Ann Med Res 2020;27(11):3044-9

Annals of Medical Research

DOI: 10.5455/annalsmedres.2020.06.564

Review Article

Covid-19 and Sars: Two corona virus pandemics encountered in the last two decades

Hilal Rumeyza Cirik, Elif Taslidere, Nigar Vardi

Department of Histology Embryology, Faculty of Medicine, Inonu University, Malatya, Turkey

Copyright © 2020 by authors and Annals of Medical Research Publishing Inc.

Abstract

The New Corona Virus Disease declared by the World Health Organization as pandemics on 11th March 2020, is the third pandemics caused by coronaviruses since the beginning of the 21st century. Other pandemics are Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome.

While the similarity between SARS-CoV-2 and MERS-CoV was 50%, the same between SARS-CoV-2 and SARS-CoV was higher than 80%. With regard to virus classification, those three viruses, causing pandemics belonged to the coronavirus (in Latin: Orthocoronavirinae) sub-family of the Coronaviridae family. The Corona Viruses are enveloped RNA viruses which cause a wide spectrum of respiratory tract infections in human, other mammals or birds.

The receptor bound by SARS-CoV and SARS-CoV-2 to penetrate to the host cell is common, namely angiotensin converter enzyme 2 receptor. Corona viruses are shown to bind to the angiotensin converter enzyme 2 receptor on the surface of human cell by means of the spike protein (S protein) being one of the structural proteins existing on its outer envelope.

As SARS-CoV-2 is a newly appearing virus, in this compilation we compared the two coronavirus pandemics, i.e. Severe Acute Respiratory Syndrome and the New Corona Virus Disease, encountered in the last two decades. We searched the function of the angiotensin converter enzyme 2 in cells, in which the angiotensin converter enzyme 2 is expressed, similarities and differences of the clinical profile of SARS and COVID-19. Our purpose is to compile the information and experience obtained from the Severe Acute Respiratory Syndrome outbreak with the understanding we gained from the New Corona Virus Disease and to assist in offering new ideas in an effort to prevent this pandemic.

Keywords: ACE2 receptor; COVID-19; SARS; SARS-CoV; SARS-CoV-2

INTRODUCTION

Since the beginning of the 21st century, the world has been suffering the third pandemics caused by coronaviruses and characterized by acute lower respiratory tract infections. These pandemics are Severe Acute Respiratory Syndrome (SARS), between 2002 and 2003, Middle East Respiratory Syndrome (MERS), more widespread in the Middle East, between 2012 and 2014 and the New Corona Virus Disease (COVID-19), which first appeared in the Wuhan state of China in December 2019 and declared as pandemics on 11th March 2020 by World Health Organization (WHO) (1,2).

COVID-19 is a contagious disease caused by the new human coronavirus (2019-nCoV) or, according to the nomenclature of the international virus classification commission, by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), primarily causing lung inflammation (2,3).

The pathological changes in the cells of the target organ are associated with production of excessive quantities of proinflammatory cytokines due to the severe local inflammatory response caused by the virus in addition to the direct damage imposed by the virus (2).

Pathogenic properties

SARS-CoV-2 is the seventh corona virus known to infect humans. The other six corona viruses are CoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV (2). Four of those, namely, CoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1 cause symptoms of cold while SARS-CoV and MERS-CoV yield in a more severe clinical picture and, are fatal for some patients (4).

Comparing the genome of SARS-CoV-2 with the genetic sequences of SARS-CoV and MERS-CoV, it was found out that those three corona viruses did have similarities, SARS-CoV-2, however, was a new virus (4). While there is 50% similarity between SARS-CoV-2 and MERS-CoV,

Received: 15.06.2020 **Accepted:** 19.11.2020 **Available online:** 20.11.2020
Corresponding Author: Hilal Rumeyza Cirik, Department of Histology Embryology, Faculty of Medicine, Inonu University, Malatya, Turkey **E-mail:** hilal.cirik@inonu.edu.tr

that between SARS-CoV-2 and SARS-CoV is more than 80%. The genome similarity with a coronavirus isolated from a bat species was reported to be 96%. As a matter of fact, the natural host of SARS-CoV-2, alike SARS-CoV and MERS-CoV is believed to be bats (5). It was reported that most of the bat species were hibernating in the end of 2019 December while in the Huanan Seafood Market, where the first cases of COVID-19 were encountered, no bats were sold. For this reason, although bats were the natural host for SARS-CoV-2, there could be an intermediate host, which has not become clear yet (6).

With regard to virus classification the viruses causing these three contagious diseases are observed to belong the coronavirus (in Latin Orthocoronavirinae) sub-family of the Coronaviridae. Coronaviruses (CoVs) are divided into four sub-groups: alpha-CoV, beta-CoV, gamma-CoV and delta-CoV (7). Betacoronavirus has four different viral strains. The beta-CoV, with a medical significance for humans come from OC43 and HKU1 A strain , SARS-CoV and SARS-CoV and SARS-CoV-2 belong to B strain while MERS-CoV belongs to C strain (8).

Coronaviruses are RNA viruses which may lead to a large spectrum of respiratory tract disorders in humans, other mammals or birds (4). Coronaviruses have envelopes with a RNA genome of positive definition, single chain and at a size of 26-32 kilobase, being the largest genome known for a RNA virus (9).

The term “Coronavirus” represents the appearance of the CoV virions observed under the electron microscopy. The term “corona” refers to the crown resemblance, with the spike-like projections from the virus envelope (7).

Similarities are reported in organization and expression of the entire corona viruses. The coronavirus genome possesses 6-to-7 major open reading frames (ORFs) in the characteristic gene order in the 5′ to 3′ direction: ORF1a and 1b which comprise two-thirds of the genome and encode the nonstructural polyproteins, and four ORFs downstream that encode structural proteins: spike protein (S), envelope protein (E), membrane protein (M) and nucleocapsid protein (N) (10). The first ORF representing approximately 67% of the entire genome encodes 16 non-structural proteins (nsps), while the remaining ORFs encode accessory proteins and structural proteins (11). The envelope of the virus resembles the cell membrane consisting of double layer lipid and membrane proteins. The nucleocapside within the virus has a symmetrical spiral structure formed by the combination of positive strand RNA and capside protein (N) (12).

Like all viruses, coronaviruses cannot reproduce independently. They synthesize their viral proteins only through the protein synthesis system of the cell they infected, and reproduce by RNA polymerase associated with the RNA coded by them. There by, the viruses reproducing in the host cell are released and infect more cells (7).

Tang et. al. (13) found out that SARS-CoV-2 genome had 149 mutation zones and developed two sub-types: type L and type S, depending on the population genetic analyses. As a result of the study, the type L, being a SARS-CoV-2 virus (~70%), is more pervasive and aggressive than type S (~30%).

Cell receptor

The studies have shown that the coronaviruses are bound to the host cells using the spike protein (S protein) being one of the structural proteins on the outer envelope of the virus through the combination of the specific protease molecules (receptors) on the surface of human cell (7). S protein is a ligand for the cell surface receptors. The ligand and receptors are bound specifically while their affinity is associated with the virus pathogenicity and infectivity. The S Protein consists of two sub-units. Amino (N) terminal end forms the S1 sub-unit and carboxy (C) terminal end forms S2 sub-unit. The receptor binding domain (RBD) is located in the S1 zone (5).

The SARS-CoV receptor in human cells is angiotensin converter enzyme 2 (ACE2) (14,15). The studies have verified that the ACE2 on the surface of human cells is also a receptor for SARS-CoV-2 (6,16). The affinity between SARS-CoV-2 S protein and ACE2, is 10 to 20 times higher than that between SARS-CoV S protein and ACE2. This situation explains as to why SARS-CoV-2 is more contagious and how it has turned out to be such a global epidemics (2).

In the molecular level, the human endothelial angiotensin converter enzyme (ACE) was first cloned in 1988 by Soubrier et al. and was described as 170 kDA glycoprotein containing two homologous active zones (17). ACE2 is a homologue to ACE and was discovered in 2000. In spite of the similarities between ACE and ACE2, the functions of those two enzymes are totally different (18). ACE catalyzes formation of angiotensin II from angiotensin I, thereby plays a key role in cardiorenal function and blood pressure control (19). ACE2 serves as balancer against ACE. ACE2 disunites the C-terminal aminoacid of the angiotensin II and hydrolyzes to angiotensin 1-7 derivatives (20,21). ACE2 thereby antagonizes such effects as vasoconstriction, sodium retention or fibrosis of the angiotensin II (21). Furthermore, ACE2 hydrolyzes many peptides such as bradiquinin, appeline, neurotensin, dynorphin A and ghrelin (22).

The organs with high expression of ACE2, being a common receptor for SARS-CoV and SARS-CoV-2 and a membrane protein with a protease activity are considered to be the main target organs for the COVID-19 infection. The cells which evidently express ACE2 are: Type 1 and Type 2 alveolar epithelial cells, intestinal epithelial cells, cardiomyocytes, renal distal tubule epithelial cells and monocytes-macrophages (23).

Harmer et al. (24) in the 72 various human tissues extracted from six donors, using quantitative reverse transcriptase polymerase chain reaction (RT-PCR) determined the ACE2 distribution and expressions levels. After the study it was

found out that ACE2 was expressed in many tissues but showed less distributed expression than ACE. The ACE2 expression was high in gastrointestinal and cardio-renal tissues, while it was lower in the central nervous system and lymphoid tissues.

Ding Yanqing et al. (25,26) used immunohistochemistry in-situ hybridization and RT-PCR in order to show existence of SARS-CoV virus in the autopsy tissues of the four patients deceased due to SARS. In the end, SARS-CoV was found in many organs particularly in the lungs, trachea and bronchi, as well as in stomach, small intestine, renal distal tubule, sweat glands, parathyroid, pituitary glands, pancreas, adrenal gland, liver or cerebrum. In addition to those, the organs in which the virus was not found were esophagus, thyroid, spleen, lymph nodes, bone marrow, testicles, ovarium, uterus, heart, aorta, cerebellum and muscles. These results show that the primary target of the SARS-CoV could be, in addition to the respiratory system, the gastrointestinal system. Ding Yanqing et al. (25,26) encountered SARS-CoV virus in the lungs, gastrointestinal system and kidneys consistently with the ACE2 expression levels measured in the tissues. On the other hand, in spite of the high levels of ACE2 expression, it is not definite as to why heart and testicle cells are not infected by SARS-CoV.

In another study, prognosis of the COVID-19 was found to be related to age and sex but the ACE2 expression level was not a significant factor which influences the patient prognosis. The reason for this was stated to be higher ACE2 expression in the youngers than others, also, higher in the females than males, but COVID-19, on the contrary is encountered more frequent in the older and males (27,28).

Furthermore, due to acting of ACE2 for SARS-CoV-2 as a receptor, whether or not the effect of such pharmaceuticals as ACE inhibitors and angiotensin receptor blockers (ARB) usually preferred as anti-hypertensive would have an influence on the COVID-19 pandemic virulence raises serious concerns. ACE inhibitors and ARBs (Renin-angiotensin-aldosterone system inhibitors – RAAS inhibitors) have various effects on the angiotensin II, being the primary substrate of ACE2. These pharmaceuticals are observed to have indirect and varying influences on ACE2. In spite of the structural similarities between ACE and ACE2, they do have different enzyme activation localizations. The ACE inhibitors therefore do not directly affect ACE2 and their effects could be variable. The human studies aimed at the effects of ACE inhibitors on ACE2 are very limited and generally, animal models were employed. In addition to the studies showing that there was no influence on the angiotensin 1-7 levels associated with the ACE inhibitors, there are also studies stating, in the long term use, that angiotensin 1-7 levels increased. While in some of the studies carried out with the ARBs, an increase in the ACE2 levels, based on the increment in the RNA expression was shown, no influence was observed in some studies. There is no data on RAAS inhibitors' effect on ACE2's specific expression in the lungs. Moreover, even if the ACE2 levels and activities change, the clinical data related to easing of binding and entry of the SARS-CoV-2 virus is scarce. RAAS inhibitors are known to have protective effect on heart and kidneys. Because of this, discontinuing medication in the COVID-19 patients impose another risk by increasing decompensation. Accordingly, in spite of the concerns and uncertainties related to RAAS inhibitors, the studies carried out suggest that administration of such medicine on the patients who carry risk for COVID-19, and are under diagnostic process and diagnosed stable patients should be continued until additional data is available (21).

Pathological mechanism

As stated before, SARS-CoV and SARS-CoV-2 are two corona viruses of the same strain that use the same cell surface receptor (ACE2). Because of this, we believe that the target organs, pathogenic mechanisms, clinical symptoms and treatment principles could have many similarities (2).

The frequent clinical picture with SARS has been reported as fever, shivering, muscular pain, headache, vertigo and cough. Considering the laboratory findings, leukocyte was mostly in the normal range, leukopenia (34%) was encountered from time to time, mostly lymphopenia was observed (70%) and there could be a rise in lactate dehydrogenation (LDH) (71%) and aminotransferase (AST and ALT) (24%) (29). COVID-19 could be roughly classified as mild (including mild and ordinary) and severe (including serious and critical). 85% of the cases are mild and 15% severe. While fever and fatigue are counted among the most frequent symptoms observed in COVID-19, unproductive cough was reported to be the most common respiratory system symptom. Such gastrointestinal symptoms as diarrhea or vomiting are stated to be much less frequent (2). In a study carried out by Nanshan Chen et al. (3) in 99 COVID-19 patients, it was reported that though leukocyte is mostly within the normal range (57%), leukocytosis was observed (24%) from time to time, most patients had lymphopenia, there was a rise in LDH levels (76%) and, while not so frequent, a rise in the AST and ALT levels could also be observed (43%).

The drop in the absolute count of the peripheral blood lymphocytes in a considerable majority of COVID-19 patients according to laboratory test results is worthy to notice. It was reported that in the severe patients, there was a progressive reduction in lymphocytes (particularly CD8 positive T lymphocytes) while neutrophil / lymphocyte ratio increased. These parameters are reported to assist in determining the severity of the disease (30). Some researchers claimed that such drop in the lymphocyte numbers of the COVID-19 patients could be associated with redistribution of the lymphocytes to the affected organ tissues. Another opinion is, as is the case with SARS, that there could be a drop in the lymphocyte numbers in COVID-19 related to suppressing of bone marrow due to virus (31).

The studies carried out have shown that a series of pathophysiological changes caused by SARS-CoV in

human was, in addition to direct cytopathic effect of the virus, due to production of excessive amounts of cytokines triggered by the virus. Excessive release of cytokines as a result of infection of human cells by coronavirus, causes non-specific activation of mononuclear macrophages and lymphocytes. Those cytokines not only stimulate proliferation of monocytes – macrophages but also induce large lymphocyte apoptosis (particularly T cells) causing immune deficiency on the other (26,32-35). In the studies performed for SARS-CoV-2, among the organ damage mechanisms caused by the virus is the cytokine storm triggered by an unbalanced response by type 1 and type 2 T helper (Th). Furthermore, it was stated that interleukin 6 (IL-6) could be an indicator of mortality in COVID-19 patients (36).

In the early phase lung radiographies of the SARS patients, typically single sided, predominantly peripheral consolidation zones were observed. Approximately 1 week thereafter, in correlation with the impaired respiratory function, bilateral irregular consolidation zones were reported in the lung radiographies (37). In the lung radiographies of the COVID-19 patients, irregular opacities mostly suggesting bilateral pneumonia were reported (3,38).

Postmortem tissue analysis was carried out for the purposes of finding out postmortem pathological changes in the lungs due to SARS. In the microscopic examination of the lungs, histopathological findings belonging to different phases of the diffuse alveolar damage in different zones were reported. In the early phase, hyaline membrane and pulmonary edema implying the early phase of Acute Respiratory Distress Syndrome (ARDS) were observed. In the organization phase however, exudate containing fibromixoid cells was found out. Furthermore, evident and small number of lymphocytic infiltration in the intercititium attracted attention (37). Ding Yanqing et al. (2), in an effort to show the pathological changes caused by SARS-CoV, analyzed the autopsy tissues of the patients passed away due to SARS. In the macroscopic examination of the lung, large consolidation zones, focal bleeding and necrosis foci were reported. In the microscopic evaluation, lung epithelial cells and fibrosis exudate were observed. The exudate was reported to contain a high number of monocytes, lymphocytes and plasma cells. Furthermore, formation of pervasive hyaline, type II pneumocyte hyperplasia and inflammatory cell infiltration in the interstitial zone were observed.

Zhe Xu et al. (39) extracted lung, liver and heart biopsy samples from a patient who passed away due to COVID-19. In the microscopic examination of the lung, an evident desquamation in the pneumocytes, hyaline membrane and fibromixoid cell containing exudates were found out. In the intercititium, mononuclear inflammatory cell infiltration was observed where lymphocytes were found to be dominant. Due to viral cytopathic influence, the large nucleus, evident nucleolus and amphophilic granular cytoplasm expected in the cells within the intraalveolar space, characteristically in the ARDS attract attention. Moderate microvesicular steatosis was reported in the liver biopsy. The reason for this in the liver was reported to be SARS-CoV-2 infection or the medicine employed. In the heart biopsy however, a few mononuclear inflammatory cell infiltration was seen in the interstitial area, but no significant histological variation was observed.

Sufan Tian et al. (31), in their study, extracted and analyzed lung, liver and heart biopsy samples from four patients who deceased due to COVID-19. In the microscopic study of the lungs, although each case had histological differences, all were reported to be in compliance with the pervasive alveolar damage. In the lung biopsies: hyaline membrane formation, fibrin exudates, alveolar epithelial damage and type II pneumocyte hyperplasia were observed. In addition to those, in the case 1, lung biopsy revealed pneumocyte desquamation, syncytial giant cells and focal lymphocyte infiltration, probably representing chronic lymphocytic leukemia (KLL) history. In the lung biopsy examination of the case 2, who had a history of cirhosis, the number of inflammatory cells was reported to be low. In the case 3, having diabetes and hypertension, focal intercititial thickening was observed. The case 4, who was in 3rd month following a renal transplantation revealed further changes in the lung biopsy. Pervasive intraalveolar hemorrhage, intraalveolar fibrine accumulations and hyaline membrane were observed. Fibrinoid necrosis was noticed in small veins. Additionally, stromal cells increased in the alveolar wall, fibrine accumulation, mononuclear cell infiltration and type II pneumocide hyperplasia causing interstitial thickening were observed. In the latter patient, intraalveolar neutrophyl infiltration suggesting superimposed bacterial infection was also encountered. The histological changes observed in the liver biopsies presented differences probably in line with the underlying disorder of each patient, while the common histopathological finding for the four patients was to be a mild sinusoidal dilatation, being a pervasive non-specific variable. Heart biopsies were taken only from case 1 and 4. In the endocardium and myocardium layers, no inflammatory cell infiltration was observed. Focal edema, interstitial fibrosis and myocardial hypertrophy of various levels were reported probably associated with the underlying disorders.

After comparison of the clinical symptoms of SARS and COVID-19, laboratory results, lung radiographic images, immune system responses and the pathological changes in the organs, it was observed that the two diseases had a similar pathophysiological mechanism. This must however be confirmed by means of further studies (2).

CONCLUSIONS

Since ACE2, a SARS-CoV-2 receptor is commonly found in human tissues and organs, it is probable that COVID-19 could be a systemic disease.

The affinitiy of SARS-CoV-2 S protein to ACE2 is 10 to 20 times higher than SARS-CoV virus. This situation could

be deemed as one of the possible definitions as to why COVID-19 is more infectious and how it has turned out to be epidemics.

Comparing SARS and COVID-19, the two diseases were found to have a similar pathophysiological mechanism. But this parameter must be verified through more studies.

SARS-CoV-2 has been reported to be the seventh corona virus known to have infected humans. Considering the large spectrum of the corona viruses, periodical occurrence of new coronavirus strains is considered possible due to frequent recombination of its genomes and increasing human-animal interface activities (4).

The new coronavirus pneumonia caused by SARS-CoV-2 is the most serious public health problem of the century. In this compilation, we compared COVID-19 with SARS encountered seventeen years ago, trying to state similarities and differences between the two. We believe that combining the information and experience obtained from SARS outbreak with our current understanding of COVID-19 concept would be beneficial for prevention and treatment of new corona virus pneumonia.

Competing interests: The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

REFERENCES

1. WHO Coronavirus disease 2019 (COVID-19) Situation Report – 65. WHO Coronavirus disease 2019 (COVID-19) Situation Report – 65 [Internet]. [cited 2020 May 3]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200325-sitrep-65-covid-19.pdf?sfvrsn=ce13061b_2
2. Wang X, Ding YQ. From SARS to COVID-19: pathogens, receptor, pathogenesis and principles of the treatment. Chinese J Pathol 2020;2;49:E012.
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;15;395:507-13.
4. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;20;382:727-33.
5. Zhou P, Yang X Lou, Wang XG, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;12;579:270-3.
6. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:565-74.
7. Su S, Wong G, Shi W, et al. Epidemiology, Genetic Recombination, and Pathogenesis of Coronaviruses. Trends in Microbiology. Elsevier Ltd; 2016;24:490-502.
8. Betacoronavirus - Vikipedi [Internet]. [cited 2020 May 15]. Available from: https://tr.wikipedia.org/wiki/Betacoronavirus
9. Weiss SR, Navas-Martin S. Coronavirus Pathogenesis and the Emerging Pathogen Severe Acute Respiratory Syndrome Coronavirus. Microbiol Mol Biol Rev 2005;69:635-64.
10. Hu B, Ge X, Wang LF, et al. Bat origin of human coronaviruses Coronaviruses: Emerging and re-emerging pathogens in humans and animals Susanna Lau Positive-strand RNA viruses. Virol J 2015;12:1-10.
11. Wu A, Peng Y, Huang B, et al. Genome Composition and Divergence of the Novel Coronavirus (2019-nCoV) Originating in China. Cell Host Microbe 2020;11;27:325-8.
12. Peiris JSM, Guan Y, Yuen KY. Severe acute respiratory syndrome. Nature Medicine 2004;10:88-97.
13. Xiaolu Tang, Changcheng Wu, Xiang Li, et al. On the origin and continuing evolution of SARS-CoV-2 National Science Review 2020;3
14. Li W, Moore MJ, Vasllieva N, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. Nature. 2003;27;426:450-4.
15. Ge XY, Li JL, Yang X Lou, et al. Isolation and characterization of a bat SARS-like coronavirus that uses the ACE2 receptor. Nature 2013;503:535-8.
16. Wan Y, Shang J, Graham R, et al. Receptor Recognition by the Novel Coronavirus from Wuhan: an Analysis Based on Decade-Long Structural Studies of SARS Coronavirus. J Virol 2020;29;94.
17. Soubrier F, Alhenc-Gelas F, Hubert C, et al. Two putative active centers in human angiotensin I-converting enzyme revealed by molecular cloning. Proc Natl Acad Sci U S A. 1988;85:9386-90.
18. Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol 2020;1-5.
19. Dzau VJ. Angiotensin converting enzyme inhibitors and the cardiovascular system. J Hypertens Suppl 1992;1:3-10.
20. Vickers C, Hales P, Kaushik V, et al. Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem 2002; 26:14838-43.
21. Mcmurray JJ V, Pfeffer MA, Ph D, et al. Special Report Renin – Angiotensin – Aldosterone System Inhibitors in Patients with Covid-19. 2020;1653-9.
22. Anjiyotensin dönüştürücü enzim 2 - Vikipedi [Internet]. [cited 2020 May 15]. Available from: https://tr.wikipedia.org/wiki/Anjiyotensin_dönüştürücü_enzim_2.
23. Turner AJ, Hiscox JA, Hooper NM. ACE2: From vasopeptidase to SARS virus receptor. Vol. 25, Trends in Pharmacological Sciences. Elsevier Ltd; 2004;291-4.

24. Harmer D, Gilbert M, Borman R, et al. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett 2002;4;532:107-10.
25. Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: Implications for pathogenesis virus transmission pathways. J Pathol 2004;203:622-30.
26. He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARS patients: Relation to the acute lung injury and pathogenesis of SARS. J Pathol 2006;210:288-97.
27. Xudong X, Junzhu C, Xingxiang W, et al. Age- and gender-related difference of ACE2 expression in rat lung. Life Sci 2006;4;78:2166-71.
28. Soro-Paavonen A, Gordin D, Forsblom C, et al. Circulating ACE2 activity is increased in patients with type 1 diabetes and vascular complications. J Hypertens 2012;30:375-83.
29. Tsang KW, Ho PL, Ooi GC, et al. A cluster of cases of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;15;348:1977-85.
30. Liu J, Liu Y, Xiang P, et al. Neutrophil-to-Lymphocyte Ratio Predicts Severe Illness Patients with 2019 Novel Coronavirus in the Early Stage. medRxiv. 2020;12;807.
31. Tian S, Xiong Y, Liu H, et al. Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies. Mod Pathol 2020.
32. Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. J Exp Med 2005;1:415-24.
33. Wong CK, Lam CWK, Wu AKL, et al. Plasma inflammatory cytokines and chemokines in severe acute respiratory syndrome. Clin Exp Immunol 2004;136:95-103.
34. Lo AWI, Tang NLS, To KF. How the SARS coronavirus causes disease: Host or organism? J Pathology 2006;208:142-51.
35. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol 2017;2;39:529-39.
36. Rizzo P, Vieceli Dalla Sega F, Fortini F, et al. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Res Cardiol 2020;115:1-8.
37. Lee N, Hui D, Wu A, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med. 2003;15:1986-94.
38. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis 2020;1;20:425-34.
39. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;1;8:420-2.