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COVID 19 Disease Caused by Coronavirus 2 (SARS-CoV-2) (Severe Acute Respiratory Syndrome)

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Authors' contributions

This study was carried out in collaboration between the two authors. Author MU designed the study, wrote the clinical protocol part of the article. Author TI prepared the basic sciences section (chapters 1-7) of the study. Both authors read and approved the final article.

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Review Article

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ABSTRACT

Coronaviruses (CoV) are a large group from the *Coronaviridae* family that cause a variety of diseases, from the common cold to more serious clinical conditions such as SARS-CoV and MERS-CoV. This pathogen, which has a single chain, positive polarity and enveloped RNA viruses and causes bilateral interstitial pneumonia, has been associated by the World Health Organization (WHO) as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The resulting disease was defined as COVID-19. SARS-CoV-2 belongs to the family of β-coronavirus. Studies have reported that SARS-CoV-2 uses membrane-bound ACE2 to access target cells. It is understood that the virus is transmitted from bats to people, from person to person by droplet or by the contact of the sick person with respiratory secretion materials into the mouth, nose and eye mucous membranes of healthy people. The most common clinical findings were fever (87.9%), cough (67.7%), and weakness (38.1%). The exact diagnosis of Covid-19 is based on virus isolation or RT-PCR positivity. The sensitivity of Thorax CT in the diagnosis of Covid-19 is 97%. Most of the treatments applied are symptomatic. Remdesivir, Chloroquine, Arbidol, Kaletra, lopinavir / ritonavir and remdesivir have been proposed as antiviral agents that can be used in Covid-19 therapy. In order to be protected, attention should be paid to social distance, personal hygiene, a healthy lifestyle, a good sleep pattern, regular exercise, adequate and balanced nutrition. Although the

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outbreak started in China, it is also quite common in Europe and America. As of May 2, 2020, case reports were made from 215 countries. It has been declared as a pandemic by WHO because of its high transmission rate. The situation is of great importance for global public health. In this paper, we have systematically reviewed the SARS-CoV-2 and this report aims to give information about the genetic structure, pathogenic feature, source of infection, routes of transmission, etiopathogenesis, clinical features, diagnosis, treatment and prevention of the virus and to be a reference for future research, measures and treatments. This review aims to investigate the most current trend of COVID-19.

Keywords: SARS-Cov-2; COVID-19; coronavirus; severe acute respiratory syndrome.

1. INTRODUCTION

Coronaviruses (CoV) are a large group that causes a variety of diseases, from the common cold to more serious clinical manifestations such as Severe Acute Respiratory Syndrome (Severe Acute Respiratory Syndrome, SARS-CoV) and the Middle East Respiratory Syndrome (MERS-CoV). They can be transmitted from animals and cause disease in humans [1]. SARS-CoV-2 infection, which started in Wuhan, the capital city of Hubei province of China, was defined as a pandemic on March 11, 2020, as case reports were made from many countries according to the World Health Organization [2]. The animal reservoir of the virus has not yet been identified, but genomic of COVID-19 is so similar to bat coronavirus (98%), reinforcing the presumption that the virus was transmitted by an animal in the shopping center in Wuhan [1].

This pathogen causing bilateral interstitial pneumonia was reported to cause fever and pneumonia in Wuhan, China on December 31, 2019 [3,4]. Severe Acute Respiratory Syndrome was named Coronavirus 2 (SARS-CoV-2) by the World Health Organization (WHO) [2]. This SARS-CoV-2 related disease has been identified as coronavirus disease (COVID-19) due to its release in 2019. An outbreak has been reported by WHO in more than 215 countries outside China [2].

By May 2, approximately 3 .267 .184 cases cases of coronavirus disease (COVID-19) and more than 229. 971 deaths were reported in 2020 [2]. Turkey has so far reported 58,259 cases and 3,336 deaths [5]. Fortunately, children have rarely been affected by the virus without death. However, it has been suggested by British scientists that there may be a link between COVID-19 and an unusual inflammatory syndrome in children [6]. Our aim in this paper is to review the epidemiology, pathogenesis, clinical features, diagnostic methods, and management of patients infected with SARS-CoV-2 to better understand this deadly coronavirus and recommend prevention, treatment and management strategies. This article provides a brief overview of this new virus. Since information about this virus is developing rapidly, it should be considered that current information may change.

1.1 General Information

Coronaviruses (CoV) come from the Coronaviridae family and occur in diseases such as severe Acute Respiratory Syndrome (Severe Acute Respiratory Syndrome, SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV), HCoV -HKU1) [1]. It is a large group that causes various diseases, up to more serious clinical conditions.

According to the study of Xu et al. [7] these viruses affect the respiratory, gastrointestinal and central nervous systems of humans and animals (bats, birds, mice and many other wild animals). By transmitting from animals, they can cause disease in humans and cause outbreaks [7].Two viruses that cause Severe Acute Respiratory Syndrome (SARS) in 2003 and Middle East Respiratory Syndrome (MERS) in 2012 are also included in this group [7].

Beginning in December 2019, cases of high fever, cough, and pneumonia have been reported in Wuhan, the capital city of Hubei province, China. In December 31, 2019, this pathogen causing bilateral interstitial pneumonia was named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the World Health Organization [2]. In the disease associated with SARS-CoV-2, 2019 has been identified as coronavirus disease (COVID-19) [2].

The majority of the first patients diagnosed with Covid-19 were associated with the Seafood Wholesale Market in Wuhan [7]. In the early

stages, while the incubation period was 5.2 days, the number of outbreaks almost doubled in the size of the outbreak [7], it was thought that there could be a high transmission rate from person to person and had a pandemic feature [7]. It is transmitted from person to person by direct inhalation of the droplets formed by coughing, sneezing or talking of the sick person, or by direct or indirect contact of the sick person's respiratory secretion materials into the mouth, nose and eye mucous membranes of healthy people [8].

Covid-19 virus has much higher transmission and infection characteristics compared to the factors of SARS and MERS diseases, while the mortality rate is lower (11%, 35-50% and 5%, respectively) [8]. It was reported that it was transmitted from the bat as a result of genome analysis [8].

According to WHO's records on may 2, 2020, 3,507,557 cases have been reported as of 12.12.2019 and 245,243 cases have been lost, unfortunately [2]. During this period, case reports were made from 215 countries outside of China [2]. The rapid spread of infection and the risk of death are crucial for global public health. This report aims to provide information about the genetic structure, pathogenic feature, source of infection, routes of transmission, etiopathogenesis, clinical features, diagnosis, treatment and prevention of the virus and to be a reference for future research, measures and treatments.

1.2 Genetic Structure of SARS-CoV-2, Life Cycle

Coronaviruses are single-chain, positive polarity, enveloped RNA viruses [9]. COVID-19 is a spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein [9,10]. The envelope bears club-shaped glycoprotein projections [10,11,12]. Some coronaviruses also contain a Hem agglutinin-esterase protein (HE) (Fig. 1) [12,13,14].

Six previously known types of coronavirus can cause infection in humans, SARS-CoV-2 is the 7th virus that infects humans after SARS-CoV and MERS-CoV [14,15]. It has four subspecies: Alpha, Beta, Gamma and Delta. SARS-CoV-2 belongs to the family of β-coronavirus [16]. Because they have positive polarity, they do not contain RNA-dependent RNA polymerase enzymes, but in their genomes they encode this enzyme, they act as mRNA [16]. They have rodlike extensions on their surfaces. These viruses are named as Coronavirus based on the meaning of "corona", that is, "crown" in Latin [16].

SARS-CoV-2 (COVID-19) binds to Spike and ACE2 (angiotensin converting enzyme 2), allowing COVID-19 to enter and infect cells (Fig. 1) [13,15]. In order for the virus to complete entry into the cell following this initial procedure, the spike protein must be covered by an enzyme called protease [15]. Similar to SARS-CoV, SARS-CoV-2 (COVID-19) uses a protease called TMPRSS2 to complete this process [15]. Activation as a protease by TMPRSS2 is required to bind the virus receptor (spike protein) to its cellular ligand (ACE2) [15,16].

1.3 Comparison of Sars-Cov-2 and SARS-Cov

It was understood that after SARS disease emerged as severe acute respiratory syndrome in the world in 2003, coronaviruses caused severe infections in humans [17]. The emergence of SARS-CoV and SARS-CoV-2 viruses appears to vary between proliferation trend, mortality rates and genetic structures [17,18]. While both corona viruses were observed to have similar pathogens from the beta coronavirus family, SARS CoV originated from *Rhinolopus sinicus* bats, while SARS CoV2 was similar in 96.2% gene sequences to *Rhinolopus affinis* [19]. The gene sequences of both corona viruses were found to be 80% similar [19]. The incidence of SARS Cov infection in men and women was 1: 1.25, whereas SARS CoV- 2 was found to be 2.70: 1. While the mortality rate was 9.6% in SARS CoV, it was found to be 2.1% in SARS CoV -2 [20]. According to 2003 WHO data, 26 countries were affected by Sars CoV infection, 8096 cases were reported, and 774 deaths were observed. Half of the deaths were seen in China [17].

1.4 Pathogenic Mechanisms of SARS-CoV-2

SARS-CoV-2 uses angiotension-converting enzyme 2 (ACE2) as a receptor [21]. It is stated that the genomic characterization of SARS-CoV-2 shows only 79% and 50% similarity with SARS-CoV and MERS-CoV, respectively [22,23].

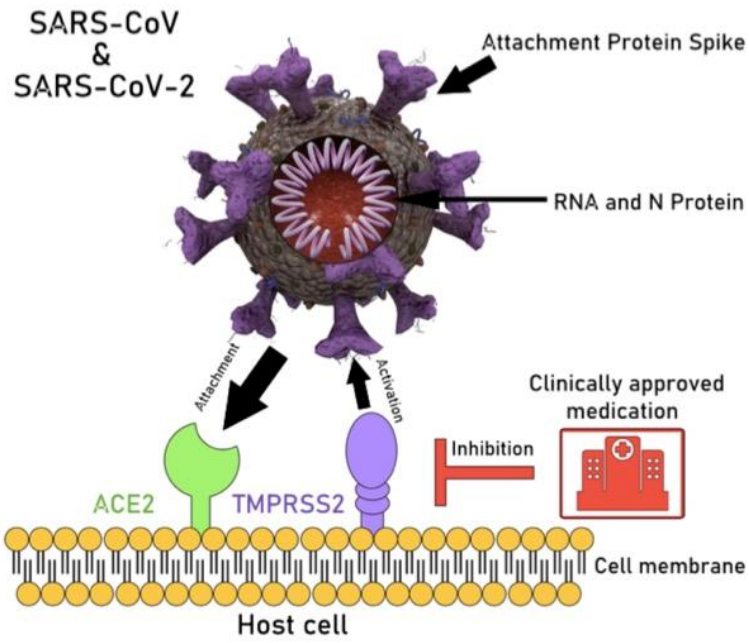

Fig. 1. The host cell receptor responsible for mediating infection of SARS-CoV-2 is ACE 2 (COVID-19) [13,15]

Type II transmembrane serine proteases (TTSPs) are expressed at the cell surface and are located to regulate cell-cell and cell-matrix interactions. new research exploits the flu and other respiratory viruses to promote the spread of TTSPs, making these proteases potential targets for intervention in cancer and viral infections The host cell receptor responsible for mediating infection of SARS-CoV-2 is ACE 2 (COVID-19) [15,16]

SARS-CoV-2 has been reported to utilize ACE2 bound to the same membrane as SARS-CoV to access target cells and the cellular protease TMPRSS2 for their activation [24,25]. Current, clinically validated drugs for TMPRSS2 inhibit SARS-CoV-2 infection of lung cells [24,25].

Coronaviruses recognize the receptor in the target cell with the S protein, enter the cell and cause infection [21]. It is thought that SARS-CoV-2 also infects people by binding the S-protein to ACE2 [21]. When SARS-CoV-2 infects most of the ciliated cells in the alveoli, acute respiratory distress syndrome (ARDS) develops as a result of an increasing amount of rash and fluid accumulation in the lungs, as these cells fail to perform their normal activities, which include cleaning the airways [21,22,23].

A recent study showed that ACE2 is highly expressed in the mouth and tongue and facilitates viral entry into the host [24]. Xu et al investigated differences in race, age, sex, and smoking status in ACE2 gene expression to identify possible differences that could lead to increased Covid-19 susceptibility among patients [24]. For this purpose, ACE2 gene expression was investigated for race (Asia and Caucasians), age (> 60 and <60) and gender (male and female) of normal lung tissue and no significant correlation was found in the data obtained [25]. However, smokers' lungs had significantly higher ACE2 gene expression than lungs of non-smokers, suggesting that smoking may be a risk factor for Covid-19 susceptibility [25,26].

1.5 Epidemiology and Natural Course of COVID-19

With regard to genomic similarity, the virus differs from its predecessors, namely SARS (79%) and MERS (50%). As indicated by genetic data, COVID-19 pathogen is classified as a member of the beta-coronavirus genus, and can bind to the angiotensin-converting enzyme 2 receptor in humans [21]. Most of the first cases have been reported in China with 84,388 cases and 4,643 deaths, mortality 5,5% [27].

Although the outbreak started in China, it is also common in Europe and America [27].

When the epidemiological features of the cases in China are analyzed, it is seen that the average incubation period is 5.4 days (2-14 days) and rarely can extend up to 27 days [27]. The infectious time of Covid-19 is not exactly known. It is thought to start 1-2 days before the symptomatic period and end with the disappearance of symptoms [28,29]. It has influenced all countries in Europe, especially Italy, Spain and France [29]. As of April 6, 2020, case reports were made from 215 countries. Covid-19 cases were seen later than other countries in Turkey, 2 May 2020 date, 58.259 Covid-19 more controlled than in other countries with a positive number of cases, and 3.336 lost cases continues [5]. Today, the USA is the most affected country with the number of cases detected (1,093,880). However, despite the high number of cases, mortality rates are lower than in Italy and Spain. Global mortality associated with Covid-19 reached 5-7% with 244.000 deaths [27,28].

In particular, Spain's 217.000 Covid-19 cases lead to 25.264 mortality, which is followed by Italy (209.000 cases, 28.710 deaths), Germany (165,132 cases, 6.812 deaths) and France (131.000 cases, 24.760 deaths) [27]. Europe has become the region with the largest disease epidemic after China. Outside Europe, America (1.160.880 cases, 67.060 deaths) and Iran (97,424 cases, 6,203 deaths) have reported a high number of cases to date [27]. When the cases that result in death are examined, it is seen that they generally have a high age average and have multiple chronic diseases. Cases were reported at the age of 14 in Spain and at the age of 21 in England [27]. The fact that some young cases reported to result in death do not have any chronic diseases showed that the young population may carry a mortality risk even if it is rare. However, serious illness symptoms requiring intensive care are very rare in young patients [28]. Given that all different age groups are at risk of getting SARS-CoV-2 infections, it is critical that all young individuals who have mild or symptom-free disease also follow self-isolation procedures to prevent the spread of the virus [30]. The average age of individuals infected with SARS-CoV-2 was 59, the average incubation period of the disease was 5.2 days and 56% of the cases were male [30]. It has been reported that the average age of death is 75 and the average time from the first symptom to death is 14 days [28,29,30]. The average time from early symptoms to death (11.5 days) in patients 70 years and older is shorter than patients under 70 (20 days) [31,32,33,34]. This shows that disease progression is faster in the elderly [31,32].

1.6 Covid-19 Comorbidity Conditions

Data from the European Center for Disease Prevention and Control (ECdC) indicate that in approximately 80% of cases with Covid-19 infection - without pneumonia or with mild pneumonia - mild disease and most of these cases heal spontaneously [33,34]. According to a report by Wang et al. that 14% of infected cases have a more severe form of the disease, and 6% are critically ill [31]. It has been found that the majority of severe cases and deaths occur in the elderly and those with chronic conditions [31] In the case of Italy, 50% of those who lost their lives as a result of Covid-19 are 70 years old or older [35]. Two or more chronic diseases were observed in 25% of cases and 3 in 50% of cases [35]. While 32% of Covid-19 patients have underlying diseases such as diabetes, hypertension and cardiovascular disease, the mortality rate in these cases has been reported to be 15% [36].

1.7 Origin of SARS-CoV-2

As the source of SARS-CoV-2, the first Pangolines, snakes, minks and other wild animals in the Seafood Wholesale Market in Wuhan were emphasized [19,20]. As a result of genome analysis studies, it has been suggested that the SARS-CoV-2 virus comes from bats. The sequence similarity of the coronavirus isolated from the SARS-CoV-2 virus and Rhinolophus Affinis has been reported to be 96% [20]. Based on these data, it suggests that bats may be a true source of SARS-CoV-2 [18,19].

1.8 Ways of Transmission of SARS-CoV-2

The transmission of the virus is thought to be by inhalation of the droplets produced by sick individuals directly by healthy individuals through the mouth and nose or by smearing it on the hand [27]. Coronaviruses are generally viruses that are not very resistant to the external environment and the duration of survival varies depending on the humidity and temperature of the environment in which it is located and the nature of the surface it is transmitted [28]. It is generally accepted that it loses its activity within a few hours on inanimate surfaces [27]. Considering the activity time on inanimate surfaces, it should be remembered that not only

the activity of the virus, but also the duration of contact [27]. It is stated that the virus can pass from mother to baby vertically. However the stiuation regarding the risk of vertical transmission in pregnant women is not clear and additional studies are needed [31,37].

1.9 SARS-CoV-2 Infection Symptoms and Clinical Features

Common symptoms of infection are fever, cough, and dyspnea. In more serious cases, pneumonia, severe acute respiratory infection, kidney failure, and even death may develop.Covid-19 has an average 3-day incubation period [27]. Patients present to clinics with complaints of high fever, dry cough and dyspnea in patients who have advanced a little more. WHO has described fever and dry cough as the most common symptoms of Covid-19 [37]. The most common clinical signs of SARS-CoV-2 infection are fever (87.9%), cough (67.7%), weakness (38.1%), and rarely diarrhea (3.7%) and vomiting (5.0%) [37]. While most patients have some dyspnea in the beginning, the time to ARDS is 9 days after the onset of symptoms. Many of these symptoms are similar to those seen in common seasonal flu and colds. However, in SARS-CoV-2 patients, fever is different from others with 38.5°C and above, no discharge in the eyes and nose, and a dry cough [38].

In severe patients, there are also risks of developing ARDS, acute heart damage, and secondary infection [38]. There is evidence that Covid-19 damages extra-pulmonary tissues and organs [38]. Studies involving Covid 19 patients also show that patients develop neurological complications, eye surface infections, arrhythmia, acute heart damage, kidney dysfunction, and liver dysfunction. [38,39,40,41].

Bilateral thorax CT findings are present in 90% of the cases, and the sensitivity of thorax CT in the diagnosis of Covid-19 is 97%. By combining thorax CT findings, clinical symptoms and laboratory test results, early diagnosis of Covid-19 pneumonia is possible. In blood tests, lymphopenia (82.1%), thrombocytopenia (36.2%) and leukocytosis were observed in some patients, but leukopenia (33.7%) was detected in some patients [40,41]. There was an increase in CRP, LDH and CK levels in patients. In Covid-19 cases, parallel to the severity of the disease, IL-6 and IL-10 levels increased, CD4 + T and CD8 + T levels decreased [42].

1.10 COVID-19 Cases in Children

The incidence of Covid-19 during infancy, childhood and adolescence is very rare (0.2%) [43,44]. Our main findings are that the course of the disease in pediatric COVID-19 is milder than adults, its prognosis is better, and deaths are extremely rare. In his review, Ludvigsson examined 45 studies on COVID-19 in children, and found that some of the children who were diagnosed with COVID-19 had negative tests, and the diagnosis could not be confirmed by laboratory tests [44]. Dong Y. et al. Found that children suspected of COVID-19 had a more severe prognosis than those whose disease was confirmed in the laboratory [45]. These findings suggest that some suspected COVID-19 cases may have been caused by other pathogens [45].

1.11 Protection from SARS-CoV-2

Specific antiviral therapy and vaccine are not yet available for SARS-CoV-2 therapy [46]. Currently, Covid-19 therapy is limited to supportive and palliative therapy. For this reason, it is very important to develop a safe and effective Covid-19 vaccine, and studies related to this are carried out by many centers. SARS-CoV-2 is an RNA virus and RNA virus vaccines are trustworthy alternatives such as measles, polio, encephalitis B virus, and influenza virus. Prevention of the transmission of the virus from person to person can be possible by vaccination of healthcare personnel and non-virus infected people [47].

Taking vitamin C, D and E increases resistance to SARS-CoV-2 [48,49]. Patients with chronic diseases such as hypertension, diabetes, coronary heart disease, and tumors have a higher risk of developing Covid-19 infection than individuals without such chronic diseases [50]. Low immunity that develops in these patients increases the risk of poor prognosis due to both chronic diseases and drugs used for these diseases [50]. Therefore, attention should be paid to social distance. The main way to strengthen the personal immune system is to take care of personal hygiene, have a healthy lifestyle, have a good sleep pattern, exercise regularly and take care of adequate and balanced nutrition. People who pay attention to personal hygiene, wear masks, wear gloves, wash their hands for at least 20 seconds with soap, use antiseptics, test and live in well-ventilated areas can prevent the transmission of infection with these protective elements [37].

1.11.1 Recommended precautions to prevent the spread of SARS-CoV-2 [37]

General measures in protection:

- Hand cleaning should be considered.
- Mouth, nose and eyes should not be touched without washing hands.
- Sick people should avoid contact (if possible, be at least 1.5 m away).
- The nose and mouth should be covered with a disposable tissue paper during coughing or sneezing,
- If leaving the house, a mask should be worn
- Eating raw or undercooked animal products should be avoided.
- If any respiratory symptoms occur within 14 days after travel, a mask should be worn to the nearest health facility.

Suggestions for precautions to be taken when coming from a country with SARS-CoV-2 or contacting a patient with Covid-19 in the last 14 days [27];

- It is recommended not to leave the house for 14 days even if there is no fever and cough.
- If leaving the house, a mask should be worn
- Public transport should not be used as much as possible
- Do not accept visitors
- Stay in a separate room
- Ventilate your room frequently
- Use a separate toilet if possible
- Separate plates and glasses should be used
- Medical masks should be worn at home

1.12 SARS-CoV-2 Diagnosis

Viral nucleic acid detection is standard in the diagnosis of COVID-19. However, the detection of SARS-CoV-2 nucleic acid is high and its sensitivity is low [51]. Therefore, false negativities are high and the duration of diagnosis is prolonged [52]. The exact diagnosis of Covid-19 is based on viral isolation in the sample taken from sputum, nose and throat, or the positivity of the polymerase chain reaction. However, it is known that the sensitivity of real-time, polymerase chain reaction (RT-PCR) detection for Covid-19 is lower than Thorax CT [53]. The sensitivity of Thorax CT in the diagnosis of Covid-19 is 97% [53].

1.13 SARS-CoV-2 Treatment

Most of the treatments applied up to this time are symptomatic. Since Remdesivir is used for treatment against most RNA viruses, Covid-19 has also been dispatched for use [54,55]. However, chloroquine has been shown to inhibit the virus *in vitro* [56]. It has proven that Chloroquine is effective in treating patients infected with Covid-19 [57]. In addition, Arbidol, Kaletra, lopinavir / ritonavir, nucleoside analogues, neuraminidase inhibitors, remdesivir and peptide EK1 have also been suggested to be antiviral agents that can be used in Covid-19 treatment [58,59,60].

Synthetic recombinant interferon α has been found to be effective in SARS patients in clinical trials [61]. MERS-CoV has been found to be an important inhibitor of replication. Based on these studies, it has been reported that interferon can be used in Covid-19 treatment [61]. Thymosin alpha-1 (Ta1) has been shown to be effective in controlling the spread of the disease as an immune system activator in SARS patients [62].

In the absence of effective vaccines and drugs, plasma from the recovered person can be considered an alternative in controlling and treating the disease [63]. In a retrospective analysis, plasma therapy was emphasized to be effective in those with severe SARS disease [64]. In the studies of Hung et al, it has been shown that the risk of death in people infected with H1N1 is significantly lower in those receiving plasma therapy [65]. Therefore, plasma globulin specific to SARS-CoV-2 can be produced by removing Covid-19 patients who have survived it [65].

Today, extracorporeal blood purification technology is used in the treatment of severe corona patients [66]. According to recent studies, ACE2 is present in the human kidney as a key receptor of SARS-CoV-2 (100 times the lung). For this reason, the kidneys may be the main attack of SARS-CoV-2. Early continuous blood purification can be effective in controlling kidney damage by reducing kidney workload [67]. Most of the patients with severe disease related to corona are affected by cytokine storm. Imbalance of pro-inflammatory factors and anti-inflammatory factors can cause immune damage. For this reason, inflammatory factors can be taken with blood purification technology, cytokine storm can be eliminated, electrolyte imbalance can be corrected and acid base balance can be

achieved [67]. With this logic, the patient's symptoms can be improved and the blood oxygen level can be increased.

2. CONCLUSION

As a result, COVID-19 is an important and severe viral infection table caused by SARS-CoV-2. The main initial symptoms are fever, cough and fatigue. In the following periods, dyspnea may accompany the picture. It is transmitted by droplet or by mucous contact with infected ingredients. SARS-CoV-2 has a high transmission rate. Therefore, life in some patients threatens global health and safety in the society. Therefore, it is the most important goal to prevent the spread of the disease and reduce mortality. Since there is no vaccine or specific treatment currently available, it is important to be able to control the source of infection, interrupt transmission routes and use the drugs available to prevent disease progression. Specific drug and vaccine development studies are ongoing to reduce morbidity and mortality of the disease and ensure the safety of human life. Given the high transmission rate of this virus between humans and pandemics, it is important to determine the basis of its replication, structure, and pathogenicity to find a suitable route to specific treatment or prevention.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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