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Update on the First Year of COVID-19

Birinci Yılında COVID-19 Güncellemesi

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Abstract

The current outbreak of the Coronavirus, severe acute respiratory syndrome Coronavirus-2, which originated in the Wuhan province of the People's Republic of China became a pandemic. Although the clinical findings of the infection vary in adults, the most common symptoms are fever, dry cough, and shortness of breath. The diagnosis of the Coronavirus disease-2019 (COVID-19) is made by clinical symptoms, laboratory tests, and radiological methods. Many drugs such as antivirals, antibiotics, and corticosteroids are used in the treatment of COVID-19. For the successful control of the pandemic, prevention strategies are the key. There is strong consensus that, in addition to wearing masks, hand hygiene, and social distancing, an effective COVID-19 vaccine is probably the most effective approach to sustainably control the pandemic. In this article, current information about the pathogenesis, epidemiology, risk groups, diagnosis, treatment, prevention strategies, and vaccination of the disease in the first year of the COVID-19 pandemic are discussed.
Keywords: COVID-19, SARS-CoV-2, pandemic, vaccine, prevention

Öz

Çin Halk Cumhuriyeti'nin Wuhan eyaletinde başlayan koronavirüs şiddetli akut solunum sendromu Koronavirüs-2 salgını birçok ülkeye yayıldı. Erişkin yaş grubunda enfeksiyonun klinik bulguları değişiklik gösterse de en sık görülen semptomlar ateş, kuru öksürük ve nefes darlığıdır. Koronavirüs hastalığı-2019 (COVID-19) tanısı klinik semptomlar, laboratuvar testleri ve radyolojik yöntemlerle konur. Tedavide kullanılan çok çeşitli ilaçlar, özellikle antiviraller, antibiyotikler ve kortikosteroidler bulunmaktadır. Pandeminin kontrolünde, önleme stratejileri başarının anahtarıdır. Maske takmaya, el hijyenine ve sosyal mesafeye ek olarak, etkili bir COVID-19 aşısının salgını sürdürülebilir bir şekilde kontrol altına almak için muhtemelen en etkili yaklaşım olduğu konusunda güçlü bir fikir birliği vardır. Bu yazıda, COVID-19 pandemisinin ilk yılında hastalığın patogenezi, epidemiyolojisi, risk grupları, tanısı, tedavisi, önleme stratejileri ve aşılaması ile ilgili güncel bilgiler gözden geçirilmektedir.
Keywords: COVID-19, SARS-CoV-2, pandemi, aşı, korunma

Introduction

Coronavirus disease-2019 (COVID-19) disease, caused by the severe acute respiratory syndrome-Coronavirus-2 (SARS-COV-2) virus appeared in the Wuhan province of China in December 2019 and then affected the entire world within a short time[1]. The term SARS-COV-2 was formally declared by the Virus Taxonomy International commitee, and then, the World Health Organization (WHO) stated the formal noun of the infection caused by SARS-CoV-2 as COVID-19. On March

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11, 2020, the WHO changed the status of COVID-19 from an epidemic to a pandemic[2,3]. Coronavirus disease-2019 has been spreading rapidly around the world, with a total of more than 166,486,814 million definite cases and 3,457,853 deaths reported worldwide by May 21, 2021[3]. In this article, the viral classification of the COVID-19 agent SARS-CoV-2, its mutations, pathogenesis, epidemiology, high-risk groups for infection, diagnosis, treatment methods, prevention strategies, and current COVID-19 vaccine updates are discussed to provide a multidirectional perspective.

Severe Acute Respiratory Syndrome-CoV-2 and Viral Classification

The SARS-CoV-2 virus belongs to the Coronaviridae family as they share similar nucleic acid sequences to SARS-CoV and Middle East respiratory syndrome Coronavirus (MERS-CoV) viruses. In 2002 and 2013, SARS-CoV in China and MERS-CoV in Saudi Arabia caused serious human infections like severe pneumonia and bronchiolitis. The coronavirus family is divided into four classes: alpha (α), beta (β), gamma (γ), and delta (δ). Seasonal pathogenic viruses such as Human Coronavirus-OC43, HKU1, NL63, and 229E are among the α-coronaviruses. β-coronaviruses include SARS-CoV and MERS-CoV zoonotic viruses. Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses. They are responsible for upper respiratory and digestive tract infections. Based on its sequence of genomes, SARS-CoV-2 shares almost 76% of the amino acid sequence to SARS-CoV in the Spike (S)-protein sequence and 80% with the CoV ZXC21 (bat isolate)[4,5]. Severe acute respiratory syndrome CoV and SARS-CoV-2 utilize the similar receptor, angiotensin-converting enzyme-2 (ACE-2), for entry into the target cells[6,7].

Viral Mutation and Bioinformatics

For sharing and distributing the information of virus genomes, mutations, and their evolution, the Global Initiative on Sharing All Influenza Data, public-private-partnership initiative has played a key role[8]. Coronavirus-Genes Linked by Underlying Evolution, one of the COVID-19 databases, has been developed and funded by the COVID-19 Genomics United Kingdom (UK) Consortium. Coronavirus-Genes Linked by Underlying Evolution database interprets and analyzes the SARS-CoV-2 virus genome sequences, with a focus on amino acid sequence variation[9]. Sequencing, especially next generation sequencing (NGS) enabled scientists to identify SARS-CoV-2. It also allowed the scientific community to develop proper diagnostic tests to control the outbreak[10]. Coronavirus genome sequencing efforts and related bioinformatic studies played an important role in monitoring the virus spread and its evolution. They played an important role in determining the diagnosis and treatment options in COVID-19 research, epidemic management, and many different scientific areas. Genome sequencing is required for protein generation and primer preparation for the diagnostic tests. In addition, mutations were followed by a genome analysis, and the resistance or susceptibility of new variants to antiviral therapy was tried to be determined.

In research efforts, the special and novel genetic makeup of SARS-CoV-2 has created many obstacles, but the scientific community has finally discovered some potential drugs and vaccines, thanks to the application of mathematical modeling and computational simulation techniques through computational biology. Over the past few decades, the benefits of bioinformatics in viral science has provided a turning point. Genome-wide association studies and NGS studies have led to advances in COVID-19 research methodologies, computer-aided drug design, and similar areas. These studies will also contribute to the production of vaccines developed against SARS-CoV-2.

With the use of NGS, it has been established that the SARS-CoV-2 genome is between 29.8 kb and 29.9 kb, and genomic differences and similarities with the previous human coronaviruses, including SARS-CoV and MERS-CoV[10]. In the COVID-19 pandemic, metagenomics applications have been used to discover some important new knowledge about SARS-CoV-2. Some studies investigated SARS-CoV-2 and other coinfections in patients' nasopharyngeal throat swabs, detection of the intermediate host in transmitting the infection to the human body, and sampling of the homologous sequence of SARS-CoV-2 in other species[11-13]. There were several studies that were conducted to understand the genomic structure and variations in SARS-CoV-2 complete genome sequences and identify of the potential genetic factors involved in the prognosis of COVID-19[14,15]. Moreover, researchers used the benefits of computer-aided drug design, such as structure-based drug design and network-based drug design, to classify new drug candidates against the viral proteins such as the S-protein[16]. In addition to predicting novel molecules against SARS-CoV-2, some commonly used antiviral synthetic drugs, such as chloroquine (malaria), hydroxylchloroquine (malaria), zanamivir (influenza A and B virus), indinavir (HIV), saquinavir (HIV), remdesivir (SARS-CoV), raltegravir (HIV), streptomycin, and ciprofloxacin, were also evaluated for their treatment potentials using computer-aided drug design[17].

Globally, several SARS-CoV-2 variants are in circulation. In the fall of 2020, several new variants appeared, the most notable of which was SARS-CoV-2 variant known as "B.1.1.7" which appeared in the UK with a significant number of mutations. This variant was also found in many countries[18]. This variant has a

spike protein receptor binding domain (RBD) mutation (position 501), in which asparagine (N) is substituted with tyrosine. The *N501Y* mutation represents the 69/70 deletion and S1/S2 furin, which has a region of high coronavirus heterogeneity, is thought to cause a conformational change in the *P681H* S-protein near the cleavage site.

Another variant of SARS-CoV-2, known as "B.1.351," emerged in South Africa. This variant has few changes similar to those of "B.1.1.7" Many countries outside South Africa have detected cases linked to this variant. At the end of January 2021, this variant was identified in the US. The spike protein of this variant has several mutations, including *E484K*, *K417N*, and *N501Y*. Unlike the "B.1.1.7" lineage, this version lacks the deletion at location 69/70. There is some evidence to suggest that the neutralization power of some polyclonal and monoclonal antibodies may be influenced by the *E484K* S-protein mutation[19,20].

A variant of SARS-CoV-2 known as "P.1" has been found in four Brazilian travelers at the Japanese airport. This variant has 17 unique changes, three of which are in the S-protein's RBD. At the end of January 2021, this variant was found in the United States. In the spike protein RBD, it has *K417T*, *E484K*, and *N501Y* mutations. Some of the mutations may affect its transmissibility and antigenic profile[21].

According to the April 2021 data of the Ministry of Health, the UK variant was detected in 180,448 samples in 81 provinces in our country. The South African variant was detected in 169 samples in 11 provinces. The Brazilian variant was detected in four samples in two provinces[22].

Viruses, including SARS-CoV-2, will continue to evolve. Genetic differences will emerge that may contribute to the development of new mutants that may have different characteristics. Based on our past experiences, our progress in bioinformatics will enable us to respond quickly to any pandemics that may arise in the future[19].

Pathogenesis

1. Innate Immunity to SARS-CoV-2

Innate immune response is the first line of antiviral immunity, and it is initiated with immune sensing of pathogen-associated molecular patterns. Severe acute respiratory syndrome-CoV-2 is recognized within the cell via cytosolic RIG-I-like receptors and endosomal Toll-like receptors. These receptors are known as pattern recognition receptors[23,24].

When virions attach to receptors in the lower respiratory tract, they specifically select type-2 pneumocytes and multiply[23]. Infection-induced CXCL chemokines invite neutrophils and macrophages to the battlefield. Both these cell types work together, and their activation may trigger COVID-19 associated cytokine storm. Cytokines such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-α have inflammatory potential. The release of vascular endothelial growth factor, monocyte chemoattractant protein-1, IL-8, as well as reduced E-cadherin expression on endothelial cells cause vasodilation and increase capillary permeability. The plasma enters interstitial spaces and alveoli. The decrease in surfactant level due to fibroblast proliferation and alveolar edema causes alveolar collapse. This inflammatory condition and alveolar collapse constitute the clinical and radiological features of COVID-19. Activated neutrophils secrete reactive oxygen species and proteases which destroy both infected and uninfected type-1 and type-2 pneumocytes. Broken alveolar structure leads to reduced gas exchange and alveolar space due to filling by fluid, cell debris, neutrophils, and macrophages. This alveolar microenvironment causes pulmonary consolidation and pulmonary fibrosis[23-25].

High serum myeloperoxidase-DNA, citrullinated histone H3, and neutrophil extracellular traps (NETs) levels in COVID-19 patients indicate neutrophil activation. NETs and the neutrophils activated and potentiated by C3, factor B, and properdin trigger the alternative pathway of the complement system during SARS-CoV-2 infection. NET formation leads to a hyper-inflammatory immune response that damages and destroys the surrounding tissue. This abnormal complement activation leads to the well-recorded clinical manifestations observed in cases of COVID-19, such as acute respiratory distress syndrome (ARDS) and even just pulmonary inflammation. Impaired neutrophil extracellular trap formation (NETosis) and complement activation induce the production of excessive thrombin and subsequently generate C5a. Lung tissue from severe COVID-19 patients revealed significant deposits of MBL, MASP-2, C3, C4a, C4d, and C5b-9 (components of the membrane-attack complex), suggesting that the complement system contributes to lung injury[23-26].

Neutrophil extracellular traps may potentiate microvascular thrombosis in COVID-19 patients. Many autopsy studies have revealed NET-containing microthrombi and neutrophil-platelet infiltration in the microvasculature of the lung, kidney, and heart. Severe acute respiratory syndrome-CoV-2 may directly and indirectly induce NET formation, which may contribute to the COVID-19 pathology[23,24,26].

The complement system plays a dual role during SARS-CoV-2 infection. While it may effectively contribute to the control of this infection in many asymptomatic individuals or in patients with mild symptoms, it may also contribute to several pathologies observed in some severe COVID-19 patients, due to its potent proinflammatory effect[26].

2. Adaptive Immunity to SARS-CoV-2 Infection

Similar to other viral infections, specific antibodies, CD4+T cells, and CD8+T cells are important in response to SARS-CoV-2 infection. The initial step of the adaptive immune response against viral infections is antigen presentation on the major histocompatibility complex-2 molecules to naive CD4+T cells. After antigen presentation, T cells differentiate to effector subgroups such as T helper (Th)1, Th2, Th17, and others. Activated Th cells helps B cells in cognate communication and CD8+T cells by mainly secreting cytokines. After Th-dependent activation, B cells secrete antiviral antibodies and act against the virus through various mechanisms, including neutralization, opsonization, and activation of complement proteins[23-27].

Peak antibody response occurs between the second and third week after the infection. It is characterized by the presence of immunoglobulin (Ig)A, IgM, and IgG in plasma and saliva. Severe acute respiratory syndrome-CoV-2 antibodies may be directed against all viral proteins, although S- and nucleocapsid proteins are the main targets of humoral response. Beyond their neutralizing activity, antibodies have additional functions depending on their isotype. Antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity (CDC) are the important Fc-dependent functions that are associated with protection in SARS-CoV-2 infections. In addition, antibodies also promote infection itself or cause the antibody-dependent enhancement of the disease, increasing its symptoms. This phenomenon is mediated by antibody receptors (FcRs) and the complement system, both of which may cause worsening symptoms[25,27].

The activated CD8+T cells lyse virus-infected cells. Unfortunately, the inefficient or insufficient adoptive response and lymphopenia have been reported in many COVID-19 patients. Reduced numbers of CD4+T cells, CD8+T cells, B cells, and natural killer cells are common in most of the mild and severe cases (Figure 1). Besides lymphopenia, lymphocytes in severe COVID-19 patients exhibit an exhausted phenotype, characterized by impaired effector functions. In mild symptomatic cases, there is a highly expanded clonal CD8+T cell response, and a strong cellular immune response that helps to control the disease. T cell activity is crucial for virus clearance and innate immune inflammation shutdown. The inability to eliminate the virus due to lymphocyte exhaustion is both the cause and consequence of a high antigenic stimulus[24,27].

As a result, a rapid and well-coordinated immune response is necessary for a potent defense against SARS-CoV-2, but an excessive inflammatory response may lead to tissue damage at the systemic level. The massive production of cytokines and chemokines detected during COVID-19 infection, the so-called "cytokine storm," is mainly responsible for the broad and uncontrolled tissue damage. The cytokine storm resembles cytokine release syndrome and results in plasma leakage, increased vascular permeability, and disseminated intravascular coagulation. These excessive proinflammatory host responses are major factors for pathological outcomes such as acute lung injury and ARDS seen in severe SARS-CoV-2-infected patients[23].

Epidemiology

1. Origin of the Pandemic

There are various mutants of coronaviruses in humans that may be easily transmitted from person to person[28-31]. The reservoir of SARS-CoV-2 is still under investigation. All available evidence for COVID-19 suggests that SARS-CoV-2 originated from a zoonotic source. Although still unclear, available data point to wild animals sold in the Huanan Seafood Wholesale Market. Since it is transmitted from person to person, the main source of COVID-19 is symptomatic/asymptomatic COVID-19 patients[30].

The Centers for Disease Control researchers in China collected 585 samples in Wuhan, Hubei Province, China on January 1 and 12, 2020 to identify the zoonotic source of COVID-19. They identified 33 samples containing SARS-CoV-2 and stated that this was due to commercially available wild animals. Lab results showed that SARS-CoV-2 was similar to some β-coronavirus strains identified in bats. Next generation sequencing results show that SARS-CoV-2 and SARS-CoV approximately 79%, SARS-CoV-2 and MERS-CoV approximately 50%, SARS-CoV-2 and *bat-SL-CoVZC45* 87.9% and SARS-CoV-2 and *bat-SL-CoVZXC21* have 87.2% sequence identity. A high degree of genome similarity was found between the *Pangolin-CoV* and

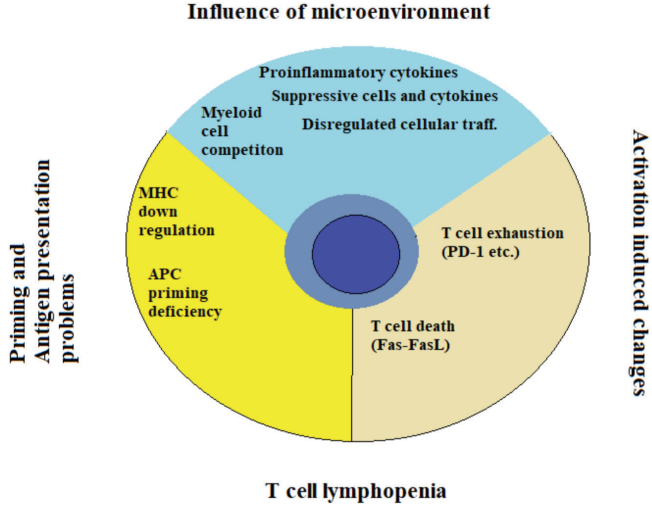

Figure 1. Main causes of Coronavirus disease-2019 associated T cell lymphopenia

MHC: Major histocompatibility complex

the SARS-CoV-2, which may point to another possible source of SARS-CoV-2[32-34].

2. Transmission

The viruses are mainly transmitted through droplets. In addition, they are transmitted by the other people touching the surfaces where droplets were emitted by sick individuals through coughing and sneezing[28]. It may also be transmitted by the aerosol transmission in closed environments. Hospital contamination is another important problem in terms of the risk of transmission to other patients and healthcare professionals[32]. It is also transmitted by procedures such as intubation and bronchoscopy, which are risky in terms of the transmission of aerosol and droplet infections[33]. There are also studies showing that SARS-CoV-2 may be detected in the tears and conjunctival secretions of pneumonia patients with conjunctivitis, suggesting that ocular infection may also be a source of infection. Viral nucleic acids have been found in stool specimens and in anal swabs of some COVID-19 patients[32]. The virus is rarely found positive in blood and urine. The virus does not pose a safety problem in terms of blood banking. The virus has not been detected in milk, vaginal swabs, and sperm samples[28]. Different results have been reported on whether there is vertical transmission from a pregnant woman with COVID-19 to the baby. There is no evidence of intrauterine or transplacental transmission, but it may be transmitted from the infected mother to baby after birth by a close contact orby droplets during breastfeeding. In another study, maternal viremia was observed at a low rate of approximately 1%, and SARS-CoV-2 was not detected in cord blood[35]. Since viruses have been detected in the respiratory tract secretions of asymptomatic people, these individuals are also contagious[28]. It is known that the duration of SARS-CoV-2 contagiousness is 10-14 days. However, in a surveillance study conducted in Canada, it was reported that the duration of transmission may extend from the first day of symptoms and 0-21 days after the onset of symptoms in immunosuppressed patients[33,36].

3. Clinical Features

Common symptoms of infection are respiratory symptoms, fever, cough, and dyspnea. Symptoms such as headache, sore throat, runny nose, muscle and joint pain, extreme weakness, loss of smell and taste, and diarrhea are also seen. Although the disease may be asymptomatic, pneumonia, renal failure, and even death may develop in severe cases[28].

The International Severe Acute Respiratory and Emerging Infections Consortium reported that the five most common symptoms at the time of admission are fever, shortness of breath, cough, fatigue/weakness, and confusion in a study on 25,849 hospitalized COVID-19 patients with a wide clinical spectrum[31,33,37].

Risk Groups

Although all populations are susceptible to SARS-CoV-2, healthcare workers, pregnant women, and the elderly are at higher risk[31]. Healthcare workers are the most risky occupational group in terms of encountering the agent[28]. Men, those >50 years of age, those with comorbidities (hypertension, heart disease, diabetes, malignancy, COPD, kidney disease, etc.), and those living in care and rehabilitation centers, school, barracks, detention houses, and immigration camps are vulnerable to COVID-19[28].

The increased number of cells to which the virus may bind due to the presence of ACE-2 receptor in specific organs is related to the severity of the disease. It is shown that ACE-2 levels are higher in men with diabetes or cardiovascular disease; therefore, male patients, diabetics, and people with cardiovascular diseases are more likely to have a severe disease course and and death[38].

In children, the clinical picture is mild, recovery is quicker, the prognosis is better, and the incidence of pneumonia is lower. This difference may be due to the different distribution, maturity, and function of viral receptors in children[29]. Due to physiological changes in the respiratory tract of pregnant women, it is possible for them to experience more severe disease when infected with viral respiratory tract infections such as COVID-19 and influenza[31].

Diagnosis

1. Laboratory

To diagnose the disease and decrease its transmission, a quick and early laboratory diagnosis is crucial. Reverse transcription-polymerase chain reaction (RT-PCR) is the method designated by WHO as the gold standard for diagnosing COVID-19. Severe acute respiratory syndrome-CoV-2 positivity detected by other methods such as serology should be confirmed by molecular methods[39].

It is important to take appropriate samples in the laboratory diagnosis of COVID-19. Upper respiratory tract, nasopharyngeal swab, oropharyngeal swab, nasopharyngeal irrigation, sputum, tracheal aspirate, and bronchoalveolar lavage samples are the most widely accepted samples used for diagnosis[40].

2. Radiology

The findings of COVID-19 in chest X-ray (CXR) vary from normal to unilateral or bilateral lung opacities, and sometimes, basilar and peripheral distribution in the early stage of the disease are observed[41]. Typical chest computed tomography (CT) appearance in COVID-19 pneumonia is in the form of bilateral peripheral opacities in the lung [usually ground glass opacity (GGO)][42]. Additional imaging patterns

resembling organized pneumonia include a perilobular opacification pattern and an "inverted halo" sign defined as a focal, rounded area of the GGO surrounded by a denser consolidation ring or arc[43].

Because the CDC does not currently recommend CXR or CT to diagnose COVID-19, viral diagnostic tests (RT-PCR) remain the only specific diagnostic method. Verification of the viral test is required even if radiological findings suggest COVID-19 on CXR or CT[44,45].

Treatment

The drugs used in treatment can be divided into groups.

1. Antivirals

Antivirals used in the treatment of COVID-19 include remdesivir, favipiravir, lopinavir/ritonavir, umifenovir (arbidol), and ivermectin. Remdesivir is the only Food and Drug Administration (FDA)-approved antiviral. Favipiravir is used for routine treatment in individuals diagnosed with the COVID-19 in our country[46,47].

2. Cytokine Antagonists (IL-1, IL-6)

IL-1 and IL-6 antagonists, which are used to treat cytokine storm developing during the disease, which have fallen from the agenda due to microemboli and disruption in the coagulation mechanism. Studies have reported that increased liver enzymes, bacteremia, and thromboembolic events develop during the use of cytokine antagonists in the treatment of COVID-19 patients[48,49]. Today, all known treatment guidelines do not recommend the use of these drugs. In a limited number of retrospective and prospective case-control studies, it was observed that use of these drugs had no positive effects on the mortality of the patients with a diagnosis of COVID-19 and high IL-1 and IL-6 levels[50].

3. Corticosteroids

The use of corticosteroids has a positive effect on recovery in patients with pulmonary involvement or a respiratory rate >30/min, SpO_2 <90%, and accompanied by ARDS and septic shock. It has also been shown to delay mechanical ventilation, shorten the duration of mechanical ventilation, and reduce 28-and 60-day mortality. In the guide of the Ministry of Health in our country, as an equivalent glucocorticoid, 6 mg IV, PO dexamethasone, 32 mg methylprednisolone, or 40 mg prednisolone may be used for 10 days (or until discharge). It is recommended that the total duration should not be <5 days. In cases where the administration period is longer than one week, discontinuation should be done by decreasing the dose. It should be kept in mind that these patients are at a risk of hepatitis B, herpes, and tuberculosis reactivation[47,51]. Close follow-up is required in intensive care patients to check for opportunistic bacterial and fungal super infections[51-54].

4. Anticoagulant Therapy

Thromboembolic conditions are known to be common in cases of COVID-19. In patients with pulmonary involvement, alveolar microthrombus is seen nine times more frequently[55]. Coagulopathy was observed to be maximum on the 7th day of the disease. Low molecular weight heparin should be administered to all inpatients during treatment[48]. Between retrospective therapeutic dose (enoksaparin 1 mg/kg) and prophylactic dose (enoksaparin 40 mg/day) studies, mortality was higher with the therapeutic dose[56].

5. Plasma Treatment

Convalescent plasma therapy is a treatment method used in our country. However, according to the NIH and some other guidelines, experience is still lacking for an indicator of effectiveness in this practice. In randomized controlled studies, the plasma treatment added to the standard treatment in severe clinical conditions has no positive effect on 28-day mortality[57].

6. Monoclonal Antibodies

Renegeron is an antibody cocktail. Emergency use has been granted by the FDA in a selected patient group. It is a combination of *REGN10933* (Casirivimab) and *REGN10987* (Imdevimab). Specific antibodies block the S-protein. It is applied in the severe patient group[58].

Bamlavinimab is a combination of *LY-CoV555* and *LY3819253*. Specific antibodies block the S-protein receptor binding site. It prevents the virus from entering the cell.

Even though the FDA has given emergency approval for both monoclonal antibodies, there is not enough knowledge to date regarding the widespread use of these products according to organizations such as NIH[59,60].

7. Vitamins and Zinc (Zn^{2+})

One of the most discussed issues, especially since the beginning of the epidemic, is the administration of vitamin C and vitamin D supplements. Even though there are case reports stating that high-dose vitamin C administration prevents aggravation of COVID-19 in patients due to its antioxidant effect, the level of evidence is low. Although high doses of vitamin C (200 mg/kg/day for a total of four days) are used in intensive care with sepsis-induced ARDS, there is no study reporting that it is used in COVID-19 patients[61].

The ionized form of Zn^{2+} prevents the replication of RNA viruses by inhibition of RNA-dependent RNA polymerase in cell cultures[62].

Just like vitamin D, Zn^{2+} deficiency has been observed in people with severe COVID-19 infection[63]. In retrospective studies, mortality was lower in patients diagnosed with COVID-19 and receiving Zn^{2+} supplements. In addition, it was observed that there was a decrease in intensive care admission and oxygen need and that the recovery period was significantly shorter[64].

In clinical studies that are currently ongoing in the USA, Zn^{2+} is being investigated alone or in combination with other drugs to protect against COVID-19 infection[65].

8. Antibiotics

Antibiotics are not recommended for routine treatment. However, it is necessary to be careful about coinfection and super infection. Although coinfections were uncommon in retrospective studies, it was observed to be more common in patients with chronic obstructive pulmonary disease and severe heart failure. Superinfection, on the other hand, was significantly more common in intensive care inpatients[66].

Doses and durations of drugs administered in Turkey are summarized in Table 1[67].

Protective Measures Against COVID-19

Coronavirus disease-2019 protection measures include minimizing the risk of transmission, cleaning surfaces for this purpose, avoiding crowded environments, maintaining physical distance, hand hygiene, and using masks[68].

Fillation is an important element in the control of the COVID-19 outbreak. In medical literature; It means the connection or contact tracking of situations that arise from each other[69]. By fillation, people infected with COVID-19 are identified using national PCR testing programs, and an attempt is made to find and isolate those who are infected[70].

1. Vaccination

The primary goal of all studies on COVID-19 vaccines is the production of S-protein neutralizing antibodies in vaccinated subjects[71]. One of our domestic vaccines, which has started phase studies against COVID-19, is an inactive vaccine, but there are difficulties in producing large amounts of the virus. The Chinese origin (Coronovac-Sinovac) vaccine is also an inactive vaccine. Oxford and Russian (Sputnik V) COVID-19 vaccines are examples of a viral vector vaccine[72]. German (Biontech-Pfizer) and American (Moderna) COVID-19 vaccines are examples of mRNA vaccines. Severe allergic reaction (e.g., anaphylaxis) to any component of the Pfizer-BioNTech COVID-19 vaccine is a contraindication to vaccination[73]. Selcuk University has conducted an mRNA vaccine study[74]. In addition, virus-like particle type domestic vaccines are among the COVID-19 vaccines that are being developed. Various characteristics of the different COVID-19 vaccine types are shown in Table 2.

The technology and infrastructure required for the development of inactive vaccines is available. Inactive vaccine studies have been carried out for many diseases before the pandemic. They may be used with adjuvants to increase their immunogenicity. CoronaVac (Sinovac, China) contains aluminum as adjuvant and is inactivated with formaldehyde. However, it requires boosters to maintain immunity. It also requires the use of large numbers of viruses and maintenance of the integrity of the immunogenic particles. When all the S-proteins of the virus are administered, the level of neutralizing antibodies formed in the body may be lower than when a specific part of the virus is administered[75].

The emergence of new SARS-CoV-2 variants raises concerns about their effects on infectiousness, severity of the disease, reinfection rates, and the possibility of decreased vaccine efficacy. With regard to vaccine-induced immunity evasion, some reduction in neutralization activity of variant "B.1.1.7" has been reported in serum samples from vaccinated persons[76].

Among the vaccinated subjects, the serum neutralizing activity for the *501Y.V2* variant was 1.6-8.6-fold lower for the Sinopharm, Pfizer, and Moderna vaccines but was 86-fold lower for the AstraZeneca vaccine. Among the vaccinated subjects, the neutralizing activity for the P.1 variant was 6.7-fold lower for the Pfizer vaccine and 4.5-fold lower for the Moderna vaccine[77].

Long-COVID-19

In many cases, after COVID-19 infection, it is observed that multiorgan symptoms persist for ≥6 months due to the presence of ACE-2 receptors in many organs. Some of these clinical signs are cough, shortness of breath, lung capacity pathologies, weakness, headache, palpitations, chest pain, joint pain, depression, insomnia, gastrointestinal disorders, and odor loss.

Although it is called long-COVID-19 for now, there are not enough criteria about its definition, diagnostic criteria, predisposing conditions, types, causes, duration, prognosis, complications, sequelae, rehabilitation needs, and approaches.

Table 1. Overview of the drug treatment scheme in Turkey

Drug	Doses	Times (day)	Warning
Favipiravir 200 mg	2×1600 mg loading, after 2×600 mg	5	Favipravir treatment may be extended to 10 days in patients with pneumonia who require hospitalization.

Considering the acute phase of the disease and the clinical definitions of long-COVID-19, acute COVID-19 infection is considered to be the first four weeks. Additionally, the concepts of reinfection, reactivation, and relapse in COVID-19 are also determined by PCR results and clinical evaluation (Table 3)[78].

Conclusion

As a result, the main reason for the increase in the infection rate is the difficulty in controlling person-to-person transmission, and for mortality rate is the lack of proven medical treatment specific to the COVID-19 and the severe course of the disease in

Table 2. Various characteristics of the Coronavirus disease-2019 vaccines developed

Vaccine technology	Working method	Advantages	Disadvantages	Other vaccines samples	Approved COVID-19 vaccines	Effectiveness of the vaccines
Virus-based (classical method)	Inactivated virus is used.	It is expected to generate a good immune response.	It is difficult to produce. It is produced at high security level (4th class) using large amounts of viruses.	Measles, scarlet fever, mumps, smallpox, chickenpox, hepatitis A, influenza.	1- Sinovac (China) 2- Wuhan Institute of Biological Products/ Sinopharm 3- Beijing Institute of Biological Products/ Sinopharm 4- Bharat Biotech (COVAXIN)	1- Sinovac (protection against disease: 50-91%)[79] 2- Wuhan Institute of Biological Products/ Sinopharm (protection against disease: 79.4%)[80] 3- Beijing Institute of Biological Products/ Sinopharm (protection against disease: 79%)[80] 4- COVAXIN (protection against disease: 81%)[81]
Protein based	Virus proteins are used either directly from the virus or artificially produced.	Less side effects. Fast production of synthetic proteins.	Adjuvants and booster shots may be required	Influenza vaccine	1- Novavax	1- Novavax (protection against disease: 96.4%)[82]
Nucleic acid-based (RNA & DNA) vaccines	DNA or RNA parts containing genes encoding virus proteins are used.	Fast production, lower cost. Quick update opportunity against mutations that may develop. High immunity at the cellular level.	mRNA vaccine is a new technology.	First example of COVID-19 vaccines.	1- BioNTech/Fosun Pharma/Pfizer (mRNA) 2- Moderna/NIAID (mRNA)	1- BioNTech (protection against disease: 91.3%)[83] 2- Moderna (protection against disease: 94.1%)[84]
Viral vector based	The genetic material of the virus is placed in other viruses that do not cause disease and then applied to humans.	Rapid development and production.	Low immune response in individuals who have had previous contact with harmless viruses (as adenovirus).	Ebola	1- ChAdOx1-S/nCoV-19/ University of Oxford-AstraZeneca 2- CanSino Biological Inc./Beijing Institute of Biotechnology 3- Gamaleya Research Institute 4- Janssen Pharmaceutical	1- ChAdOx1 (protection against disease: 81.5%)[85] 2- CanSino Biological Inc./Beijing Institute of Biotechnology (protection against disease: 79%)[86] 3- Gamaleya Research Institute (protection against disease: 92%)[87] 4- Janssen Pharmaceutical (protection against disease: 76.7-85.4%)[88]

COVID-19: Coronavirus disease-2019

Table 3. Coronavirus disease-2019 reinfection, relapse, and polymerase chain reaction re-positive criteria (modified from Yahav et al. 2021)[78]

Factor	Clinical manifestations	PCR	Cell culture	Time since primary infection	Isolation preventions	Supplementary evidence
Confirmed reinfection	Typical clinical signs	+	+	>3 months	Recommended measures should be taken.	Viral RNA sequencing at both stages indicates different species.
Clinical reinfection	Typical clinical signs	+	+		Recommended measures should be taken.	There is no other factor than the known exposure or epidemic situation.
Epidemiological reinfection	With/without symptoms	+	+		Recommended measures should be taken.	Known exposure or epidemic situation.
Relapse/ reactivation	Typical clinical signs	+	+	<3 months	It should be evaluated.	No new exposure, little spread.
Repositivity	Without symptoms	+	–	<3 months	Not suggested.	-

PCR: Polymerase chain reaction

the elderly who have a weak immunity. It is difficult to predict the future direction of the epidemic[89].

Disease prevention and control efforts take precedence over the treatment for a highly contagious disease such as COVID-19, so adherence to individual and community protective measures is essential. Although positive results are obtained with the supportive treatment options applied today, there is still a 5-10% risk of a severe clinical course and death in COVID-19 patients. Thus, the pandemic remains a public health threat.

It is an indisputable fact that not only patients with clinical findings, but also asymptomatic patients and contacts should be screened in order to control the epidemic. More randomized controlled studies are needed to understand the effectiveness of each treatment method and to be included in the guidelines.

Ethics

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: M.A., Design: M.A., Data Collection or Processing: E.P.K.K., Analysis or Interpretation: E.P.K.K., M.A., Literature Search: E.P.K.K., M.A., Writing: E.P.K.K., M.A., K.Y., İ.Ö.T., D.B., S.Ö., A.Ş., M.N.İ.

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