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REVIEW ARTICLE **OPEN ACCESS**

The Effect of Renin angiotensin System on Covid 19

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ABSTRACT
Coronaviruses (CoV) are zoonotic viruses classified in the Coronaviridae family. While the Coronaviridae family includes four genera, alpha, beta, gamma and delta, species within the alpha genus cause self-limiting upper respiratory tract infections in humans. However, after 2002, severe Acute Respiratory Syndrome virus (SARS-CoV), Middle East Respiratory Syndrome virus (MERSCoV) and SARS-CoV-2 species formed in the Sarbecovirus subgenus of the Betacoronavirus 2b genus have become important pathogens threatening public health.
This article evaluated the clinical status of COVID-19 and the presence of ACE2 receptors by looking at its effect with SARS-CoV-2. The pathogenesis of COVID-19 begins with the binding of the spike protein SARS-CoV-2 to the ACE2 receptor of host cells. The clinical situation of COVID-19 is no longer limited to the pulmonary system, but also to the extra pulmonary systems, as ACE2 receptors find too much in other organs. Moreover, genetic variations of the viral spike protein and the site binding protein of the ACE2 receptor have led to the emergence of clinical signs of COVID19. The dynamic interaction between SARS-CoV-2 and the receptor ACE2 has great impact on clinical findings. The genetic variation of the Virgo protein SARS-CoV-2 also plays a role in its virulence. Genetic variations of the human receptor ACE2 affect susceptibility or resistance to infection.
Keywords: *Covid 19, Angiotensin, ACE2 receptors.*

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INTRODUCTION

Coronaviruses (CoV) are common zoonotic pathogens that cause upper respiratory infections. To date, 4 types of CoV (human CoV-229E, human CoV-NL63, human CoV-HKU1, human CoV-OC43) have been identified and identified in different tissues and organs of animals such as birds, bats, mice, cattle, cats, and dogs (Figure 1) [1]. There are 30 types of coronavirus. Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Severe Acute Respiratory Syndrome-2 coronaviruses, which have emerged in the last 20 years, spread all over the world, causing fatal lower respiratory tract infections and pose a significant threat to public health [2].

In December 2019, cases of pneumonia of unknown cause emerged in people working in the seafood and livestock market in Wuhan province of the People's Republic of China, and it was determined that the disease agent was a new type of coronavirus [3]. Subsequently, the genome sequence of the virus was determined and identified as 2019 novel coronavirus (2019-nCoV) by the World Health Organization (WHO) [4]. The first cases outside of China emerged in Thailand and Japan, and the virus spread across continents within a few weeks. The virus declared a "pandemic" on March 11, 2020 [2].

The SARS-CoV-2 pandemic has taken over the world and has become one of the world's biggest global problems. Currently, at least 15 different drug molecules are used for symptom treatment in COVID-19 patients; Other therapeutic methods such as a monoclonal antibody, plasma transfer, and stem cell are used [5].

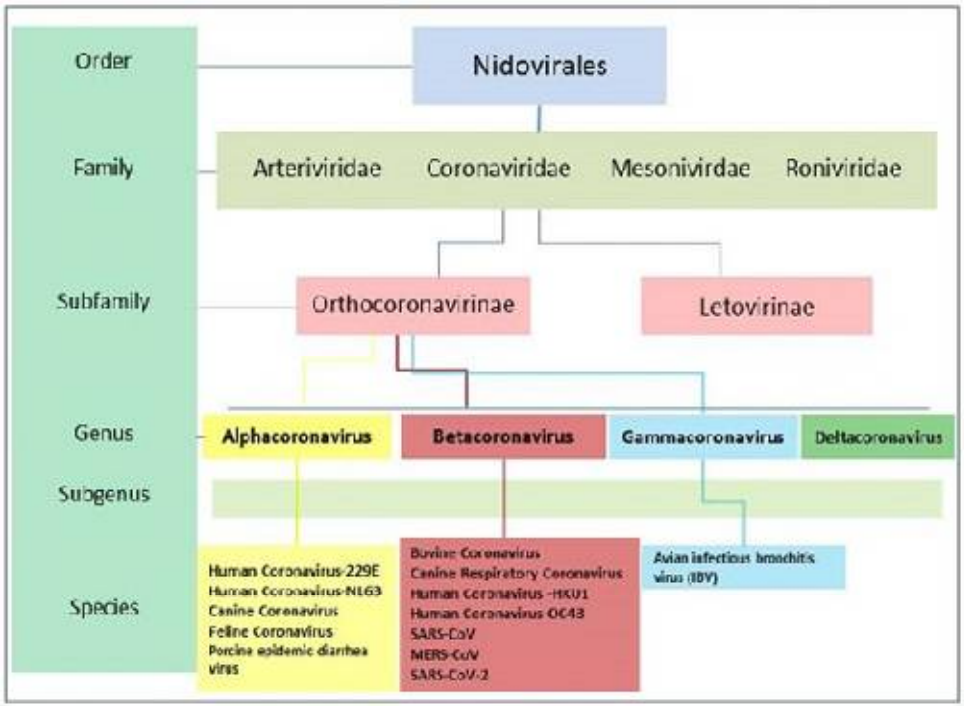

Figure 1: Classification of important human and animal coronavirus

More than one million died due to COVID-19, causing the severe acute respiratory syndrome. For this reason, important information on viral pathophysiology, an effective vaccine or treatment option can facilitate the pandemic process. Additionally detection viral replication inhibitors, another option would be to block the cellular goal of the virus, angiotensin-converting enzyme-2 (ACE2) [6].

Four structural proteins in coronaviruses are involved in the formation of virions and the emergence of infection. These are S (Spike) protein, E (Envelope) protein, M (Membrane) protein, and N (Nucleocapsid) proteins (Figure 2). The S protein is responsible for the formation of spikes on the surface of the coronavirus, which permits the virus to attach to the host cell receptors, allowing it to enter the cell [7,8 and 9].

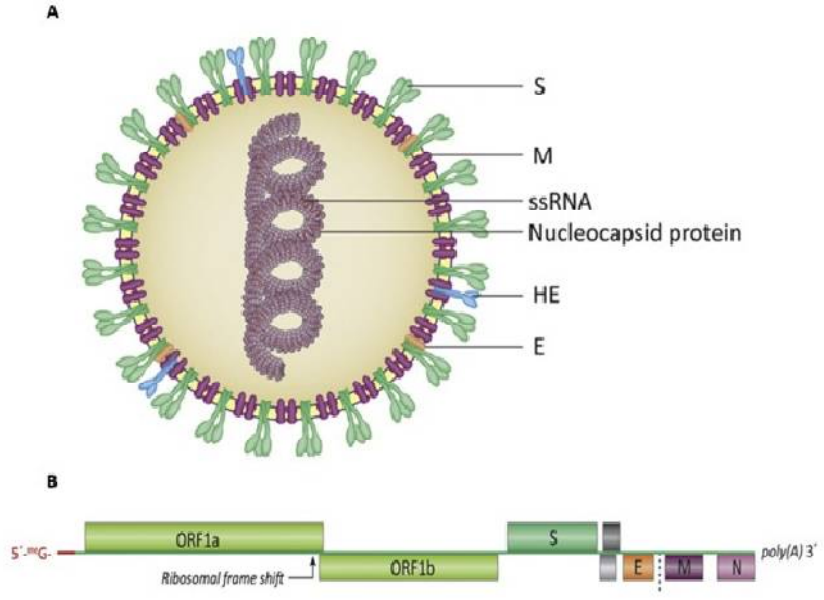

Figure 2: Schematic structure of the coronavirus

The M protein, with its three different transmembrane regions, allows the virion to be shaped, the virus-cell membrane to be curved, and binds to the nucleocapsid. E protein plays a role in viral pathogenesis by

the packaging and release of the virus. N protein contains regions in the RNA structure that bind to the viral genome. N protein binds with nsp3 ("nonstructural protein 3": nonstructural protein 3), allowing the genome to bind to the replication-transcription complex and the encapsulated genome to be packaged in the virion [10].

ACE2 is an important receptor of SARS-CoV-2, which plays an important role in the pathogenesis of COVID-19 as it enables viral entry into host cells (Figure 3). Binding proximity between ACE2 and the receptor-binding domain (RBD) of the SARS-CoV-2 spike glycoprotein,

It is 10 to 20 times higher than the affinity of the RBD of SARS-CoV; this supports the higher pathogenesis of SARS-CoV-2 infections. ACE2 is a transmembrane protein that characteristically has carboxypeptidase activity and a physiological role in the renin-angiotensin system. ACE2 hydrolyzes angiotensin II to its metabolite, angiotensin 1--7, and angiotensin I to angiotensin 1--9 to protect tissues from injury (Figure 3) [11]. ACE2 is expressioned at various levels in various organs. It is found in the lungs (on the surface of type II alveolar epithelial cells), heart (myocardial cells, coronary vascular endothelial cells, and vascular smooth muscle), kidney (proximal tubule cells), and small intestine (enterocytes).

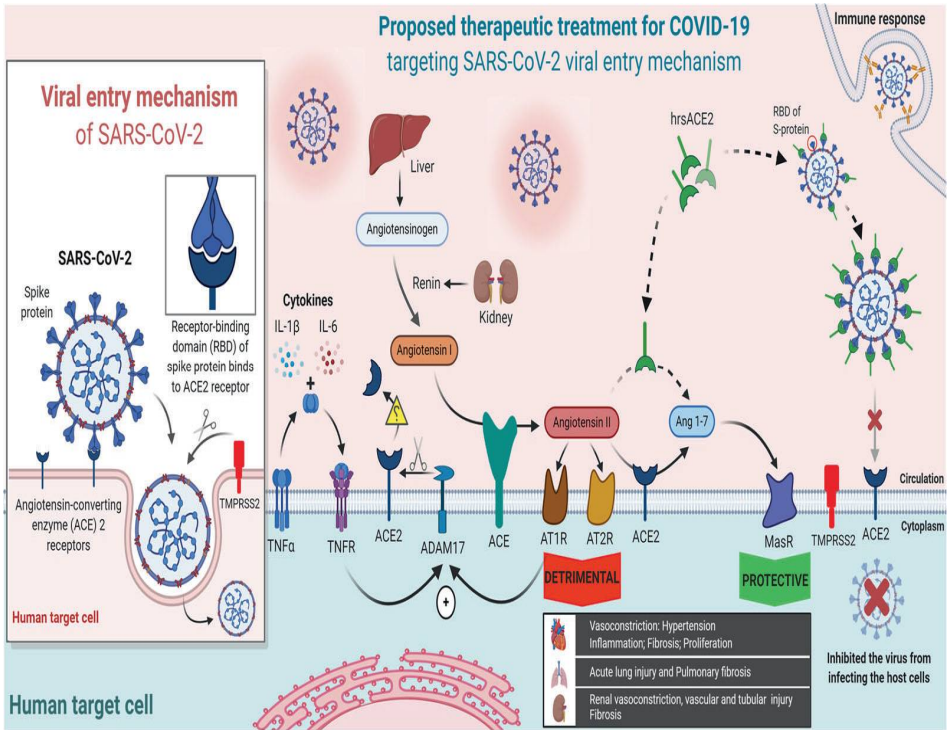

Figure 3: Schematic representation of the renin-angiotensin system

While membrane-bound ACE2 may mediate entry into the cell of SARS-CoV-2, a genetically replaced form of ACE2, termed hrsACE2, can reduce cell entry of SARS-CoV-2, which is persistent for membrane-bound ACE2. Therefore, it can reduce the cell entry of SARS-CoV-2 to minimize lung injury and multi-organ dysfunction (Figure 3). The experimental work for this theory came from in vitro studies where hrsACE2 was found to reduce the viral growth of SARS-CoV-2 by 1000--5000 folds in cell culture, engineered human blood vessels, and kidney organoids [12].

CHARACTERISTICS OF THE CLINICAL TABLE

Since the pandemic continues, the distribution of clinical features detected in patients with infection may change over time. Fever in approximately 83-98% of the cases, cough in 76-82%, muscle aches, weakness, and fatigue were observed in 11-44% of the cases, headache, sore throat, abdominal pain, and diarrhea may accompany the clinical picture. is observed [13]. Anosmia (inability to smell) has been declared as a distinctive symptom in patients diagnosed with COVID-19 [14,15].

Pneumonia is the most common serious finding of infectionPneumonia is classified as mild and severe pneumonia. It has symptoms such as fever, muscle/joint pain, cough, sore throat, nasal congestion, respiratory distress, tachypnea and SpO_2 <93%, underlying diseases (cardiovascular diseases, diabetes mellitus, hypertension, cancer, chronic lung diseases, especially poor prognostic criteria in blood tests performed at admission (blood lymphocyte count <800 / µL or C-reactive protein (CRP)> 40 mg/L or

ferritin, under 50 years of age, normal chest radiography and/or computed tomography The clinical picture in individuals without> 500 ng/mL or D-Dimer> 1000 ng/mL] is considered to be an uncomplicated disease. In the mild course pneumonia category, respiratory rate is <30 / minute, room air SpO_2 level above 90%, underlying no disease, under 50 years of age, with mild pneumonia on chest X-ray or computed tomography, poor prognostic criteria in blood tests performed at the time of presentation. patients not present are included; Patients with a respiratory rate of 30/minute, SpO_2 level below 90% in room air, bilateral diffuse pneumonia findings on chest X-ray or tomography, and poor prognostic criteria in blood tests performed at the time of presentation are defined as severe pneumonia [16].
Acute Respiratory Distress Syndrome (ARDS) is an important complication that can develop in severe disease. Other important complications include arrhythmia, acute cardiac injury, thromboembolic complications, and shock [17]. SARS-CoV-2 infection can be seen in individuals of all ages, particularly affecting middle age and older age groups [14]. Although the symptomatic infection has been reported to be rare and mild in children, severe and complicated cases have also been reported [14,18]. No death has been reported in cases with mild disease. Some patients with mild symptoms at the beginning had their clinical worsening within a week. It is stated that the recovery period may take approximately two weeks in mild disease and 3-6 weeks in severe disease [14]. There are cases reported that Guillain-Barré syndrome developed within 5-10 days following the initial symptoms. [19].

LABORATORY FINDINGS

While lymphopenia is detected in most of the cases, varying degrees of leukopenia or leukocytosis can be seen. In the biochemical analysis, it is generally stated that high levels of lactate dehydrogenase (LDH) and ferritin, and an increase in aminotransferase levels can be detected. It has been reported that serum procalcitonin levels were within normal limits in most cases with pneumonia on admission, but they could be found to be increased in those who needed intensive care. High D-dimer levels and the presence of deep lymphopenia have been associated with mortality [13,19].

IMAGING FINDINGS

The main imaging findings in patients with pulmonary involvement are usually patchy infiltrations in both lungs on chest radiography, and computed tomography evaluation of the lung indicates that opacifications in ground-glass density consistent with viral pneumonia are prominent. It is observed that tomographic findings are mostly bilateral, spread to the peripheral and the involvement begins especially in the lower lobes. Less commonly, the presence of signs such as pleural thickening, pleural effusion, and lymphadenopathy are also reported [13.14]. It has been reported that lung involvement can progress during the course of the disease, and the involvement can reach its highest level around 10-12 days after the initial symptoms [14].

HISTOPATHOLOGICAL FINDINGS

Although the information on histopathological findings is limited, it has been reported that hyaline membrane formation, interstitial mononuclear inflammatory cell infiltration, and multinuclear giant cells were observed in the lung tissue, similar to the findings observed in SARS and MERS cases at autopsy [21].

CASE-FATALITY RATE

The case-fatality rate varies by country. The case-fatality rate is high in adults with severe respiratory symptoms with comorbidities such as cardiovascular disease, diabetes mellitus, conical lung disease, hypertension, and cancer. The first reports from the Hubei province of China showed that the case-fatality rate observed especially in elderly people was found to be 2.3% in the whole cohort. It shows that it is higher than the case-fatality rate, and this criterion is 8% in the age range of 70-79 years and 14.8% in those aged 80 and over [22]. According to the current data obtained after the spread of the disease to other countries, the global case-fatality rate is evaluated as approximately 7%. The case-fatality rate is the ratio of the number of people who die of a certain disease in a given period to the number of those who have the same disease in a given period of time. The correct determination of the case-fatality rate depends on the detection of those with mild disease. Therefore, the data should be interpreted with caution [23].

DIAGNOSTIC TESTS AND SCREENING

Primers, probes, and protocols for the "reverse-transcriptase polymerase chain reaction (RT-PCR)", which is the recommended method for use in the diagnosis, have been defined by the CDC [24]. Decisions regarding the centers where countries will apply their diagnostic tests are determined by national health

authorities. For the purpose of diagnosis, a sufficient amount of samples should be taken from the appropriate region and the samples should be delivered to the laboratory where the tests will be performed under suitable conditions and within the recommended period. For this purpose, the sampling and sending procedure recommended by the laboratory where the diagnostic tests will be performed must be followed carefully. A nasopharyngeal swab to be taken from the upper respiratory tract by CDC for diagnostic purposes Sending lower airway samples such as sputum, tracheal aspirate, or bronchoalveolar lavage is preferred [25]. Choosing tracheal aspirate or bronchoscopic samples for samples to be taken from the lower respiratory tract, nasopharyngeal washing sample or sending nasal and/or oropharyngeal swab together in cases where samples cannot be taken from the lower respiratory tract or in cases without lower respiratory tract symptoms, ideally, first oropharyngeal swabbing, then the same swab It is recommended to collect a nasal sample using the same transport medium [3].

TREATMENT

Numerous clinical trials are ongoing in which new agents and drugs are being used for different indications and whose efficacy is being investigated [26]. Remdesivir, a nucleotide analog reported to show in vitro activity against SARS-CoV-2 by inhibiting viral RNA synthesis, is monitored in the hospital by the Food and Drug Administration (FDA), the clinical picture is severe (room air SpO2 94% oxygen support mechanical ventilation or extracorporeal

It has been approved for emergency use by intravenous infusion in adult and pediatric patients requiring membrane oxygenation (ECMO) [25]. However, it is not recommended in patients with alanine aminotransferase (ALT) values greater than or equal to five times the upper limit of normal; it is stated that it should be discontinued in case of an increase in ALT to specified values during treatment or in the presence of signs of liver damage. The pharmacokinetics of remdesivir in renal failure is not clearly known. Remdesivir contains cyclodextrin ("sulfobutylether β-cyclodextrin sodium"), a substance that increases solubility, and it is stated that cyclodextrin can accumulate and cause toxic effects in case of renal failure. Therefore, its use is not recommended in patients with an estimated glomerular filtration rate of less than 30 mL/min / 1.73 m2, unless the potential benefit outweighs the potential harm [27].

Emergency use for hydroxychloroquine sulphate or chloroquine phosphate has been granted by the FDA for use in adult and pediatric patients who are followed up in the hospital due to COVID-19 and who are unable to participate in clinical trials [27]. In COVID-19 cases in which hydroxychloroquine or chloroquine is planned to be initiated or who are taking these agents, especially in patients with a long basal corrected QT interval due to their potential to evaluate and monitor the risk of cardiac side effects, prolong the QT interval, and cause ventricular tachycardia, or who are using active drugs on cardiac conduction it is recommended to avoid use and to seek cardiology department support when necessary [4]. The use of azithromycin in addition to hydroxychloroquine in COVID-19 cases has also been reported to contribute to treatment, but there are controversies regarding the method and sample size of the study, and concerns that there may be an increase in cardiac side effects with combined use [27].

RNA polymerase used in influenza treatment in Japan Its inhibitor, favipiravir, has also been approved in China to be used in the experimental treatment of COVID-19 and has been used in treatment protocols in our country [13]. In addition, clinical studies in which its efficacy is being evaluated in different countries are planned [26]. Tocilizumab is a monoclonal antibody that acts by competitively inhibiting the binding of interleukin-6 (IL-6) to its receptor, IL-6R, and is used in the treatment of some rheumatological diseases. There are clinical studies in which the efficacy of tocilizumab in severe cases of COVID-19 with elevated IL-6 levels is being evaluated, and the efficacy of other agents targeting the IL-6 pathway, siltuksimab, and sarilumab, are also available [17].

During the course of the disease, especially the management of coagulopathy, supportive therapy and approaches to complications are critical. It should not be forgotten that these recommendations can be updated in line with the new developments and results in the treatment of COVID-19, and should be followed from the relevant source. One of the most important components of treatment in patients who require follow-up in the intensive care unit is providing intensive care support appropriate to the patient's clinical condition [4].

CONCLUSION

It is difficult to predict when and where a contagious viral disease will occur. But the use of spatial epidemiology and mathematical modeling can predict the occurrence of emerging diseases such as COVID-19. In addition to RNA recombination and mutations, factors such as globalization, increase in the human population, and change in ecosystem play a role in the formation of viral infectious diseases. Therefore, it is possible that new pandemics caused by similar viruses will occur in the coming years. Valitutto et al. In their study, investigated coronavirus by sequence analysis in 48 samples collected from

seven bats in Myanmar (seven rectal swabs with one oral each) and 40 bat feces pooled samples. According to the results of the study, different new coronaviruses have been identified, including three alphacoronaviruses and three beta-coronaviruses, which were unknown to date. None of the viruses have been found to be closely related to SARS-CoV, MERS-CoV or SARS-CoV-2 [28]

The SARS-CoV-2 pandemic has once again demonstrated the need for more scientific research on the mutations of viruses in nature. Only in this way, potentially dangerous viruses can be detected earlier and precautions can be taken and a pandemic can be prevented. It is important to examine the genomic sequences submitted to the National Center for Biotechnology Information database in the development of preventive and therapeutic strategies for COVID-19. Genomic diversity must be studied in samples collected from around the world in order to develop effective treatments and vaccines. In addition, genomic characterization will help us to accurately describe the origin and evolution of the virus. Demonstrating the mechanism of SARS-CoV-2 replication in various cell-based models, understanding the pathogenesis, and developing effective antiviral drugs can help us identify specific targets.

Diagnostic tests developed in a short time to combat the rapidly advancing COVID-19 pandemic, effective treatments against the virus, With the development of safe and highly effective vaccines, a significant decrease in the rate of spread of the epidemic will be observed as soon as possible.

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