–1238.

36. Yan, R.; Zhang, Y.; Li, Y.; Xia, L.; Guo, Y.; Zhou, Q. Structural Basis for the Recognition of SARS-CoV-2 by Full-Length Human ACE2. Science 2020, 367, 1444–1448.

37. Gautret, P.; Lagier, J.C.; Parola, P.; Hoang, V.T.; Meddeb, L.; Mailhe, M.; Doudier, B.; Courjon, J.; Giordanengo, V.; Vieira, V.E.; et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 2020, 56, 105949.

38. Gao, J.; Tian, Z.; Yang, X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci. Trends 2020, 14, 72–73.

39. Shanmugaraj, B.; Siriwattananon, K.; Wangkanont, K.; Phoolcharoen, W. Perspectives on Monoclonal Antibody Therapy as PotentialTherapeutic Intervention for Coronavirus disease-19 (COVID-19). Asian Pac. J. Allergy Immunol. 2020, 38, 10–18.

40. Koka, V.; Huang, X.R.; Chung, A.C.; Wang, W.; Truong, L.D.; Lan, H.Y. Angiotensin II Up-Regulates Angiotensin I-Converting Enzyme (ACE), but Down-Regulates ACE2 via the AT1-ERK/p38 MAP Kinase Pathway. Am. J. Pathol. 2008, 172, 1174–1183.

41. Henry, C.; Zaizafoun, M.; Stock, E.; Ghamande, S.A.; Arroliga, A.C.; White, H.D. Impact of angiotensin-converting enzyme inhibitors and statins on viral pneumonia. Bayl. Univ. Med. Cent. Proc. 2018, 31, 419–423.

42. Soto, M.; Bang, S.I.; McCombs, J.; Rodgers, K.E. Renin Angiotensin system-modifying therapies are associated with improved pulmonary health. Clin. Diabetes Endocrinol. 2017, 3.

43. Fosbøl, E.L.; Butt, J.H.; Østergaard, L.; Andersson, C.; Selmer, C.; Kragholm, K.; Schou, M.; Phelps, M.; Gislason, G.H.; Gerds, T.A.; et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use with COVID-19 Diagnosis and Mortality. JAMA 2020, 324, 168–177.

44. 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 Cardiol. 2020, 5, 825.

45. Reynolds, H.R.; Adhikari, S.; Pulgarin, C.; Troxel, A.B.; Iturrate, E.; Johnson, S.B.; Hausvater, A.; Newman, J.D.; Berger, J.S.; Bangalore, S.; et al. Renin-Angiotensin-Aldosterone System Inhibitors and Risk of Covid-19. N. Engl. J. Med. 2020, 382, 2441–2448.

46. Ferrario, C.M.; Jessup, J.; Chappell, M.C.; Averill, D.B.; Brosnihan, K.; Bridget Tallant, E.; Ann Diz Debra, I.; Gallagher Patricia, E. Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2. Circulation 2005, 111, 2605–2610.

47. Sodhi, C.P.; Wohlford-Lenane, C.; Yamaguchi, Y.; Prindle, T.; Fulton, W.B.; Wang, S.; McCray, P.B., Jr.; Chappell, M.; Hackam, D.J.; Jia, H. Attenuation of pulmonary ACE2 activity impairs inactivation of des-Arg9 bradykinin/BKB1R axis and facilitates LPS-induced neutrophil infiltration. Am. J. Physiol. Lung Cell. Mol. Physiol. 2018, 314, L17–L31.

48. Paraskevis, D.; Kostaki, E.; Magiorkinis, G.; Panayiotakopoulos, G.; Sourvinos, G.; Tsiodras, S. Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event. Infect. Genet. Evol. 2020, 79, 104212.

49. Benvenuto, D.; Giovannetti, M.; Ciccozzi, A.; Spoto, S.; Angeletti, S.; Ciccozzi, M. The 2019-new coronavirus epidemic: Evidence for virus evolution. J. Med. Virol. 2020, 92, 455–459.

50. Li, Q.; Guan, X.; Wu, P.; Wang, X.; Zhou, L.; Tong, Y.; Ren, R.; Leung, K.S.M.; Lau, E.H.Y.; Wong, J.Y.; et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. N. Engl. J. Med. 2020, 382, 1199–1207.

51. Guo, Y.-R.; Cao, Q.-D.; Hong, Z.; Tan, Y.-Y.; Chen, S.; Jin, H.; Tan, K.S.; Wang, D.Y.; Yan, Y. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak—An update on the status. Mil. Med. Res. 2020, 7, 11.

52. Hamming, I.; Timens, W.; Bulthuis, M.L.C.; Lely, A.T.; Navis, G.J.; Van Goor, H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. J. Pathol. 2004, 203, 631–637.

53. Wang, T.; Du, Z.; Zhu, F.; Cao, Z.; An, Y.; Gao, Y.; Jiang, B. Comorbidities and multi-organ injuries in the treatment of COVID-19. Lancet 2020, 395, e52.

54. Xu, Z.; Shi, L.; Wang, Y.; Zhang, J.; Huang, L.; Zhang, C.; Liu, S.; Zhao, P.; Liu, H.; Zhu, L.; et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir. Med. 2020, 8, 420–422.

55. Hui, D.S.C.; Zumla, A. Severe Acute Respiratory Syndrome. Infectious Dis. Clin. N. Am. 2019, 33, 869–889.
56. Yang, X.; Yu, Y.; Xu, J.; Shu, H.; Xia, J.; Liu, H.; Wu, Y.; Zhang, L.; Yu, Z.; Fang, M.; et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: A single-centered, retrospective, observational study. Lancet Respir. Med. 2020, 8, 475–481.