A General Evaluation on Current Global Threat of Coronavirus (Covid-19) Immuno Responsibilities

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ABSTRACT

Covid-19 SARS-CoV-2 (severe acute respiratory syndrome-coronavirus-2) is a new type of coronavirus known as an infectious upper respiratory tract infection disease. The coronavirus, which poses a great threat to human health worldwide, emerged in Wuhan, China in December 2019. The most important reason for coronavirus epidemics to become a pandemic that the disease was easily transmitted by droplets in close proximity with infected people. The disease spread rapidly all over the world within a few months and it was declared a worldwide epidemic by the World Health Organization in March 2020. It poses a risk for severe diseases such as hypertension, diabetes, cardiovascular disease, cancer, chronic lung disease and chronic kidney disease in the advanced age group. Considering the mortality rates to date, great efforts have been made both worldwide and in our country to manifacture successful drugs and vaccines against Covid-19 infection. The main purpose of this review is to assist in an immune response and preventive work for Covid-19, thanks to the available information about the coronavirus epidemic that deeply affects humanity and the diseases it causes.

Mevcut Küresel Koronavirüs Tehdidinin (Covid-19) İmmün Sorumlulukları Hakkında Genel Bir Değerlendirme

ÖZ

Covid-19 SARS-CoV-2 (şiddetli akut solunum sendromu-koronavirüs-2), bulaşıcı bir üst solunum yolu enfeksiyonu hastalığı olarak bilinen yeni bir koronavirüs türüdür. Dünya genelinde insan sağlığı için büyük bir tehdit oluşturan koronavirüs, Aralık 2019'da Çin'in Wuhan kentinde ortaya çıkmıştır. Koronavirüs salgınlarının pandemi haline gelmesinin en önemli nedeni, hastalığın enfekte kişilerin yakınında bulunan damlacıklar yoluyla kolayca bulaşmasıdır. Birkaç ay içinde hızla tüm dünyaya yayılan hastalık, Mart 2020'de Dünya Sağlık Örgütü tarafından dünya çapında bir salgın olarak ilan edilmiştir. İleri yaş grubunda hipertansiyon, diyabet, kardiyovasküler hastalık, kanser, kronik akciğer hastalığı ve kronik böbrek hastalığı gibi ağır hastalık tablosu için risk oluşturmaktadır. Bugüne kadar ölüm oranları göz önüne alındığında, Covid-19 enfeksiyonuna karşı başarılı ilaçlar ve aşılar üretmek için hem dünya çapında hem de ülkemizde büyük çabalar sarf edilmektedir. Bu derlemenin temel amacı, insanlığı derinden etkileyen koronavirüs salgını ve neden olduğu hastalıklar hakkında elde edilen mevcut bilgiler sayesinde Covid-19 için bir bağışıklık müdahalesine ve önleyici çalışmalara yardımcı olmaktır.

1. Introduction

Sars-Coronavirus (Covid-19) is a coronavirus that was first seen in China in February 2003 and causes severe acute respiratory failure. This family of viruses is zoonotic and they can infect humans from animals (Yücel and Görmez, 2019; Akpınar and Üstün, 2020). It is thought to be of bat resource. Direct contact with wild animal hosts and respiratory droplets of infected patients are the main sources of transmission of the disease Coronaviridae family. Coronaviruses are viruses with the largest genome known as an RNA virus. They are single-stranded, enveloped viruses with positive-sense RNA genome, approximately 26-32 kilobase in size. The term 'coronavirus' was given the name 'corona', which means crown in Latin, because of the sharp protrusions formed from the virus membrane resembles a crown when observed under the electron microscope (Figure 1).
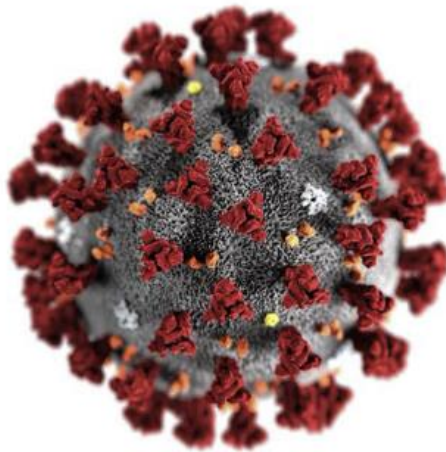

Figure 1. SARS-CoV-2 virus (Sohrabi et al., 2020)

In the observations made so far, it has been revealed that the incubation period of SARS-CoV-2 is on average 5,2 days (4,1-14) (Alimoğlu and Erol, 2020; Buruk and Özlü, 2020; Esakandari et al., 2020). Common symptoms of Covid-19 at the end of the incubation period are respiratory distress, cough and fever. It is also contagious through droplet infection and close person-to-person contact. It can also be made through sweat, feces, urine and respiratory secretions (Prajapat et al., 2020). The agent may be symptom-free or manifest with mild symptoms or severe respiratory distress (Alkan Çeviker and Dindar Demiray, 2020). Severe illness occurs in 14% of viral pneumonia cases. Some patients' respiratory distress progress to worsen gradually and develop acute respiratory distress syndrome (ARDS), which usually requires mechanical ventilation support that extends to the third week (İnal İnce et al., 2020; Örs, 2020). At the beginning of the epidemic, it was observed that the first cases detected were linked to the marketplace where live animals were sold in Wuhan and later closed, considering it could be a source of disease. However, as time passed, it was understood that the disease spread from person to person. Although it is seen in all age groups, in people with underlying

systemic diseases, both the clinical picture worsens and the mortality rates increase in the population over 65 (Su et al., 2016; Uğraş Dikmen et al.,2020; Yılmaz, 2020; Shi et al., 2020).

Covid-19, which has been widely seen around the world in the last few years, is one of the major pandemics. There is a need for much more information and documents regarding the unknown aspects and treatment, especially day by day. In this review, it is aimed to contribute to future studies by providing the necessary information about the general characteristics and treatment possibilities of Covid-19, which has become a relentless disease.

2. General Information

2.1. Virology of Coronavirus

Coronaviruses are capsid structured viruses with helical symmetry single-stranded positive-polar RNA genome. Their genomes are among the largest RNA genomes. It is approximately 26-32 kb in size. The spike protein, envelope and membrane on the surface of the coronavirus are embedded in the host membrane derived lipid bilayer surrounding the helical nucleocapsid containing viral RNA. Four structural proteins make up the outer structure of the coronavirus. In this way, it protects the RNA inside. Spike protein, namely homotrimers of S proteins, form distinct crown-like spike structures on the surface of the virus. S protein is a viral fusion protein containing S_1 and S_2 subunits. The main function of the S_1 protein is to bind to the host cell receptor. The S_2 subunit of the S protein is mainly responsible for membrane fusion. In addition to having three transmembrane domains, the M protein is responsible for attaching to the nucleocapsid by shaping virions. The E protein known as the envelope protein, is responsible for the assembly of the virus in viral pathogenesis. Hemagglutinin esterase protein, on the other hand, is the protein on the envelope and enables the virus to attach to the receptors containing sialic acid (Figure 2). Coronaviruses use the ACE2 receptor (angiotensin converting enzyme) to bind to the host cell membrane. The ACE2 receptor is highly expressed in type 2 alveolar cells and goblet cells, which are the gateway to the virus and synthesize surfactants. ACE2 is also found in high concentrations in intestinal epithelium and heart cells, while low levels in monocytes and macrophages. This shows how the coronavirus can enter immune cells (Kurtuluş and Pirim, 2020; Tanrıverdi et al., 2020).
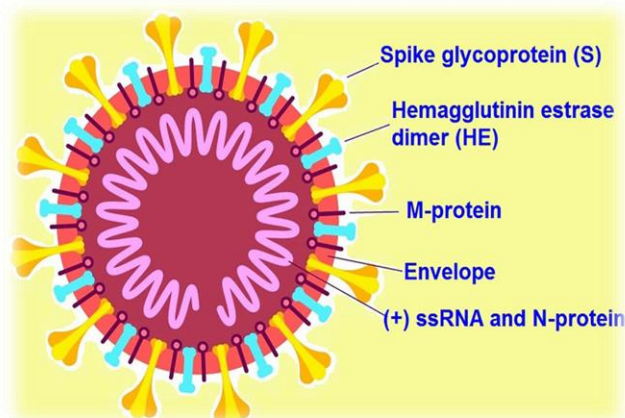
Figure 2. 2019-nCov'n structure (Esakandari et al., 2020)

3. Coronavirus Symptoms and Incubation Times

It is a respiratory disease caused by Coronavirus 2 (SARS-CoV-2) infection with severe acute respiratory syndrome. The incubation time of SARS-CoV infection is among 2 and 10 days. It reports mild symptoms (fever, coughing, shortness of breath), severe illness or death in cases infected with SARS-CoV-2. Early symptoms are flu-like symptoms such as fever, chills, cough, myalgia and headache. However, some infected patients died due to various fatal complications such as organ failure, pulmonary edema, septic shock, Respiratory Distress Syndrome (ARDS) and severe pneumonia. Acute in particular, patients in need of intensive care have been reported to have advanced age and comorbid diseases (related to cardiovascular, endocrine, cerebrovascular, respiratory systems and digestive). It has been reported that the high fever is sometimes absent in the elderly or has improved by the time respiratory symptoms appear. After that starting of the respiratory phase, a febrile phase lasted for about 3 days, patients experienced dry cough, shortness of breath and hypoxemia. The case fatality rate is between 3 and 16%. The incubation period in MERS-CoV infection is between 3-14 days. After the incubation period, symptoms of high fever, sore throat, dry cough, respiratory failure, headache, muscle and joint pain were observed. Infections have been reported to cause lower respiratory tract involvement, especially in elderly patients who are considered to be a risk group or those with underlying chronic heart, lung and kidney disease. Disease progression is similar for SARS and MERS. However, the case fatality rate of MERS is higher than SARS. According to World Health Organization (WHO), although the incubation period from the time the new virus is infected until the symptoms are seen has been reported for about 14 days, today the contagious period and the duration of the external environment of SARS-CoV-2 are not clearly known. The course of the disease ranged from mild symptoms to severe death and illness for cases of SARS-CoV-2 infected. Symptoms of fever, cough and shortness of breath may occur 2-14 days after exposure (Figure 3). Until now, it has been reported that the transmission route of the disease is through droplets (Baloch et al., 2020; Sohrabi et al., 2020; Uludağ, 2020).
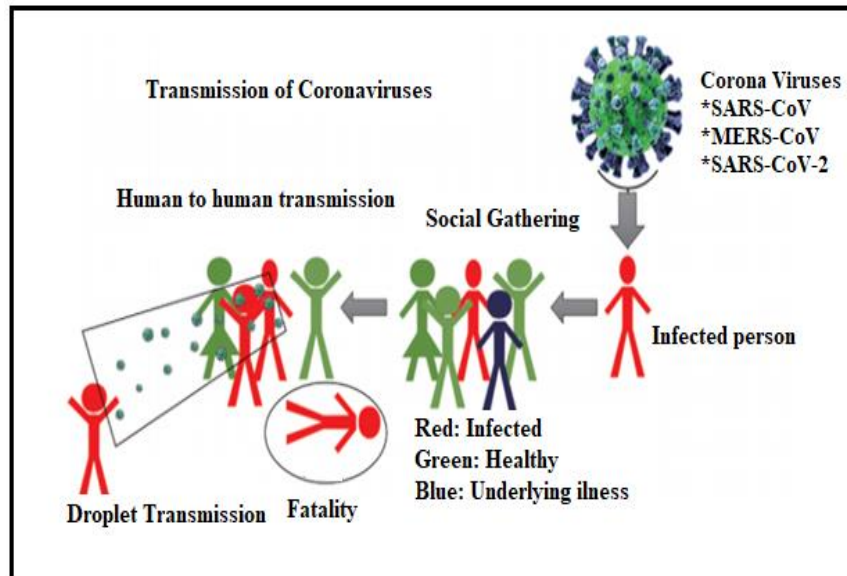
Figure 3. Coronavirus (Covid-19) spread (Baloch et al., 2020)

4. Detection Methods of Coronavirus

Nucleic acid amplification tests (NAAT) for coronaviruses are based on the detection of specific sequences of virus RNA and it necessary, verification by nucleic acid sequence analysis method. Current detection for coronaviruses involves the quantitative polymerase chain reaction (qPCR) technique that identifies viral nucleic acids when present in sufficient quantities (Figure 4). Three specific viral genes [ORF1a/b, nucleocapsid protein (N) and envelope protein (E) genes] are searched in samples using qPCR technology. These genes are identified using their fluorescence intensity. Serological tests such as enzyme linked immunosorbent assay (ELISA) or immunoglobulin M (IgM) and IgG detecting antibody tests are also used to support the diagnosis in order to show antigen antibody reactions in serum samples (Uludağ, 2020).
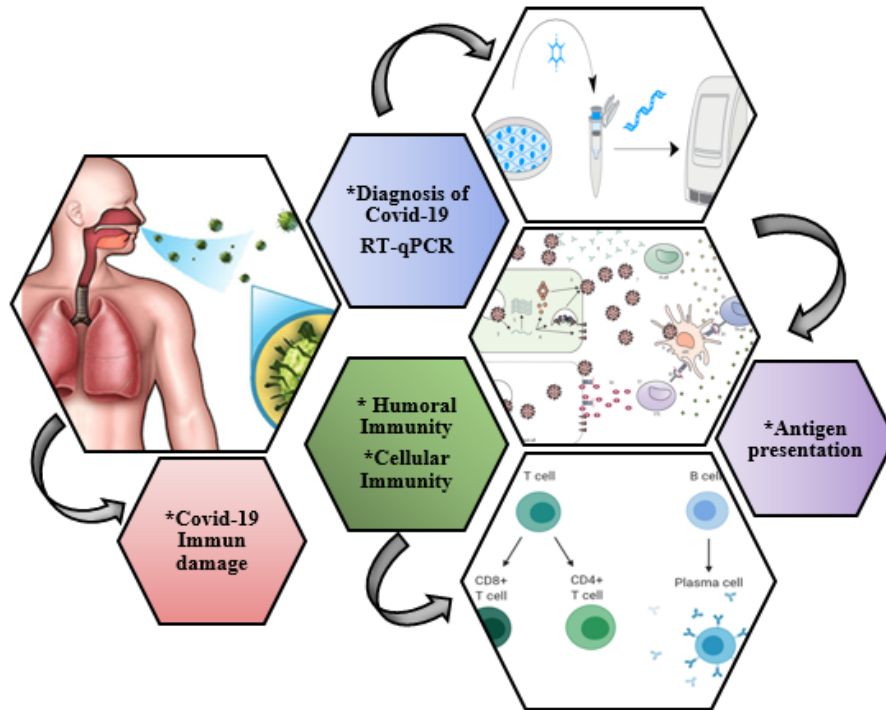
Figure 4. Coronavirus (Covid-19) treatment approaches

5. Coronavirus Treatment Methods and Precautions

Radiological evaluations are of great importance in patients with suspected Covid-19 infection. Early diagnosis of the disease is also vital for timely treatment. Typical computer tomography (CT) findings in Covid-19 diagnoses include peripherally distributed multifocal ground glass opacities. The increase in the number and density of ground glass opacities in computer tomographs indicates that the disease has progressed. Especially computed tomography (CT) plays an important role in the diagnosis of the disease. In addition, travel ban applications are one of the most effective tools to prevent the effect of the virus (Bernheim et al., 2020). Recent research has found that many medicinal herbs also provide antiviral protection. Especially with the studies in the literature, ellagic acid, turmeric and epigallocatechin 3-gallate has preservative effect against viruses such as coronavirus, human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), enterovirus 71 (EV71), ebola virus (EBOV). It has been found that they provides antiviral protection by inhibiting the infectivity and function of many viruses, including influenza A virus and Zika virus function (Dai et al., 2018; Aslan et al., 2020a; Aslan et al., 2020b).

5.1. Antimicrobial Treatment

Empirical antimicrobial agents are recommended for patients with definitive diagnosis of Covid-19. Before antibiotic treatment, blood cultures and samples should be taken from both the upper and lower airways. In patients diagnosed with Covid-19 or with an involvement consistent with viral pneumonia on chest X-ray or chest computed tomography, it is recommended to initiate antiviral therapy in the

early period. Therapeutic drug levels should be monitored in antiviral and antibiotic drugs. Lopinavir and ritonavir are antiretroviral drugs belonging to the group of drugs called protease inhibitors. They act by slowing down the spread of the infection in the body by removing the protease enzyme since viruses need to reproduce. It is recommended to use lopinavir 200 mg or ritonavir 50 mg tablets orally at a 2x2 dose for 10-14 days instead of favipiravir in pregnant patients with definite diagnosis (Uludağ, 2020; Zhu et al., 2020).

5.2. Vasoactive Agents

Norepinephrine is the leading vasoactive agent used in the treatment of Covid-19. It is recommended to use vasopressin or epinephrine, especially if norepinephrine is not available. If the target mean arterial pressure cannot be achieved with norepinephrine alone, it is recommended to add vasopressin as a second-line agent rather than titrate the norepinephrine dose. It is stated that it is more appropriate to titrate the vasoactive agent to target an arterial pressure of 60-65 mm-Hg rather than high arterial pressure targets. For patients with cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, the addition of dobutamine is recommended instead of increasing the dose of norepinephrine, and the use of dopamine is not recommended (Rollas and Şenoğlu, 2020; Uludağ, 2020).

5.3. Corticosteroids

While Covid-19 is mild in some patients, it progresses to respiratory failure requiring ventilation in others. This event starts with the activation of the immune response in response to the proliferation of the Covid-19 virus and the foreign particles reaching the lower respiratory tract due to the virus inactivating the signals. The proliferating virus binds to the ACE2 receptor and causes widespread inflammation in the alveoli within the cell. (Akyar, 2020). Although incidence data are limited, a large case series of 1300 patients with Covid-19, especially in Italy, showed that 88% of critically ill patients required mechanical ventilation. A severe, hyper-inflammatory, cytokine-mediated lung injury plays a role in Covid-19. With the excessive release of cytokines, it causes damage to the alveolar epithelial tissue, capillary tissue destruction, increased capillary permeability and therefore fluid leakage into the alveoli. All these processes lead to the development of respiratory failure. Drugs such as proinflammatory cytokines may interfere with the normal adaptive response. (Akyar, 2020; Lentz et al., 2020). In addition, the use of corticosteroids as an adjunct pharmacological treatment in the treatment of Covid-19 was evaluated. Routine use of systemic corticosteroids is not recommended in adults with COVID-19 and respiratory failure. (Uludağ, 2020; Zhu et al., 2020) Steroids are widely used in addition to other drugs during the Covid-19 pandemic. Steroid therapy is known to have a good efficacy in stabilizing hemodynamics, shortening the length of stay in the intensive care unit and mechanical ventilation (Mattos-Silva et al., 2020).

5.4. Coagulopathy Treatment

In the first case reports reported from China, more frequent deaths were observed in patients who developed coagulopathy. It has been observed that coagulopathy becomes evident on the 7th day of viremia. Plasma tissue factor and plasminogen activator inhibitor-1 were found to be higher in patients with acute respiratory distress syndrome in the lungs than in patients without acute respiratory distress syndrome in the lungs. It has been stated that in the management of coagulopathy associated with Covid-19, initiation of heparin in case of elevated D-Dimer reduces mortality. In addition to the anticoagulant effect of heparin, it has been determined that it is a very effective method by binding inflammatory cytokines, inhibiting neutrophil chemotaxis and leukocyte migration. Serum fibrinogen level in Covid-19 patients decreases especially from the 7th day. High D-Dimer and fibrin degradation products should suggest the development of disseminated intravascular coagulation (DIC). If there is major bleeding with the diagnosis of DIC, blood product replacement should be performed. It has been reported to be inappropriate in patients without bleeding unless coagulation factor replacement is required (Rollas and Senoğlu, 2020; Uludağ, 2020).

5.5. Vaccine Treatment

When the human body encounters pathogens, the immune system kicks in. The innate immune system consists of neutrophils, macrophages, natural killer cells and dendritic cells that are not antigen-specific and act to destroy the pathogen. When the antigen level in the body exceeds a certain threshold, the antigen-specific adaptive immune system consisting of humoral and cellular immunity comes into play. Acquired immunity is acquired through vaccines (Zinkernagel, 2003; Duran, 2021). Studies on vaccine research and development against the treatment of Covid-19 continue at an unprecedented pace around the world. The fact that SARS-CoV-1's genome sequencing analyzes have been performed previously and that the S glycoprotein and nucleocapsid proteins on the virus surface are known to be the appropriate antigenic regions for the vaccine has accelerated the studies on vaccine development. Some Covid-19 vaccines that have received Emergency Use Approval are now being implemented all over the world. Among these vaccines, Pfizer/BioNTech (BNT162b2) vaccine is an mRNA-based vaccine. Its effectiveness against symptomatic Covid-19 has been observed to be 95%. According to these results, it has been shown that the humoral immune response that develops after SARS-CoV-2 infection continues for at least one year. It has been reported that the humoral immune response of individuals who received mRNA vaccines after contracting the disease was significantly enhanced, including variants of SARS-CoV-2. Sinovac vaccine, on the other hand, is an inactivated whole virus vaccine. It has been determined that the efficacy of two doses of Sinovac vaccine administered between the ages of 18-59 in Turkey against symptomatic Covid-19 is 83%. AstraZeneca/University of Oxford/Serum Institute of India vaccine is a vector vaccine using nonreplicative chimpanzee adenovirus. Turcovac vaccine, which has been approved for emergency use, has been started to be implemented in Turkey (Topçu and Nasuhbeyoğlu, 2020; Dayan, 2021).

5.6. Measures to be Taken against Coronavirus

The measures needed to reduce the transmission of Covid-19 were outlined in WHO's 72nd report on coronavirus. Within the scope of this report, individual and environmental measures, isolation of cases, collective meetings, quarantine and travel measures, vaccinations and treatments are among the necessary measures. Physical and social distancing measures slow the spread of the disease by preventing the risk of transmission of Covid-19 and the emergence of new cases. While these measures reduce the physical distance between people and contact with contaminated surfaces, they increase the virtual and social connection in the society. These measures, often taken for public health, include distance education, remote and flexible working, crowd reduction and closure of unnecessary facilities and services. In particular, frequent hand washing rules against Covid-19 and the rules to be considered when coughing are of great importance in terms of individual precautions (WHO, 2019; Samancı, 2020).

6. Conclusion

The corona viruses spreads day by day, particularly as a result of close contact. Fast and effective diagnosis is vital in avoid the spread of Covid-19. Because it is necessary to stop the spread of Covid-19, isolate infected people earlier and start treatment of patients who need treatment immediately. For this reason, it is of great significant to take protective measures to prevent infection. To reduce the risk of contamination, washing hands frequently with water and soap using an alcohol-based hand sanitizer regularly, maintaining social distance, avoiding touching, nose, eyes and mouth, applying respiratory hygiene, using face masks in social areas, such as not being in crowded environments unless necessary. Precautions are of great importance. It is thought that this review may assist researchers and clinicians in the classification, diagnosis, prognosis and treatment of coronavirus illness. Since there is no effective antiviral drug in the treatment of Covid-19 caused by SARS-CoV-2, vaccination has become the most effective method in combating the disease. The interest in vaccination is increasing day by day due to the pandemic process we have experienced in the last few years and the emergence of new variants. Vaccines are one of the most important methods developed to protect people and prevent the development of variants, as well as to stop the pandemic. The aim of vaccination is to gain immunity by the society in a short time and to provide it at an equal level all over the world. In a short period of one year, Covid-19 vaccines were developed and started to be used on a global scale with emergency use approval. If enough attention is not given to vaccination, new variants and mutations will continue to emerge.

Statement of Conflict of Interest

Authors have declared no conflict of interest.

Author's Contributions

The contribution of the authors is equal.

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