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Rapid Spreading of SARS-CoV-2 Infection and Risk Factors: Epidemiological, Immunological and Virological Aspects

SARS-CoV-2 Enfeksiyonunun Hızlı Yayılımı ve Risk Faktörleri: Epidemiyolojik, İmmünolojik ve Virolojik Bakış

Hilmi Erdem SÜMBÜL[1] [ID], Fatih ŞAHİNER[2] [ID]

[1]Department of Internal Medicine, Adana Health Practice and Research Center, University of Health Sciences, Turkey.
[2]Department of Medical Microbiology, Gulhane Medical Faculty, University of Health Sciences, Ankara, Turkey.

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Correspondence: Hilmi Erdem Sümbül; Assoc.Prof., Department of Internal Medicine, Adana Health Practice and Research Center, University of Health Sciences, Turkey. E-mail: erdemsumbul@gmail.com

Abstract

SARS-CoV-2, the third coronavirus associated with severe respiratory infections in humans, spreads more easily and quickly in the community, with a higher infectiousness rate compared to the other two betacoronavirus species (SARS-CoV and MERS-CoV). The SARS-CoV-2 pandemic, in which the number of cases worldwide has exceeded 30 million, has been the biggest global epidemic of the last century with serious concerns and socio-economic impacts. Educational activities, meetings, worship, tourism, trade and sports organizations came to a halt in many countries during the pandemic period and national and international travel restrictions were applied. Also, in most countries, to protect the population at risk and to slow/stop the spread of infection; nationwide or regional curfew restrictions have been imposed according to risk analysis, and public health measures such as the obligation to wear a mask and quarantine precautions have been taken. The starting time of implementation of these measures, duration and controlling of the restrictions has been one of the important parameters determining the degree of countries affected by the epidemic. Studies on transmission routes of SARS-CoV-2 infections provide new information on epidemiological, immunological and virological parameters that are effective in the community spread of the virus. Epidemiological parameters generally include age, gender, presence of concomitant diseases/conditions, sociocultural habits, the role of asymptomatic persons and reservoir animals, seasonality of infections. Immunological factors include conditions associated with the immune response, such as susceptible individuals with immunodeficiency, the role of people who shed the virus for a long time, the level and duration of protective immunity in recovered people, effectiveness of active and passive immunization, the importance of viral load in the transmission and clinical course. Among the virological parameters that can affect the spread of the infection include the resistance of the virus to environmental conditions and disinfectants, receptor affinity and the degree of adaptation to humans, possible mutations associated with immune escape and virulence. In this article, by mentioning the situations that may pose a risk for the transmission, social spread and clinical course of infections, the main protective measures under the related topics are highlighted.

Keywords: Asymptomatic, Reverse zoonosis, Immunodeficiency, Receptor affinity, Mutations.

Özet

İnsanlarda ciddi solunum yolu enfeksiyonları ile ilişkili üçüncü koronavirus olan SARS-CoV-2 diğer iki betakoronavirusa (SARS-CoV ve MERS-CoV) kıyasla yüksek bulaştırıcılık hızı ile toplumda daha kolay ve hızlı bir şekilde yayılmaktadır. Dünya genelindeki vaka sayısının 30 milyonu geçtiği SARS-CoV-2 pandemisi neden olduğu ciddi endişeler ve sosyo-ekonomik etkiler ile son yüzyılın en büyük küresel salgını olmuştur. Pandemi sürecinde birçok ülkede eğitim faaliyetleri, toplantılar, ibadet, turizm, ticaret ve spor organizasyonları durma noktasına gelmiş ve ulusal ve uluslararası seyahat kısıtlamaları uygulanmıştır. Yine çoğu ülkede risk altındaki popülasyonu korumak ve enfeksiyonun yayılımını yavaşlatmak/durdurmak için ülke genelini kapsayan ya da risk analizlerine göre bölgesel sokağa çıkma kısıtlamalarına gidilmiş, maske takma zorunluluğu ve karantina önlemleri gibi halk sağlığı tedbirleri alınmıştır. Bu tedbirlerin uygulamaya başlama zamanı, uygulama süresi ve denetimi ülkelerin salgından etkilenme derecelerini belirleyen önemli parametrelerden biri olmuştur. SARS-CoV-2 enfeksiyonlarının bulaşma yollarına ilişkin çalışmalar virüsün toplumsal yayılımında etkili olan epidemiyolojik, immünolojik ve virolojik parametrelere dair yeni bilgiler sunmaktadır. Epidemiyolojik parametreler genel olarak yaş, cinsiyet, eşlik eden hastalıkların varlığı, sosyokültürel alışkanlıklar, asemptomatik kişilerin ve rezervuar hayvanların rolü, enfeksiyonların mevsimselliği gibi özellikleri içerir. İmmünolojik faktörler arasında bağışıklık yetmezliği olan duyarlı bireyler, uzun süreli virüs saçan kişilerin bulaştaki rolü, iyileşen kişilerde koruyucu bağışıklığın düzeyi ve devam süresi, aktif ve pasif immünizasyon uygulamalarının etkinliği, viral yükün bulaş ve klinik seyirdeki önemi gibi immün yanıt ile ilişkili durumlar yer alır. Enfeksiyonun yayılmasını etkileyebilecek virolojik parametreler arasında ise virüsün çevresel koşullara ve dezenfektanlara direnci, reseptör afinitesi ve insanlara adaptasyon derecesi, immün kaçış ve virülans ile ilişkili olası mutasyonlar gibi özellikler bulunur. Bu makalede enfeksiyonların bulaşı, toplumsal yayılımı ve klinik seyri için risk oluşturabilen durumlara değinilerek ilgili konu başlıkları altında temel koruyucu önlemlere dikkat çekilmiştir.

Anahtar Kelimeler: Asemptomatik, Ters zoonoz, İmmün yetmezlik, Reseptör afinitesi, Mutasyonlar.

Introduction

In the last two decades, three SARS (Severe Acute Respiratory Syndrome)-related zoonotic coronaviruses have emerged [1]. SARS-CoV (2003), MERS-CoV (Middle East Respiratory Syndrome-Coronavirus) (2012) and finally SARS-CoV-2 [1]. SARS-CoV-2 infections first appeared in Wuhan, China at the end of 2019-December and soon spread to many other regions of China and following to the worldwide [2-4]. When we reach September 2020 in the pandemic, the number of cases worldwide exceeded 30 million and nearly 1 million people died [5].

SARS-CoV-2 infections; (i) in some people it may be asymptomatic, (ii) may also be accompanied by fever, dry cough, fatigue, and sputum production (iii) or could present as coronavirus disease-2019 (COVID-19) with a range of respiratory clinical manifestations ranging from shortness of breath, pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS) [2,6,7]. In some patients, symptoms such as sore throat, headache, hemoptysis, nausea, vomiting and diarrhea, decreased appetite, loss of sense of smell and taste, myalgia were also reported in different observational studies [6,8,9].

Transmission routes of SARS-CoV-2 infections exhibit similar characteristics to other human beta-coronaviruses such as SARS-CoV and MERS-CoV [10]. The main transmission route of the SARS-CoV-2 infection is assumed to be respiratory droplets, however, the virus can also be detected in other body fluids and feces, so new research is being conducted on other possible transmission routes (e.g. airborne, direct contact, transplasental) [11-15]. In this article, it is aimed to present an overview of epidemiological, immunological and virological factors that facilitate the individual transmission and community spread of SARS-CoV-2 infections.

Epidemiological Parameters and Risk Factors

Knowing the incubation period of an infection is essential for epidemiological follow-up of cases and helps determine the quarantine and medical observation time of close contacts [16]. Available data show that the incubation period for SARS-CoV-2 infections is in the range of 1-14 days, mostly 3-7 days [17-19]. However, it has also been observed that this period may extend up to 19 days in some cases and may have an extreme range of 0-24 days [7,20]. In another article, a case with a long incubation period (38 days) was presented [16]. In summary, systematic reviews in which data from different studies were analyzed indicate that the incubation period is 2-14 days and the mean is around 5 days and is similar to SARS-CoV and MERS-CoV infections at 95% confidence interval [21-23]. In a secondary analysis that included more than 25 studies from China, Italy and Singapore, it was reported that the pre-symptom transmission rate ranged from 33.7% to 72.7% (Wuhan and Hong Kong, respectively) [24]. In the same study, the average infectious period was calculated as 1.72 days before symptom onset for Wuhan and 2.05 days after onset of symptoms for Hong Kong. According to the data obtained from different studies, it is thought that SARS-CoV-2 infectious period starts 1-2 days before the symptomatic period and ends with the disappearance of symptoms [25,26].

Although SARS-CoV-2 infections can be occurred in all age groups and have a good prognosis in most patients, it has been reported that "acute respiratory distress syndrome (ARDS), septic shock that may be associated with cytokine storm, severe metabolic acidosis and coagulation dysfunction" have been rapidly develop in elderly individuals, and also in individuals of any age group with underlying secondary diseases (such as hypertension, severe obesity, chronic obstructive pulmonary disease, asthma, diabetes, cardiovascular disease, chronic kidney and liver disease) [2,8,17,27]. The infection has a high mortality rate in these patients. Morbid obesity, hypertension and diabetes are defined as the most important risk factors in young adults with COVID-19 [28]. Individuals with a weakened immune system who use corticosteroids, receive cancer treatment, have congenital or acquired immunodeficiency such as Human immunodeficiency virus (HIV) infections may also at risk [27,29], however, the clinical course in this patients may differ from than expected (discussed below) [30].

Smoke inhaled with cigarette tobacco triggers coughing or sneezing, producing aerosols containing SARS-CoV-2 and contaminating environmental surfaces [31]. Tobacco is also a major risk factor for non-infectious diseases such as cardiovascular disease, cancer, respiratory disease and diabetes, and people with these conditions are at a higher risk of developing serious illness when affected by COVID-19; current research shows that smokers are at a higher risk of serious illness and death. [32]

***1.** Gender and age as a risk factor*

Current clinical observations revealed that gender and age are two independent risk factors for susceptibility to COVID-19, men and older people are more susceptible to infection and the development of serious diseases [8]. Previous studies revealed that SARS-CoV-2 infections are more common in men with rates of 54.3% to 58.1% [17]. In addition, according the recent studies hospitalization and mortality rates are higher in men than in women [33] This difference has been associated with stronger T cell responses in women in some studies [34]. Hormonal and genetic differences were also emphasized, but the reason for this difference has not been clarified yet [35]. Although there were reports of higher rates of infection in boys, 56.6% (2135 children in total) and 65% (20 children in total) [36,37], other studies did not support this information [38].

In a report [39], published by the Chinese Center for Disease Control and Prevention, it was reported that as of February 11, 2020, only 965 (2.16%) of 44,672 SARS-CoV-2 cases were under the age of 19 [416 (0.9%) children are between the ages of 0-9, while 549 (1.2%) children are between the ages of 10-19]. In the same report, 1 death case was observed in the 10-19 age group and the mortality rate in this group was calculated as 0.18% [39]. Research results indicate that the most common form of transmission in children is household transmission. In an article by the Chinese Medical Association and Pediatric Association, as of February 7, 2020, 285 (0.8%) child-patients were detected among 34,546 approved cases, and 71.2% (183/257) of infected children had a domestic contact history [40]. In another study in which 11 case series consisting of 333 infants and children were examined, 83% of the children had a history of contact with family members, and the incubation period ranged from 2 to 25 days, with an average of 7 days, and virus can be isolated from nasopharyngeal secretions for up to 22 days and stools for more than 30 days

[41]. In the same article, it was emphasized that, contrary to the initial reports, recent studies show that children are more likely to be infected than adults but cause fewer symptoms and less serious illness. Unlike the cases where children are at the forefront of infection spread such as CMV infections [42], in SARS-CoV-2 infections, it seems that the high level of household transmission to children is due to the closure of schools, the fact that their education is carried out online, and other social restrictions, such as children staying at home, and by bringing the disease from the outside and infecting children due to the compulsory mobility of the parents. As a matter of fact, according to official report of the Ministry of Health the rate of children and young people in infected patients has increased in the summer when restrictions on children are lifted in Turkey. As of the end of August-2020, there are a total of 269,550 laboratory-approved COVID-19 cases in Turkey, with a total of 6,326 deaths reported and approved by the Ministry of Health [43]. In this report, 49% of all reported cases are women and 51% are men. While 18,563 (6.9%) of all cases were children aged 15 and under, 37,456 (13.9%) cases between the ages of 15-24, 133,078 (49.4%) cases in the age group of 25-49, 50,303 (18.7%) cases between the ages of 50-64, 23,358 (8.7%) cases are in the 65-79 age group, 6,791 (2.5%) cases are 80 years old and above [43].

***2.** Asymptomatic infections*

A significant portion of SARS-CoV-2 infections are asymptomatic, and these cases are thought to be one of the factors that play an important role in the community spread of the infection [44,45]. In a recent study, it was reported that 56.5% of patients with SARS-CoV-2 infection were asymptomatic at the time of diagnosis and 23.1% remained asymptomatic for 7 days [46]. In addition, there are studies in which 10 to 35% of the cases in the childhood age group were reported as asymptomatic [41,47]. In a cohort study of 303 people with SARS-CoV-2 infection at a community treatment center in South Korea, viral load interpreted on Ct values was similar for symptomatic and asymptomatic patients [45]. The results were assessed as that isolation of asymptomatic patients may be required to control the spread of SARS-CoV-2. These results are generally discussed as follows patients with COVID-19 may be contagious before symptoms begin, and a 14-day isolation after diagnosis may be enough in completely asymptomatic cases. However, in a study examining 37 asymptomatic individuals diagnosed with RT-PCR approved SARS-CoV-2 in Wanzhou region of China [48], viral shedding (positive nasopharyngeal swab) in the asymptomatic group was found a median of 19 days, which was significantly longer than symptomatic group (log-rank P = 0.028). It has been shown that antibody levels to decrease more rapidly in people who have asymptomatic SARS-CoV-2 infections, and these individuals are considered to be at risk for secondary infections [discussed in reference 49].

***3.** Nosocomial transmission*

SARS-CoV and MERS-CoV were spread between humans mainly through nosocomial transmission, resulting in more frequent infections among healthcare workers and their relatives [50]. Compared to these two viruses, SARS-CoV-2 spreads more easily in the society (especially in social activities), but similarly, hospitals are among the places where transmission is most common (Figure 1) [51,52]. In a meta-analysis, which included 40 studies on nosocomial infections in COVID-19, SARS and MERS patients; among confirmed patients, rates of nosocomial infections for these infections were 44.0%, 36.0%, and 56.0%, respectively [51]. In the same study the most affected among infected healthcare personnel were identified as nurses and doctors [51]. In order to prevent hospital-acquired infections, it is important to provide personal protective equipment of healthcare personnel from the beginning of the epidemic, develop educational materials, provide adequate environmental cleaning, room ventilation, sanitation of protective clothing and proper use and disinfection of toilet areas, isolation of cases and contact restrictions [52,53].

Short-term interactions such as entering the patient's room for a short time without direct contact with the patient or patient's secretions or short talking with a patient not wearing a face mask on the triage table are less likely to result in conduction [12]. Contact with surfaces and objects contaminated with patient materials is seen as one of the potential routes of transmission, especially in areas with poor sanitation [54,55]. During the 2003 SARS epidemic, one report stated that three hospital cleaners were infected due to possible fomite transmission without direct patient contact [56]. Under these circumstances, precautions should be taken for all hospital staff, including strict precautions, adequate protective equipment, and infection control training, especially staff and cleaners who handle the excreta of these patients, and those who disinfect the toilet should follow standard precautions, including masks, gloves and protective clothing [57]. Mask wearing by everyone in the hospital (universal use) significantly reduces the risk of developing COVID-19 in healthcare professionals [58].

4. Laboratory-acquired infections and risks

Laboratory-acquired SARS-CoV infection reported as a case report in Singapore in 2003 [59]. In this case, it was reported that a researcher working with a nonattenuated West Nile virus strain in a biosafety level 3 (BSL-3) laboratory where SARS-CoV, dengue virus and Kunjin virus were also studied, to be infected with a laboratory SARS-CoV strain. Laboratory-acquired SARS-CoV-2 infection potential making the biosecurity of samples vital during transport and laboratory diagnosis [60]. While samples containing inactivated viruses (nucleic acid and serological tests) are being studied in BSL-2 laboratories [61], CDC recommends that "procedures that concentrate viruses, such as precipitation or membrane filtration, can be performed in a BSL-2 laboratory with unidirectional airflow and BSL-3 precautions", but "virus isolation in cell culture and initial characterization of viral agents recovered in cultures of novel SARS-CoV-2 should be conducted in a Biosafety Level 3 (BSL-3) laboratory using BSL-3 practices" [62,63]. From this point of view, in order to reduce the risks arising from the transportation and use of bio-samples for diagnosis; it is important that VTMs used in the transport of samples collected for routine analysis contain substances (guanidine thiocyanate or ethanol) that inactivate the virus, while maintaining the stability of DNA and RNA [60].

5. Reservoir animals and animal infections

Bats are known to harbor a wide variety of coronavirus types, including viruses like SARS-CoV and MERS-CoV [50]. It is estimated that both viruses are transmitted from bats to intermediate hosts and from intermediate hosts (palm civets and camels) to humans [50,64]. Bats are suspected to be natural hosts of the virus for SARS-CoV-2 due to 96% total genome sequence similarity between bat viruses and SARS-CoV-2, and also it is thought that unknown intermediate hosts (such as pangolin) play a role in the transmission of the virus to humans from bats [17,19,65,66]. Understanding whether SARS-CoV-2 is transmitted directly from bats or through intermediate hosts will help define zoonotic transmission patterns.

SARS-CoV-2 can also be transmitted from humans to animals (reverse zoonosis) (Figure 1). Cases have been reported that SARS-CoV-2 can be transmitted from humans to dogs (2 cases), domestic cats (2 cases), tigers (4 cases) and lions (3 cases) [67-69]. Although dogs do not develop clinical symptoms, vomiting, diarrhea, and breathing difficulties have been reported in a domestic cat, as well as dry cough and wheezing in tigers and lions [67]. In addition, preliminary studies have shown that SARS-CoV-2 can spread among cats (cat to cat) and the production of specific neutralizing antibodies against SARS-CoV-2 in cats [70,71]. It has been shown that experimentally infected cats transmit the virus to other susceptible cats and these new infected cats shed the virus on nasal swab samples [68], so that transmission between cats has been documented. SARS-CoV-2 has been spread among American minks (*Neovison vison*) in four different fur farms in the Netherlands, and it has been noted that the first source of infection originated from caregivers with COVID-19-like symptoms, and animals showed gastrointestinal and respiratory symptoms [72]. In an experimental infection model in which ferrets were infected with SARS-CoV-2, it shown that these animals were susceptible to infection [73]. Intranasally infected ferrets exhibit; (i) high body temperatures, (i) virus shedding for up to 8 days after infection in nasal washing, saliva, urine and feces samples, (iii) and transmit the virus effectively by direct or indirect contact [73]. In another study that included cats living in homes with COVID-19 patients and animal shelter between January and March 2020, blood and swab samples were taken from 102 cats, and it was shown that 15 of these cats were antibodies against coronavirus [74]. The high positivity rate in serological tests of these cats, which do not show any signs of disease, suggests that the infection may have spread more than expected. Proactively assessing the potential effects of "reverse" zoonoses is suitable for establishing management strategies that reduce the "potential for adverse effects" on relevant animal populations and also try to control the future recirculation of adapted animal viruses to humans [67].

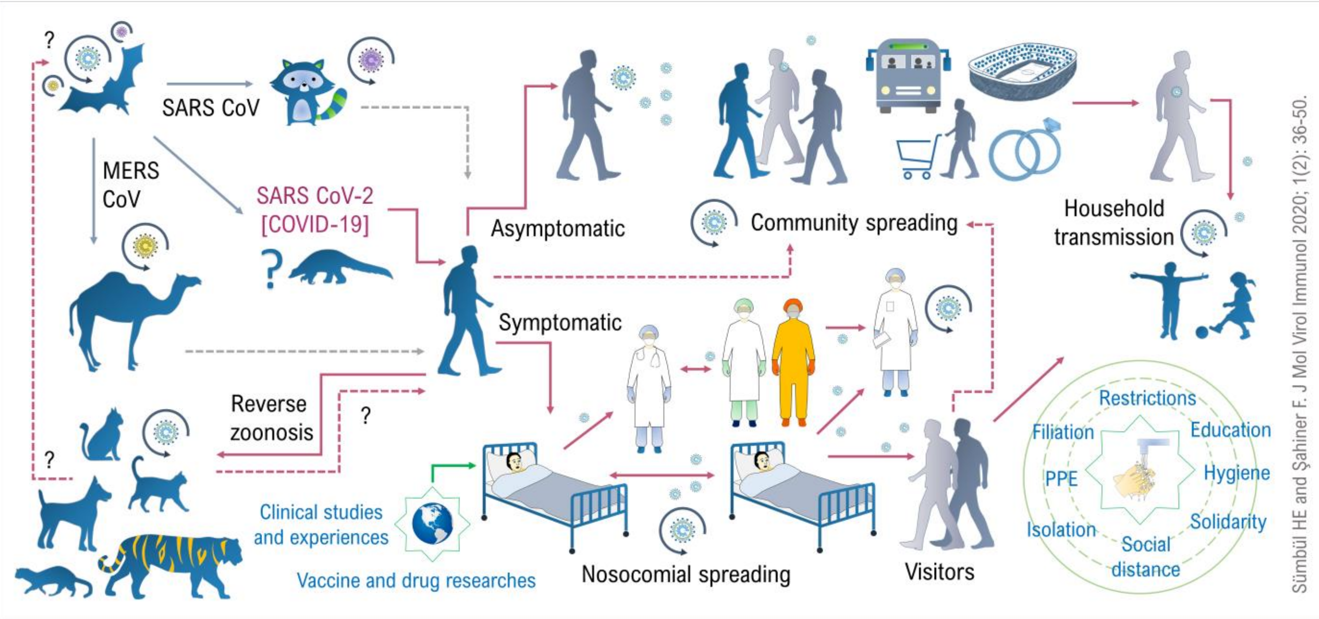

Figure 1. Spreading characteristics of SARS-CoV-2 infections and preventive measures. (PPE: personal protective equipment. ?: Transmission route and circulation are unknown)

6. *Seasonality*

Some human respiratory pathogens such as influenza and rubella virus are seasonal, with an annual increase in their incidence each winter, but there are differences in the timing of increases and in the magnitude of their increases [75]. Similarly, most animal coronaviruses also exhibit a significant seasonal incidence in their natural hosts (bovine coronavirus-associated dysentery and feline infectious peritonitis virus and others) [75]. Also known as common coronaviruses, HCoV-229E, HCoV-NL63, HCoV-OC43 and HCoV-HKU1-related infections are also sharply seasonal, it has been observed that these viruses have a similar transmission potential to influenza A (H3N2) in the same population, depending on the serial interval and the risks of secondary infection [76]. In a 3-year follow-up study in the UK, it was confirmed that seasonal coronaviruses are generally more common in December and April (winter season) and have a seasonal distribution comparable to the pattern seen in influenza viruses [77]. However, in the following year, it was reported that HCoV-229E did not exhibit seasonality and progressed as sporadic cases [77]. The first studies on seasonal predictions indicate that the distribution pattern of SARS-CoV-2 is consistent with the behavior of seasonal respiratory viruses [78]. In conclusion, seasonal characteristics of other pathogens associated with respiratory tract infections (such as influenza, pneumococcus) and other coronaviruses, including animal viruses, indicate that the spread of this new coronavirus (SARS-CoV-2) may be limited in the summer months [75,76]. However, the seasonality may not be observed in the early years of the pandemic due to the high contagiousness of the virus, and especially considering that the susceptible population that has not encountered this virus is still very large.

7. *ABO blood group and risk*

Human blood can be divided into groups, a method of blood classification based on the presence or absence of hereditary erythrocyte surface antigens that can elicit an immune response. According to the International Blood Transfusion Association, 341 blood group antigens have been defined in 35 blood group systems [79]. Landsteiner's ABO blood groups are carbohydrate epitopes found on the surface of human cells. Various viral infection susceptibility such as Norwalk virus, HIV and Hepatitis B have been determined to be associated with the ABO blood group [79,80]. In a study published in 2005 that included a small number of patients (34 patients), it was reported that individuals with blood type O were less likely to be infected by the SARS-CoV [81]. More comprehensive study results for COVID-19 patients have recently been presented. In a study investigating the relationship between susceptibility to COVID-19 in 1,775 patients from three hospitals in Shenzhen, China it has been suggested that people with blood type A have a significantly higher risk of acquiring COVID-19 compared to non-A blood groups, whereas blood type O has a significantly lower risk of infection than blood groups without O [82]. In different studies, it was concluded that the disease was more severe in patients with blood type A and milder in patients with O [83,84]. In a study, it has been found that women in group A are more susceptible to COVID-19 infections [85]. As a result, the present results show that there is a relationship between ABO blood groups and the risk of contracting the disease and the severity of infection.

Immunological Features and Risk Factors

Immunological parameters include the importance of individuals who have the infection asymptomatically and those who spread the virus for a long time in the spread of the infection, contagiousness of people with high viral load, the possibility of recovered people to become re-infected, the clinical course of the infection in immunocompromised individuals, possible effectiveness of passive and active immunization in slowing the spread of infection [86,87].

1. *Secondary infection (re-infection) risk*

Although 90% of the people recovered from SARS-CoV-2 had antibodies against the virus, the level and duration of protective immunity and whether they are susceptible to secondary infections has been a major concern in societies [19]. Protective antibodies detectable in blood for up to two years in SARS-CoV 2003 infections, demonstration of cross reaction between SARS-Cov-2003 and SARS-CoV-2, convalescent plasma therapy results and demonstration of neutralizing antibody formation according to the preliminary results of SARS-CoV-2 vaccine studies are indicate that the antibodies formed in SARS-CoV-2 infections may have some degree of protective efficacy [88-91]. However, the first confirmed SARS-CoV-2 reinfection case, 33 years old, detected by airport screening on his return from Europe to Hong Kong, the second SARS-CoV-2 infection shows that the virus can continue to circulate among human populations despite community immunity due to "natural infection or vaccination" [92].

In 176 patients with SARS-CoV infection, it was shown that antibodies specific to the infection were preserved for an average of 2 years, and a significant decrease in the percentage of immunoglobulin G (IgG) positivity and titers in the third year [89]. Therefore, it was predicted that SARS patients could be re-infected 2 years after the initial exposure. A similar duration can be predicted for SARS-Cov-2 [88]. Apart from the antibody response, the cellular immune response against SARS-CoV-2 infections is another parameter that determines the course of re-infections [34,35]. As a result, although people with SARS-CoV-2 infection will not develop lifelong absolute protective immunity, secondary infections should be expected to have a milder course, as the response to the second infection will be stronger than the first infection. However, new parameters to be added to the equation, such as secondary risk factors and immunodeficiency states that will occur in the person in the period after the first infection, will change the course of the infection. Also, the level of immune response gained during the initial infection is critical in the emergence of secondary infections. In a study, 37 asymptomatic and 37 symptomatic individuals examined, researchers observed that IgG and neutralizing antibody levels decreased within 2–3 months after infection [48]. At 8 weeks, asymptomatic patients were seronegative for IgG more than symptomatic patients (40% vs. 13%), and asymptomatic individuals exhibited lower levels for 18 pro- and anti-inflammatory cytokines [48]. These data may indicate that asymptomatic individuals have a weaker immune response to SARS-CoV-2 infection. Based on this information, it can be thought that people who have the asymptomatic primary infection are more susceptible to the second infection risk. However, this information needs to be verified.

2. *Primary and secondary immunodeficiency*

Another of the immunological parameters is the course of SARS-CoV-2 infections in immunocompromised individuals (HIV infections, transplant patients receiving chemotherapy or patients with malignancy). Viral infections, especially chronic and latent infections, can easily become fatal in the presence of immunosuppression [30]. There are currently a small number of SARS-CoV-2 infections reported in immunocompromised patients. A 61-year-old male patient with type 2 diabetes mellitus and HIV who recovered from a coronavirus-associated pneumonia was reported to recover after SARS-CoV-2 infection, but it was emphasized that patients with suppressed immune systems such as HIV infection should be considered as a vulnerable group [93]. Case reports continue about patients who lost their lives and recovered from the infection [94-96]. However, in order to define the clinical course of the infection in this patient group and in special subgroups at risk, it is necessary to wait comprehensive study results. An interesting result has been reached from one of these studies, as follows; in a systematic review included 110 immunosuppressed patients mostly presenting cancer, it was concluded that immunocompromised COVID-19 patients were numerically fewer and that negative consequences were seen less than other comorbidities [97]. These results were interpreted as a weaker immune response may have a presumptive protective role or be related to underdiagnosis due to a milder disease presentation. However, researchers it has been suggest that this special population should be monitored carefully [97]. Also transplant recipients using steroids and other immunosuppressive drugs may exhibit unusual clinical courses (for example, fever may not be observed) resulting from coronavirus infection [30].

3. *Active and passive immunization*

Although the use of convalescent plasma and hyperimmunoglobulin may be useful indirectly in controlling the SARS-CoV-2 epidemic, a prophylactic use of these products is not on the agenda yet [91]. The most cost-effective and effective strategy is an effective preventative vaccine in preventing the spread of viral infections in populations and worldwide, and in reducing disease-related mortality and morbidity. Human and animal studies are ongoing on vaccines that stimulate humoral immunity and even cellular immunity in addition, and their results are followed carefully all over the world [90,98,99]. Although there are a few vaccines that have started Phase 3 studies for SARS-CoV-2 [100], there is no vaccine approved for use yet, and FDA declared that a COVID-19 vaccine should be prevent disease or decrease its severity in at least 50% of people who are vaccinated for approval [101].

Interestingly, some live vaccines (BCG, oral polio vaccine, measles) induces heterologous protection against infections by epigenetic, transcriptional, and functional reprogramming pathways by enhancing innate immune responses [102]. This mechanism also called "trained immunity" and it is thought that susceptibility to SARS-CoV-2 and the severity of infection can be reduced in this way [102].

4. *Viral load in infectious particles*

One of the topics discussed is that the viral load taken during transmission at the beginning of the infection is directly related to the severity of the infection [49]. In viral infections where host immune responses play a dominant role in viral pathogenesis, high-dose viral inoculum taken during infection can suppress and disrupt innate immune defenses, increasing the severity of the disease. A recent study revealed that in SARS-CoV-2 hamster-infection model more severe COVID-19 symptoms developed when given at high virus doses [103]. Based on this point, a new article emphasized that if viral inoculum is important in determining the severity of SARS-CoV-2 infection, face masks can reduce the viral inoculum the user is exposed to and the clinical impact of the disease [104].

Virological Characteristics and Risk Factors

Virion structure, genetic characteristics, receptor affinity and tissue tropism are parameters that can be addressed in this topic. With their enveloped virion structure, coronavirus particles are sensitive to heat, lipid solvents, non-ionic detergents, formaldehyde, oxidizing agents, UV irradiation, ethanol-containing antiseptics and chlorine or bleach-containing disinfectants and SARS-CoV-2 can be neutralized quite easily with many commonly used disinfectants [105,106].

1. *Structural features and stability of the virus*

A recent study has shown that SARS-CoV and SARS-CoV-2 can remain infectious in aerosols for up to 3 hours (infectious titer with a decrease from for SARS-CoV 104.3 TCID50 to 103.5 per liter of air, similarly 103.5 TCID50 to 102.7 for SARS-CoV-2) [54]. In the same study, it was reported that both viruses showed the longest durability on stainless steel and plastic (the estimated average half-life of SARS-CoV-2 was found to be approximately 5.6 hours in stainless steel and 6.8 hours in plastic) [54]. The stability of SARS-CoV-2 is similar to that of SARS-CoV under the tested experimental conditions, and differences in the epidemiological characteristics of these viruses are thought to be due to other factors, including high viral loads in the upper respiratory tract, differences in upstream receptor affinity, and the potential for transmitting the virus when SARS-CoV-2 infected persons were asymptomatic [20,54,107-109].

It has been shown that SARS-CoV is affected by temperature and low ambient temperature supports the persistence of the virus on surfaces [110]. This information was supported by another study published in 2011; in which the stability of the SARS-CoV at different temperatures and relative humidity on smooth surfaces were studied [111]. In the study, dried virus on smooth surfaces has been shown to maintain its viability for 5 days at 22-25°C and 40-50% relative humidity (i.e. typical air-conditioned environments) [111]. However, at higher temperatures and higher relative humidity (e.g. 38°C and relative humidity >95%) viability of the virus is rapidly lost (> 3 $\log_{10}$). The better stability of SARS-CoV in low temperature and low humidity environment has been interpreted as the social transmission of the virus may increase in the spring months and in air-conditioned environments [111]. This is likely to be the case for SARS-CoV-2, which has similar structural features. In a new study in which potential diffusion characteristics for COVID-19 are analyzed and discussed according to temperature, humidity and latitude changes, it has been suggested that absolute humidity above 10 g/m^3 may slow the transmission of 2019-nCoV [78].

2. *Receptor affinity and S gene mutations*

SARS-CoV-2 uses the same cellular receptor as SARS-CoV, namely the human angiotensin converting enzyme 2 (hACE2) receptor to enter cells [1]. Unlike SARS-CoV, it is thought that one of the factors that is responsible for the easier spread of SARS-CoV-2 in the society is its high receptor affinity. As a matter of fact, it has been reported in different studies that SARS-CoV-2 binds to the ACE2 receptor 4 to 10 - 20 times stronger than SARS-CoV [108,109]. Furthermore, high receptor affinity is thought to be one of the most important factors that affect the easy adaptation of the virus to humans and the rapid social spread of the disease [1].

In a study supported by National Institutes of Health it has been suggested that there is a new mutated variant of the SARS-CoV-2 spike variants called D614G, which is much more contagious but has a milder transmission [112]. The SARS-CoV-2 spike (S) protein variant, D614G, was not present in the hypothetical common ancestor of this zoonotic virus, but was first detected in China (hCoV-19/Zhejiang/HZ103/2020) and Germany (hCoV-19/Germany/BavPat1-ChVir929/2020) in late January. The frequency of the D614G variant has steadily increased and now accounts for >

97% of isolates worldwide, raising the question of whether the D614G offers a proliferative advantage to SARS-CoV-2. Structural models predict that the S protein of D614G will disrupt the contacts between the S1 and S2 domains and cause significant changes in conformation [112].

3. *Virulent strains and mutations*

Possible effects of mutations in the SARS-Cov-2 genome on virulence and infectiousness has been a subject that has been followed and researched with curiosity in the world of science and society. Viral genome sequence variants that occur during an outbreak can be exploited to map the trajectory of the virus. Although such variants generally have no functional significance, in some cases they may allow the virus to become more easily transmitted, alter the severity of the disease, or resist antiviral treatments [112]. Early studies indicated that the mutation tendency remained within certain limits. In a study examining 95 full-length genomic sequences of SARS-CoV-2 strains from NCBI (National Center for Biotechnology Information) and GISAID databases [113], homology among all viral strains was found to be as high as 99.99% (99.91% - 100%) at the nucleotide level and 99.99% (99.79% -100%) at the amino acid level. In the same study, although the total variation in ORF regions is low, 13 regions of variation were identified in 1a, 1b, S, 3a, M, 8 and N genes and high mutation rates were found in "ORF 8 nt28144" and "ORF 1a nt8782" 30.53% (29/95) and 29.47% (28/95) respectively. In subsequent studies, studies in which different evaluations were made on virulence and infectiousness were published. In a study where population genetic analyzes of 103 SARS-CoV-2 genomes were presented, two common SARS-CoV-2 variants were identified; L type (~ 70%, more prevalent) and S type (~ 30%) [114], and a new study [115] suggests that the mutation in NSP2 and NSP3 plays a role in the infectious ability and differentiation mechanism of SARS-CoV-2. As a result, available data suggest that SARS-CoV-2 may be less virulent than SARS-CoV and MERS-CoV, so that currently analyzed COVID-19 mortality is 3.4%, lower than SARS (9.6%) and MERS (approximately 35%) mortality [17]. Although researchers have catalogued more than 12,000 mutations in SARS-CoV-2 genomes, but different SARS-CoV-2 strains haven't yet had a major impact on the course of the pandemic, but they might in future [116].

Conclusion

SARS-CoV-2 exhibits similar properties to SARS-CoV with its virion structure, but significantly differ from this virus in terms of epidemiological, clinical and immunological parameters. Better understanding of the characteristics of the virus is important in terms of how long the epidemic will continue, predicting the success possibilities of vaccination studies, and allowing the reorganization of protective measures by determining risk situations.

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Supplement: Translated version of Figure 1 (to Turkish language).

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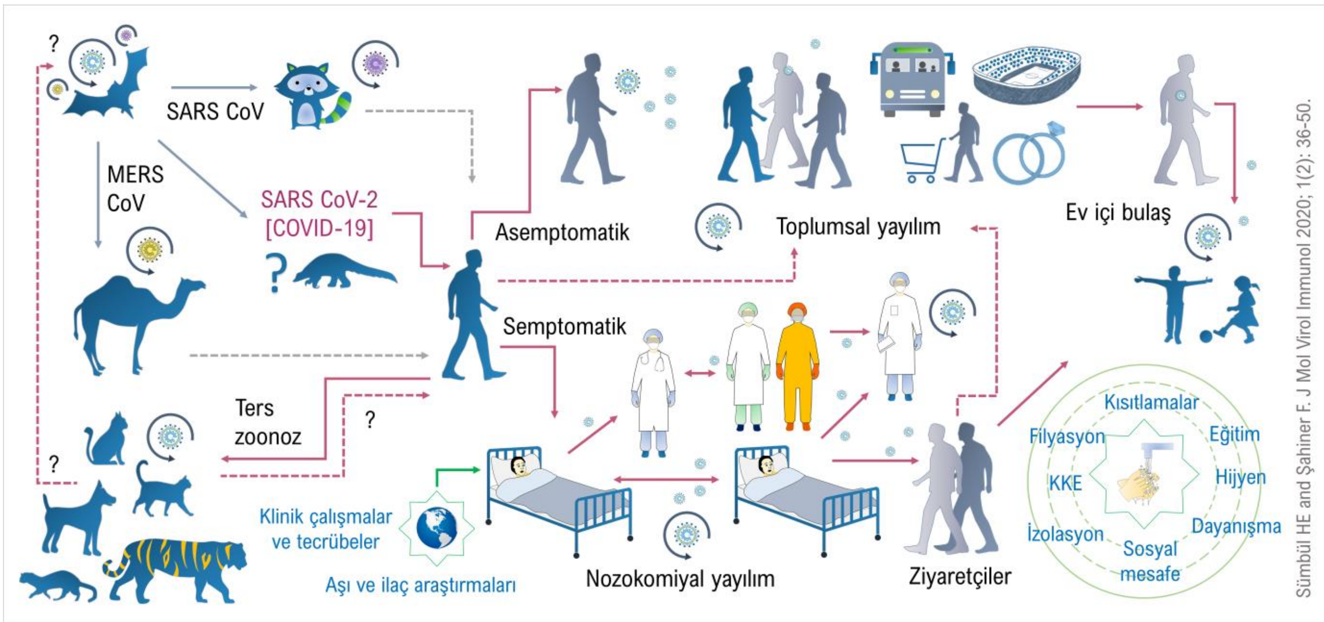
Supplement: Translated version of Figure 1 (to Turkish language).



Şekil 1. SARS-CoV-2 enfeksiyonlarının yayılma özellikleri ve önleyici tedbirler. (KKE: kişisel koruyucu ekipman, ?: Bulaşma yolu ve döngüsü bilinmiyor)