DOI:10.4274/tnd.2020.73669
Turk J Neurol 2020;26:58-108

Guide / Kılavuz

The COVID-19 from Neurological Overview

Nörolojik Bakış Açısından COVID-19

Türkan Acar[1], Esra Acıman Demirel[2], Nazire Afşar[3], Aylin Akçalı[4], Gülşen Akman Demir[5], Aybala Neslihan Alagöz[6], Tuğçe Angın Mengi[7], Ethem Murat Arsava[8], Semih Ayta[9], Nerses Bebek[5], Başar Bilgiç[5], Cavit Boz[10], Arman Çakar[5], Neşe Çelebisoy[11], Mehmet Uğur Çevik[12], Firuze Delen[13], Hacer Durmuş Tekçe[5], Hakan Ekmekçi[14], Ayşe Deniz Elmalı[5], Oğuz Osman Erdinç[15], Füsun Ferda Erdoğan[16], Fettah Eren[17], Ufuk Ergün[18], Yeşim Gülşen Parman[5], Haluk Gümüş[14], Demet İlhan Algın[15], Rana Karabudak[8], Ömer Karadaş[19], Özlem Kayım Yıldız[20], Emine Rabia Koç[21], Demet Özbabalık Adapınar[22], Atilla Özcan Özdemir[15], Şerefnur Öztürk[14]*, Ayşe Sağduyu Kocaman[3], Şevki Şahin[23], Esen Saka Topçuoğlu[8], Özden Şener[24], F. İrsel Tezer[8], Rıfat Erdem Toğrol[25], Ayşe Bora Tokçaer[26], Mehmet Akif Topçuoğlu[8], Neşe Tuncer[27], Ali Ulvi Uca[28], Kayıhan Uluç[27], Erdem Yaka[29], Mehmet İlker Yön[30]

[1]Sakarya University Faculty of Medicine, Department of Neurology, Adapazari, Turkey
[2]Bulent Ecevit University Faculty of Medicine, Department of Neurology, Zonguldak, Turkey
[3]Acibadem Ecevit University Faculty of Medicine, Department of Neurology, Istanbul, Turkey
[4]Gaziantep University Faculty of Medicine, Department of Neurology, Gaziantep, Turkey
[5]Istanbul University Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey
[6]Kocaeli University Faculty of Medicine, Department of Neurology, Kocaeli, Turkey
[7]Nigde Training and Research Hospital, Clinic of Neurology, Nigde, Turkey
[8]Hacettepe University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[9]University of Health Sciences Turkey, Haseki Training and Research Hospital, Pediatric Neurology Unit, Istanbul, Turkey
[10]Karadeniz Technical University Faculty of Medicine, Department of Neurology, Trabzon, Turkey
[11]Ege University Faculty of Medicine, Department of Neurology, Izmir, Turkey
[12]Dicle University Faculty of Medicine, Department of Neurology, Diyarbakir, Turkey
[13]University of Health Sciences Turkey, Kanuni Sultan Suleyman Training and Research Hospital, Clinic of Neurology, Istanbul, Turkey
[14]Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey
[15]Osmangazi University Faculty of Medicine, Department of Neurology, Eskisehir, Turkey
[16]Erciyes University Faculty of Medicine, Department of Neurology, Kayseri, Turkey
[17]University of Health Sciences Turkey, Konya Training and Research Hospital, Clinic of Neurology, Konya, Turkey
[18]Kırıkkale University Faculty of Medicine, Department of Neurology, Kirikkale, Turkey
[19]University of Health Sciences Turkey, Gulhane Training and Research Hospital, Clinic of Neurology, Ankara,Turkey
[20]Cumhuriyet University Faculty of Medicine, Department of Neurology, Sivas, Turkey
[21]Uludag University Faculty of Medicine, Department of Neurology, Bursa, Turkey
[22]Acıbadem Eskişehir Hospital, Department of Neurology, Eskisehir, Turkey

Address for Correspondence/Yazışma Adresi: Şerefnur Öztürk MD, Selcuk University Faculty of Medicine, Department of Neurology, Konya, Turkey
Phone: +90 332 224 40 10 E-mail: serefnur.ozturk@noroloji.org.tr ORCID: orcid.org/0000-0001-8986-155X
Received/Geliş Tarihi: 08.05.2020 **Accepted/Kabul Tarihi:** 10.05.2020

[23]Maltepe University Faculty of Medicine, Department of Neurology, Istanbul, Turkey
[24]Ankara University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[25]University of Health Sciences Turkey, İkinci Sultan Abdülhamid Han Training and Research Center, Clinic of Neurology, Istanbul, Turkey
[26]Gazi University Faculty of Medicine, Department of Neurology, Ankara, Turkey
[27]Marmara University Faculty of Medicine, Department of Neurology, Istanbul, Turkey
[28]Necmettin Erbakan University Meram Faculty of Medicine, Department of Neurology, Konya, Turkey
[29]Dokuz Eylül University Faculty of Medicine, Department of Neurology, Izmir, Turkey
[30]Ankara Yıldırım Beyazit University Faculty of Medicine, Ankara City Hospital, Department of Neurology, Ankara, Turkey

SARS-CoV-2 and COVID-19: GENERAL INFORMATION

Terminology

Since December 2019, the disease caused by a new type of coronavirus called "New Coronavirus Disease (COVID-19)" has spread rapidly from Wuhan to other provinces of the Republic of China, and then to the entire world (1).

With this pandemic around the world and in Turkey, very strong and shocking changes occurred in the flow of life, lifestyle, habits, education, politics, and the economy. Many issues related to COVID-19 have been discussed in the media, mostly new faces, new opinions, new expressions, mostly of scientists and physicians who have rarely been seen before have started to appear in media. With this fast-developing situation threatening the existence of all humanity, the perception of life, today and the future, has differentiated, and death has been considered more than ever before. In this process, new terms and concepts, which have never been used before or used very little, have started to be used frequently.

Coronaviruses are a large family of viruses that are common in humans and animals. The word corona takes its name from the form of the virus and means "crown" or "ring of light" in Latin. The virus can pass from animals to humans; scientists believe the current spread occurred in this way. However, the source is still not known precisely (1,2,3). It has not been seen in humans before and is often referred to as the "new" or "newly released" coronavirus (2). "Severe Acute Respiratory Syndrome-Coronavirus (SARS-CoV-2)" is used as the technical term to describe this new type of coronavirus. The disease caused by the SARS-CoV-2 virus, on the other hand, was named by the World Health Organization (WHO) as COVID-19, meaning "COVID-2019", because it was in 2019 when it was first seen (1).

SARS and Middle East Respiratory syndrome **(MERS)** are diseases caused by coronaviruses. SARS caused by SARS-CoV caused an epidemic between 2002-2003, killing more than 770 people, with the most deaths seen in China and Hong Kong. MERS caused by MERS-CoV was first reported in Saudi Arabia in September 2012 and spread to 27 countries (4,5,6).

Droplet infection is an infection caused by the passage of droplets containing microorganisms that spread to the air from the mouth or nose as a result of coughing and sneezing (7). The coronavirus is transmitted in this way. The **incubation period** is the period of time until the disease emerges after contact with the virus, and this is 14 days for coronavirus (7).

The term **epidemic** defines an outbreak that occurs in society in a certain period of time, whereas **pandemic** defines an epidemic that has spread all over the world. Here, there is a disease agent that is often new and against which people have little or no immunity (4,8).

Isolation and **quarantine** are among the terms we use very often. Isolation describes whether the person who is sick or likely to become ill due to SARS-CoV-2 or another microorganism remains at home or in the hospital (7). Quarantine is a health measure applied in the form of controlling and observing a certain area or place to prevent the spread of an infectious disease. It describes the removal of people who are in contact with people with COVID-19 disease (7,8).

Social distancing is a definition proposed by the WHO. It is the distance between 120 and 200 centimeters between the personal space and the public space. When a virus-infected person coughs or sneezes, droplets scatter around, so the probability of getting infected by droplets is extremely low when this distance is maintained (7,8).

With the introduction of COVID-19 into our lives, terms such as face masks, hand-face hygiene, personal protective equipment (PPE) and diagnostic kits used in the diagnosis of the disease, patients hospitalized in intensive care, intubation process, corona vaccine, plasma therapy and stem cell therapy have begun to be heard and used very frequently (7,8).

The Process in the World and Our Country

Cases of pneumonia of unknown etiology were reported on December 31st, 2019, in Wuhan City, Hubei Province, China. Wuhan is a very busy city with more than 14 million inhabitants in the center of the Republic of China. It is a center that is very easy to reach and has considerable transportation and connection with other regions of China and overseas. The first cases were seen in the employees of Wuhan South China Seafood City Market (a wholesale fish and livestock market selling different animal species). Findings consistent with fever, shortness of breath, cough, and pneumonic infiltration of bilateral lungs were detected in the patients. As a result of research conducted on these patients, the virus was identified on January 13th, 2020 (1,9).

By March 7th, 2020, the number of cases detected in all provinces of China was 80.813 and the number of cases reported from 93 countries of the world was 21.110. This number meant the largest epidemic ever seen since the founding of the Republic of China in 1949. This virus, which had a very high spread rate, coincided with the Chinese Spring Holiday period when many

people traveled. It was very difficult to control the disease and it showed a rapid spread outside the country. Patients were detected quickly and persuaded to be isolated, stay at home, and comply with social distancing. It was reported that possible contacts were detected and treatment was initiated rapidly (9).

The WHO reported in its COVID-19 report of the Republic of China that deaths were generally in elderly patients or in patients with systemic diseases, such as hypertension, diabetes, cardiovascular disease, cancer, chronic lung diseases, or in immunosuppressed individuals. The first case outside of China was a 61-year-old Chinese woman reported from Thailand on January 13th, 2020. As the number of countries reporting cases increased steadily in the following days, countries with domestic contamination began to emerge in late February. As of the beginning of March 2020, the pandemic in China slowed down, while the cases of COVID-19 and related deaths increased rapidly in Iran, South Korea, and Italy. Again, as of the beginning of March 2020, cases from over 100 countries were reported worldwide (1,2).

The first case was reported on March 10th, 2020, in Turkey, and the first death related to the disease was reported on March 17th, 2020. As of April 19th, Turkey was ranked 7th among the countries in the number of cases, following France, surpassing China, the country where the pandemic first began. It was ranked 12th among 185 countries in the number of deaths. According to the data shared on April 10th, Istanbul was the city with the highest number (28.000) of cases, followed by Izmir, Ankara, Kocaeli, and Konya, respectively (10).

The pandemic has caused many radical decisions to be taken that have had significant impact in social, economic, political, economic, administrative, judicial, military, and religious fields. Education and training were suspended in primary, secondary, and high schools in the country, spring-term courses were canceled, and exams were postponed in all universities. All places where people could gather were closed. All sports events were canceled. In military barracks, all transactions were postponed. In order to prevent the pandemic from spreading to prisons, 90.000 prisoners and detainees were released after the execution of a discount arrangement. The Council of Judges and Prosecutors halted cases other than urgent cases and timeout cases. The Ministry of Foreign Affairs reported that more than 40.000 Turkish citizens from 75 countries were brought to Turkey by evacuation. The curfew, covering people aged over 65 years, later covered those aged under 20 years. Then a curfew was launched on April 11-12th, 2020, in Turkey's 31 provinces covering weekends (1,8,10).

The scientific committee, which was established under the presidency of the Ministry of Health in our country, closely followed and evaluated the information coming from around the world and our country during the pandemic process, and took and implemented the necessary measures. All necessary precautions were taken and important practices such as travel restrictions and bringing Turkish citizens from abroad were carried out in cooperation with other institutions and organizations such as the General Directorate of Border and Coastal Health, General Directorate of State Hospitals, and Turkish Airlines. Basic measures to prevent the spread of the outbreak were performed in line with the WHO's recommendations. Infection control measures, procurement of PPEs (surgical masks, N95/FF2 masks, gloves and face-shields) were managed by health authorities to ensure correct use. A directive has been prepared for health professionals and includes all information to prevent and control the outbreak (1,11).

Currently, COVID infections have been reported in 210 countries worldwide and the number of cases continues to increase. The epidemic was brought under control in China, the first starting place, but first Europe, and then the United States of America (USA) became the center of the pandemic. As of April 26th, 2020, the number of cases in the world was 2.912.421 and the number of deaths was 203.412. The USA, Spain, Italy, France, Germany, and England are the countries with the highest number of cases, respectively (12). Although similar measures were taken in these countries, the political authorities had different attitudes toward the pandemic at the beginning. These differences and the timing of taking measures had significant effects on the results. Unfortunately, in the USA and most European countries, not every patient was able to reach the basic healthcare they deserved, physicians had to make tough decisions on the line between death and life, some patients had to be hospitalized in hospital corridors, and serious difficulties were faced even with storing bodies in morgues and burying them (13). In Turkey, every patient with the diagnosis or suspicion of COVID-19 has been able to access adequate healthcare services thanks to our strong infrastructure in health services and timely measures. In our country, the decrease in the number of cases and deaths and the increase in the number of recovered cases indicate that the outbreak is under control.

Foreseeable Future

At the end of April 2020, we still do not know if the antibodies protect against a second infection. Measures specifically focused on protecting the elderly and slowing the spread of disease will reduce the burden of disease and death, but the danger will not be overcome completely unless a drug or vaccine has been developed and produced adequately. For a long time, we may all have to wear masks and maintain social distancing even after restrictions are lifted. It is also unknown when the probability of a second wave of the outbreak will disappear. It is still unknown how long, how intense, and how fatal the outbreak will be. Scientific advances will help in finding the answers to these questions (14).

The COVID-19 outbreak affects and will continue to affect all parts of society, particularly people with low-income, the disabled, the elderly, and young people. It is clear that pediatric patients are affected by the virus to a lesser extent. Early evidence suggests that the impact of the virus on health and economically is disproportionately overloaded by people with low-income. Homeless people, people without access to water, immigrants, refugees, and nomads will be exposed to the virus more and these people will be worse affected by the consequences of the pandemic. If the social crisis caused by the COVID-19 pandemic cannot be managed with the right policies; exclusion, separation, and worldwide unemployment will increase. These vulnerable groups need to be observed more and more precautions should be taken (15).

This pandemic affects all parameters of life all over the world, and its effects on the world economy are very important and extensive. It will take time for the world economy to recover

before it contracts. This pandemic will lead to changes in policy, finance, environment, housing, education, health, trade, business, agriculture, manufacturing, production, security and science policies, and the changes will affect future generations. Changes in consumer behavior caused by the COVID-19 outbreak will cause temporary effects in some sectors, but will cause permanent changes in other sectors. The losing sectors of the process are tourism and transportation where social interaction is physically high, whereas information technology-based sectors have strengthened. This new world order will also provide great opportunities to some countries in areas where they have not had a say in world production before. States should develop new strategies before it is too late. Countries need to build their economic development strategies from now on, considering this transformation. The Turkish economy will also receive significant damage in the short term like many other countries, but if it manages to control the outbreak early, it will be able to recover by selling goods abroad, tourism, and foreign investments (8,16).

In the postpandemic period, social life, production mechanisms, and sensitivity in the governing of countries will change. Turkey must perceive these changes well, develop new strategies, and ensure a good adaptation to the postpandemic period without delay. COVID-19 is a major biohazard and a threat to the entire world. More modern technological developments and investments are needed to control this pandemic worldwide. National and international supportive collaborative attitudes are very important for the solution.

SARS-CoV-2 and Other Coronaviruses: What Should Neurologists Know?

Coronaviruses are roughly spherical and moderately pleomorphic, approximately 125 nm in diameter, single-stranded, positive-polarized, enveloped RNA viruses with rod-shaped spike projections (Figure 1) (24).

The protrusions on the virion surface are the most prominent feature of the coronaviruses. These viruses are named as coronavirus (crowned virus) based on the meaning of "corona", that is, "crown" in Latin. Another distinctive feature of this viral family is its genome size; it has the largest genome among all RNA viruses, including RNA viruses with segmented genomes (25). This provides a unique replication strategy to the coronavirus. They do not contain RNA-dependent RNA polymerase enzymes because they have positive polarity, but they encode this enzyme in their genomes. The genome is packaged in a spiral capsid formed by the nucleocapsid protein (N) and is also surrounded by a viral envelope. The viral envelope contains three structural proteins, called matrix protein (M), envelope protein (E), and spike glycoprotein (S) (26). Certain coronavirus groups also have hemagglutinin-esterase (HE) surface proteins that are similar to spike glycoproteins but are associated with a shorter viral envelope.

Virions bind their genomes to the target cell via the fusion of the viral envelope with the plasma membrane and/or with an endocytic vesicle, by binding to specific host cell surface receptors via the spike glycoprotein, which is key to viral tropism. The entire replication cycle takes place in the cytoplasm, and the viral genome acts as a template. Coronaviruses have the ability to adapt to new environments through mutation and recombination, so they are programmed to efficiently change their range of hosts and tissue tropism (26).

SARS-CoV-2 and Other Coronaviruses

Molecular clock dating analysis in coronaviruses showed that the last common ancestors of these viruses existed 10.000 years ago (27). But in the early 1930s, the scientific world met coronaviruses with the demonstration that a virus known as avian infectious bronchitis virus caused acute respiratory infection in domestic chickens. The discovery of the first human coronaviruses was towards the late 1960s (28).

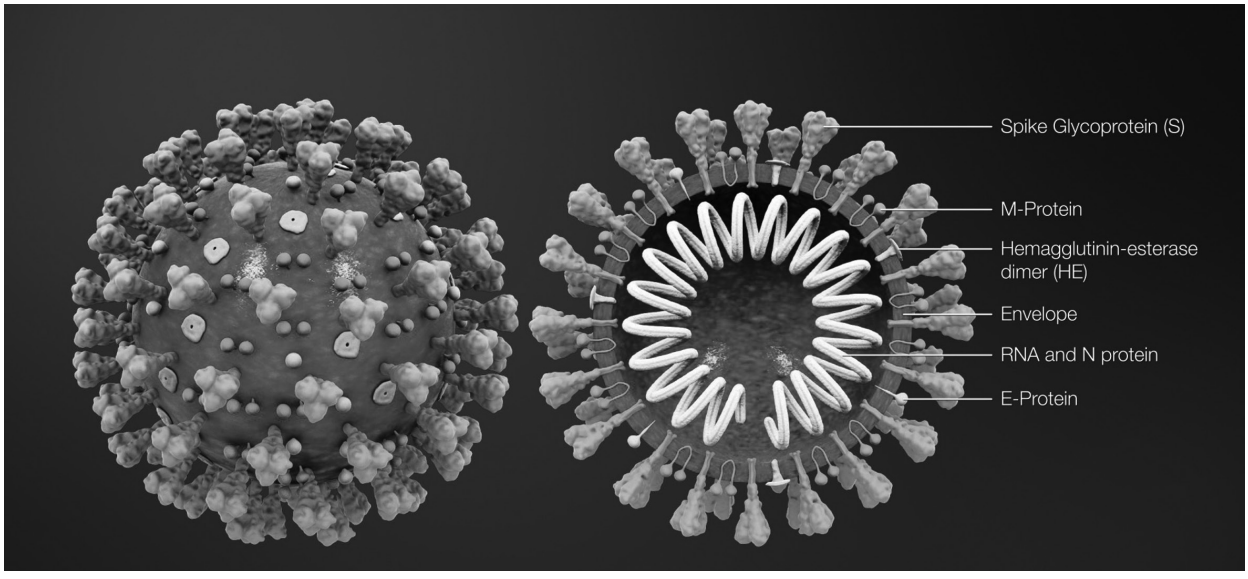

Figure 1. Coronavirus section model*
*Reference: https://www.scientificanimations.com/coronavirus-symptoms-and-prevention-explained-through-medical-animation/

The International Virus Taxonomy Committee has classified coronaviruses into four genera in the nidovirales family, the coronaviridae family, orthocoronavirinae sub-family: these are alpha, beta, gamma, and delta coronaviruses (29). Alpha and beta coronaviruses only infect mammals, and gamma and delta coronaviruses mostly infect birds (30). Alpha and beta coronaviruses usually cause respiratory disease in humans and gastroenteritis in animals. Highly pathogenic viruses such as SARS-CoV, MERS-CoV, and SARS-CoV-2 cause syndromes such as SARS, MERS, COVID-19, which cause severe respiratory problems in humans (31). Although four other human coronaviruses (HCoV-NL63, HCoV-229E, HcoV-OC43 and HcoV) only cause mild upper respiratory tract diseases, these viruses can cause severe infections in infants, young children, and the elderly (32). Alpha and beta coronaviruses can also create a heavy burden of disease in livestock. These include pig infectious gastroenteritis virus, pig enteric diarrhea virus, and pig acute diarrhea syndrome coronavirus (SADS-CoV) (33).

All human coronaviruses have animal origins (Figure 2). SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E are originated from bats and HCoV-OC43 and HKU1 are probably from rodents. Thirty two pets can play an important role as intermediate hosts that transmit virus from the natural hosts to humans. However, pets themselves can become infected by a coronavirus transmitted from bats or due to close relationship. SARS-CoV and MERS-CoV were transmitted from bats to musk cats, then to single-hump camels, and then finally to humans. SARS-CoV-2 has a close resemblance to bat coronaviruses, and therefore bats are assumed to be the primary source. SARS-CoV-2 is thought to be transmitted to humans through potentially illegal pangolins sold in Chinese markets (34).

While coronaviruses have caused three major pandemics such as SARS, MERS, and COVID-19 in the past two decades, SARS-CoV-2 has been transferred to the literature as the seventh coronavirus known to infect humans. The epidemiologic and clinical features of pandemics caused by SARS-CoV-2 and other important coronaviruses are presented in Table 1 (35).

Different Aspects of SARS-CoV-2

Complete genome sequencing and phylogenetic analysis reveal that SARS-CoV-2 is similar to beta coronavirus detected in bats, but is a distinctly different class from SARS-CoV and MERS-CoV (36). SARS-CoV-2 uses the angiotensin converting enzyme-2 (ACE-2) receptor found in the heart, lungs, kidneys and gastrointestinal tract, just like SARS-CoV for entry into the target cell. A variable receptor binding area (RBA) found in the SARS-CoV-2 spike protein can bind strongly to ACE-2 receptors (37). The binding affinity of spike protein to ACE-2 has been found to be an important determinant of the SARS-CoV replication rate and disease severity. Although SARS-CoV-2 is very similar to some bat viruses (RaTG13) and SARS-CoV, it contains unique sequences that have not been previously identified. Although it is compatible with pangolin coronaviruses in terms of amino acid sequences in the RBA, the area of polybasic cleavage is the product of a unique change (38).

There is some speculation about SARS-CoV-2 that a SARS-CoV-like coronavirus emerged as a result of laboratory manipulation. Andersen et al. (37) reported that the SARS-CoV-2 RBA was optimized for binding to human ACE-2, unlike what was previously known, that it would not be possible to construct it with reverse genetic design studies. On the other hand, they accepted some specific sequences of the virus as an indication that SARS-CoV-2 was not derived from any previously identified

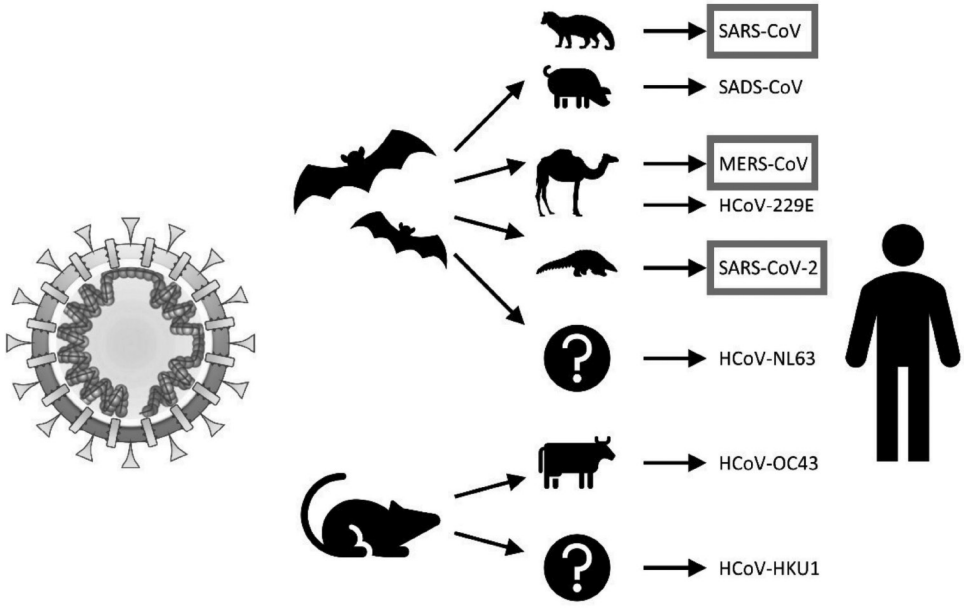

Figure 2. Animal origins of human coronaviruses*

SARS: Severe Acute Respiratory Syndrome, SADS: Sudden Arrhythmia Death syndromes, MERS: Middle East Respiratory syndrome

*Reference: Rabi FA, Al Zoubi MS, Kasasbeh GA, et al. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. Pathogens 2020;9:1-14.

Table 1. Comparison of infections caused by SARS-CoV-2 and other important coronaviruses (35)			
	SARS-CoV-2	**SARS-CoV**	**MERS-CoV**
Epidemiology			
Outbreak starting date	December 2019	November 2002	April 2012
Location of the first case	Wuhan, China	Guangdong, China	Saudi Arabia
Confirmed cases	2.846.000 (25 April 2020)	8096	2519 (2012-January 31st 2020)
Fatality	197.000 (6.9%)	744 (10%)	866 (34.4%)
First infection time 1000 patients (days)	48	130	903
Incubation period (days)	3-14	2-7	5-6
Transmission	Touching or eating an infected, not yet defined animal. Human-to-human transmission occurs through close contact	It was believed that it spread from bats that infected musk cats. It is transmitted mainly through close contact between people	By touching infected camels or consuming their milk or meat. Limited transmission among people through close contact
Clinical status			
Age, year (range)	47.0 (all age ranges)	39.9 (1-91)	53 (36-66)
Male: female ratio	1.39: 1	1: 1.25	2.03: 1
Fever	88.7%	99-100%	77±6%
Tiredness	29.4%	31.2%	80±5%
Dry cough	67.7%	25-75%	*
Muscle pain	14.8%	49.3 - 60.9%	*
Breathing difficulty	45.6%	40-42%	*
Sputum	13.3%	NA	39±11%
Sore throat	13.9%	12.5%	10-20%
Diarrhea	6.1%	20-25%	*
Headache	8.0%	35.4-55.8%	*
Nausea or vomiting	5.0%	19.4-19.6%	*
Vertigo	3.7%	4.2-42.8%	*

*No literature reached, SARS: Severe Acute Respiratory syndrome, CoV: Coronavirus, MERS: Middle East Respiratory syndrome

virus backbone and did not find laboratory manipulation possible. Although the evidence suggests that SARS-CoV-2 is not a manipulated virus, it is currently not possible to fully prove or reject these origin theories.

Prevention and Control of Transmission

In the pandemic of COVID-19, where the main passageway is through person-to-person droplets, the WHO has collected measures to prevent or reduce the spread of the virus under five headings (39):

1. **Providing triage, early diagnosis, and control of the source:** Separate sections to which these patients will be admitted should be created in order to recognize patients with possible COVID-19 early and to isolate them quickly. Trained personnel should make updated screening inquiries about the disease. Hand hygiene and respiratory hygiene are the main measures in this area.

In our country, according to the Ministry of Health COVID-19 Guidelines, the triage of patients who are admitted to the outpatient clinic is performed by healthcare personnel who are properly dressed (gowns, medical masks, face shields or goggles). The questions "Do you have a fever or a history of fever?", "Do you have a cough?" and "Do you have difficulty in breathing or shortness of breath?" are asked, if one of these questions is answered "yes", a mask is worn by the patient and the patient is directed to the area reserved for COVID-19. If the answer to these three questions is "no", the questions "Have you been abroad in the past 14 days?", "Has any of your family members come from abroad in the past 14 days?" and "Has anyone in your last 14 days been diagnosed with COVID-19 disease?" are asked, if one of these

questions is called "yes", a mask is worn by the patient and the patient is again directed to the area reserved for COVID-19 (1).

2. Application of standard measures to all patients: Standard measures include hand and respiratory hygiene, use of PPE suitable for the risk of the procedure to be performed, safe waste management, wearing appropriate clothing, environmental cleaning, and sterilization of materials used in patient care. For respiratory hygiene, it is important to ensure that all patients cover their mouths and noses with a tissue or inner face of their elbows while coughing or sneezing, and that patients with suspected COVID-19 wear surgical masks in waiting rooms, common areas and crowds, and apply hand hygiene after contact with respiratory secretions. Here are the WHO's "My 5 Moments for Hand Hygiene" approach for hand hygiene; it should be applied before touching the patient, before any aseptic or clean procedure, after contact with body fluids, the patient or the patient's environment. For hand hygiene, if hands are visibly dirty, it is recommended to use water and soap, if not, alcohol-based hand antiseptics are recommended (39). The Ministry of Health COVID-19 Guideline makes similar recommendations on hand hygiene as well as respiratory hygiene (1).

3. Taking additional measures: In this context, "Measures for contact and droplets" and "Measures against the risk of airborne spread in the processes that create aerosolization" are discussed.

Family members, visitors, and healthcare workers should take precautions in terms of contact and droplets when entering the room of a suspected or confirmed patient with COVID-19. Patients should be placed in rooms where ventilation of 60 l/second per person is provided. If a single room cannot be provided, it is recommended that suspected and confirmed patients are hospitalized in separate wards at least one meter apart. Health care professionals who deal with patients should wear medical masks, goggles or a face shield, and clean, non-sterile, long-sleeved gowns and gloves to prevent contamination with mucous membranes. When patient care is over, all these clothes should be removed and discarded, hand hygiene should be ensured, and a new set of equipment should be used for the next patient. Detailed information about PPEs is given later in this article. Equipment such as thermometer, stethoscope, and sphygmomanometer should be disposable or separate for each patient, if possible. Common used equipment should be cleaned and disinfected with 70% ethyl alcohol before the next patient. Unless medically necessary, the patient should not be taken out of the room. A portable X-ray device and other diagnostic equipment reserved for patients with COVID-19 should be used. In case of necessity, the patient should be transported in such a way that they encounter the least number of staff and other patients and visitors, by wearing a medical mask and should be taken as the last patient if possible. Healthcare professionals accompanying the transport should pay attention to hand hygiene and proper PPE. The department that will accept the patient for the examination must be informed and the necessary precautions must be taken, and the surfaces that the patient touches must be disinfected after the procedure. Access to the patient room should be restricted, only healthcare workers responsible for patient care, examination, and treatment should be allowed to enter the room, visitors should be banned, and if a companion is needed they should be one person. One of the most important points is to keep a record of everyone entering the patient room, including staff (39).

The Ministry of Health COVID-19 Guideline brings many approaches and suggestions such as contact and droplet precautions, use of PPEs, transport conditions of the patient in the hospital, and restriction of access to the patient's room. In the guidebook of the Ministry of Health, it is emphasized that the order of wearing the PPEs is gowns-mask-glasses (face shield)-gloves, and the order of removal is gloves-glasses (face shield)-gowns-mask. This order should be paid attention to, especially that the mask should be removed last after leaving the patient's room and that subsequent hand hygiene is important. It is stated that if the integrity of the glove is broken, it should be removed and a new one should be worn after hand hygiene is ensured. In addition, it is suggested that two separate medical waste bins should be kept inside and outside the patient's room for used PPEs (1,11).

The risk of spreading of coronaviruses increases in aerosol producing/forming processes such as tracheal intubation, non-invasive mechanical ventilation (NIMV), tracheostomy, cardiopulmonary resuscitation, pre-intubation ambulation, and bronchoscopy. Such procedures should be performed in properly ventilated rooms (in naturally ventilated or negative-pressure rooms that provide a minimum of 160 l/sec air flow per patient). Healthcare professionals should use US or European Union standard or equivalent masks (US National Institute for Occupational Safety and Health-NIOSH-certified N95 or European Union FFP2), constantly check whether they fit well (for example, beard can prevent mask to fit face), should wear glasses or face mask. Clean, non-sterile, long-sleeved gowns and gloves should be worn. If gowns are not waterproof, a second gown with this feature should also be worn. During the procedure, there should be a minimum number of people in the room for care and support to the patient, and the room door should be kept closed (11,39).

In addition, in the COVID-19 Guideline of the Ministry of Health, if the patient receives invasive or non-invasive breathing support that causes aerosolization, healthcare providers that give care and the personnel accompanying the patient's transportation should use glasses and a mask of N95/FFP2 type (1,11).

4. Implementation of administrative controls: Administrative checks and measures for preventing and controlling the spread of COVID-19 include healthcare providers' training, caregivers' training, early recognition of suspected patients with COVID-19, rapid implementation of diagnostic laboratory tests, especially the prevention of mass/congestion in emergency departments, the establishment of separate waiting rooms for symptomatic patients, the proper isolation of hospitalized patients, the provision of adequate PPE, and strict compliance with the principles of infection prevention and control. Adequate education and appropriate patient/staff ratio should be provided for healthcare professionals, healthcare professionals should be carefully monitored for suspected COVID-19 acute respiratory infections, and the importance of prompt medical attention should be explained to healthcare professionals and the public (39).

5. Making environmental and technical controls: Proper ventilation and proper environmental cleaning should be provided in all areas, and patients should be hospitalized at least one meter apart. Cleaning and disinfection should be performed regularly

and correctly. After cleaning the surfaces with water and detergent, applying hospital disinfectants such as sodium hypochlorite is effective and sufficient (39).

In the Ministry of Health COVID-19 Guideline, it is recommended to clean and disinfect the environment of the patient in accordance with the rules reported by the infection control committees, and to ensure the cleaning of the surfaces that are contaminated by the patient's excreta and secretions in accordance with the "Guidelines for Protection from Infectious Diseases in Pre-Hospital Emergency Health Care Services". Also, in the guide of the Ministry of Health, it is stated that after the patient vacates the room, room cleaning and ground surface disinfection are performed, and it is stated that a new patient can be taken after the room has been ventilated (1,11).

Use of Personal Protective Equipment

The use of PPE is the main step in limiting the disease by preventing transmission in infectious diseases. Especially in the COVID-19 pandemic, one of the most important issues for healthcare professionals and the general public is the use of PPE. There are two important problems in this process all over the world. The first is the lack of equipment, the second is the improper use of the equipment (40). The SARS-CoV-2 virus that causes COVID-19 is mainly transmitted by sputum and upper respiratory secretions (41). Although the virus is known to enter the bloodstream and cause viremia, there are insufficient data showing that it is transmitted through the bloodstream (41). The virus is transmitted by contact and droplets, which tend to travel up to a distance of 1 meter. Therefore, it is recommended to keep a distance of 2 meters between us and patients or people who are potential carriers. Attention should be paid to this distance because the virus can stay on a surface for hours or days and pose a potential risk for infection (42). People who touch these surfaces and do not pay attention to hand hygiene may contaminate others and spread the virus.

The most effective measures to prevent spread in the community and healthcare professionals are as follows:

1- Providing hand hygiene by using water and soap if the hands are dirty, with antiseptics containing alcohol if there is no visible pollution. The use of gloves cannot replace hand hygiene and hand washing,

2- Prevention of contact of the hands with the eye (viral contamination may also occur via conjunctiva), nose and mouth,

3- Sneezing into the bent arm or disposable tissue,

4- Use of medical masks and repetition of hand hygiene after disposal,

5- Protection of social distancing (at least 1 meter, optimum 2 meters) (43).

It is necessary to take some precautions to make the use of PPE sufficient and to prevent contact. For this, the use of telemedicine in patients, if possible, will limit admissions to health institutions (44). It is recommended to use physical barriers such as glass or plastic windows to prevent exposure to the virus. The number of entries-exits to patient rooms should be minimized. It is important not to allow patient's relatives and visitors. However, if this cannot be prevented, the length of stay with the patient should be shortened, contact should be prevented, and information about the use of PPE should be given (43).

The use of PPE varies according to the environment being studied and the health intervention performed (Table 2). The diameter of the virus has been shown to be 70-90 nm with electron microscopy (45). Surgical face masks have been found to provide little protection for 10-80 nm sizes. N95/FFP2 masks are 95% effective for 0.1-0.3 μm particles and have a protective effect over 0.75 μm 99.5% or above (46). In addition to surgical masks, especially in procedures with a high risk of contamination such as tracheal intubation, bronchoscopy, and NIMV, N95/FFP2 masks or the equivalent thereof are required in addition to surgical masks (43). Although the protective effect of these masks lasts for a long time (47), it is recommended to use these masks for up to 4 hours (48). This is due to the risk of developing skin lesions for longer use (48). Other than that, it is sufficient to use medical masks, gowns, gloves, glasses or face shields for healthcare personnel responsible for the direct care of the patient (43,49).

Adequate PPE provision and training are required for healthcare professionals to provide safe healthcare. The WHO continues to update the PPE use recommendations as a result of clinical experience, expert opinions, and studies in the COVID-19 pandemic process. In line with these recommendations, planning and training of PPE use are important in our social lives and clinics.

Community Based Measures

Hand hygiene, sneezing-coughing etiquette, and environmental cleaning at home are key elements in protecting individuals and their families from respiratory infections, including COVID-19 (50). Hand hygiene should also be provided after sneezing-coughing to the inner surface of the elbow, after contact with waste or laundry contaminated with body fluids, or if hands appear dirty. Frequently touched areas such as door handles, electrical buttons, bedside tables, toilets in homes should be cleaned first and then disinfected with 0.5% sodium hypochlorite. For frequently used devices such as telephones and computers, 70% alcohol wipes can be used. Telephones, elevator buttons, tables, toilets should be cleaned frequently and hand hygiene should be increased in workplaces and similar public areas. Shopping centers, airports, public transportation vehicles should be cleaned and disinfected regularly. According to simulation studies, if the weather is suitable, ventilation of places such as the home and office has been shown to reduce virus spread.

Social distancing measures are approaches to minimize close contact with others in the community. It includes individual quarantine and self-isolation, community-based avoidance of crowds, measures for schools and workplaces or closure and cancellation of meetings. Social distancing measures can cause secondary situations for individuals, families and communities such as loss of in come and increased need for support services. If all individuals in the community need quarantine or self-isolation, it is recommended to plan ahead for essential drugs, home supplies, and food.

Isolation is recommended for symptomatic individuals with suspected or confirmed COVID-19. The person does not go out of the house, does not use public transport. If they live alone or have a high risk of developing complications, someone should be

Table 2. Protective equipment and its use in COVID-19		
Environment	**Activity-affected health personnel**	**Personal protective equipment**
Patient room	Health worker giving care to patient with COVID-19	Medical mask, gowns, gloves, glasses or face shield
	Intubation to patient with COVID-19, taking respiratory sample from patient	N95/FFP2 mask, medical mask, gowns, gloves, glasses or face shield
	Visit patient with COVID-19	Medical mask, gowns, gloves
	Cleaning patient rooms and cleaning staff	Medical mask, gowns, gloves, glasses or face shield, boots/ closed work shoes
Service passage and corridors	Activities not requiring contact with patient with COVID-19	No personal protective equipment required (medical mask if possible)
Laboratory	Examination of respiratory samples	Medical mask, gowns, gloves, glasses or face shield
Administrative areas	Entry into areas free of contact with patient with COVID-19	No personal protective equipment required (medical mask if possible)
Outpatient clinic room	Examination of a patient with respiratory symptoms or suspected respiratory symptoms	Medical mask, gowns, gloves, glasses or face shield
Outpatient clinic waiting area	Waiting of the patient with suspected respiratory symptoms in terms of COVID-19	Medical mask, isolation from other patients, providing at least 1 meter contact distance if not possible
	Waiting of patient without respiratory symptoms	No personal protective equipment required (medical mask if possible)
Home	The situation of relatives of patients with respiratory symptoms at home	Providing at least 1 meter distance, medical mask except sleeping
	COVID-19 suspected patient's follow-up by the medical staff at home	Medical mask, gowns, gloves
	Healthcare worker providing direct care to patient with COVID-19	Medical mask, gowns, gloves, glasses or face shield
Ambulance and transfer vehicle	Healthcare worker transferring patient with suspected COVID-19	Medical mask, gowns, gloves, glasses or face shield
	suspected COVID-19 (patient compartment separate)	No personal protective equipment required (medical mask if possible)
	Driver transferring patient with suspected COVID-19 (patient compartment is not separate)	Providing at least 1 meter distance and medical mask
	Assistance in taking patient with suspected COVID-19 from a stretcher and laying them on bed	Medical mask, gowns, gloves, glasses or face shield

COVID-19: New Coronavirus Disease

determined to check the patient and their needs should be left at the door of the house. In **voluntary home quarantine** (self-isolation), individuals who are a symptomatic but at high risk for COVID-19 (such as contact with the symptomatic person or its body secretions) are asked to isolate themselves in the home to prevent early spreading of the disease. **Preventive self-separation** is recommended for people who have high risk factors for developing severe COVID-19 infection such as old age, chronic disease, and immune deficiency. People who are asymptomatic and at medium risk of exposure to COVID-19 should stay away from public activities such as concerts and sports events **(Avoiding crowded places voluntarily). Mandatory quarantine** is used to separate individuals, groups or communities for a certain time, in a specific place, to restrict their movement. These people are asymptomatic, but they may have been exposed to COVID-19. Quarantine can be used to slow down and alleviate the COVID-19 outbreak. The decision to apply mandatory quarantine requires careful consideration of the safety of the individuals and the community, expected effects, applicability, and outcomes.

COVID-19: Symptoms, Findings and Potential Neurologic Effects of the Disease

The infection caused by an RNA virus, SARS-CoV-2, is known to be highly contagious and transmitted from human to human and contaminated environmental surfaces (42). Inter-species transmission is still not clearly understood. Hand hygiene is essential in preventing contamination. In certain cases, PPE

is recommended (51). Human-to-human transmission is mainly through the aerosol pathway and is through contaminated droplets, hands, and surfaces. Viral particles present in the respiratory tract of an infected person infect other people by direct contact with their mucous membranes. There is no long latency period. The incubation period is usually 3-14 days (median 5.1 days), but it has been reported to extend up to 24 days (35,52,53). According to the Wuhan data, the incubation period was monitored as 38 days in an asymptomatic patient infected with SARS-CoV-2 (54). In asymptomatic or affected patients, infection may also occur during the incubation period (55).

Real-time polymerase chain reaction (RT-PCR) is used to evaluate nasal swab, tracheal aspirate or bronchoalveolar lavage samples for diagnosis. Even after remission, positive pharyngeal swab results have been reported, but the virus may not be detected after the 8th day of the disease. This suggests that there is probably no correlation between the clinical picture and PCR test positivity (56).

Lung computed tomography (CT) findings are important in the diagnosis and follow-up. To date, no treatment method with proven efficacy for COVID-19 has been found. Antiviral drugs, chloroquine/hydroxychloroquine and respiratory therapy are mainly used in the treatment. Despite all these treatments, the only effective intervention in reducing the transmission rate is quarantine (51). Clinical findings of COVID-19 have a wide spectrum ranging from asymptomatic infection to systemic involvement and even "Acute Respiratory Distress syndrome" (ARDS) and multiple organ failure (53).

The effects of SARS-CoV-2 infection are not limited only to the lung. After the virus enters the body, it causes symptoms through viremia (57). In patients with COVID-19, fever, dry cough, and fatigue are primary symptoms, and in some patients, sore throat, chest tightness, sputum, anorexia, abdominal pain, diarrhea, vomiting, and conjunctivitis are also observed. It can be difficult to distinguish COVID-19 from other respiratory diseases. Gastrointestinal involvement occurs relatively less frequently. Lavezzo et al. (51) showed that 50-75% of patients with positive PCR results from throat swabs were asymptomatic in an Italian population cohort study of the town of Vò Euganeo (unpublished data) in 2020. It was reported that mild flu-like symptoms developed in other cases, and in 10% of symptomatic patients, dyspnea, severe interstitial pneumonia, ARDS, and multiple organ failure were observed (51).

Although coronaviruses are not among the common causes of neurologic diseases, it has been reported that they can lead to nervous system findings with direct or indirect effects. The virus can bind to ACE-2 receptors and enter the cell and reach the brain in two ways. In the first, it reaches the brain by infecting endothelial and epithelial cells of the blood-brain barrier and blood cerebrospinal fluid barrier, or through leukocytes. In the other, the virus reaches the brain through the retrograde axonal route; this transportation usually takes place through the third, fifth, ninth, and tenth cranial nerves or peripheral nerves. While it is thought to cause muscle damage by binding directly to ACE-2 receptors and entering muscle tissue, postmortem studies have reported that no virus can be isolated from muscle tissue. Possible cytokine storm is thought to cause muscle damage (58).

In the process of infection, atherothrombotic and cardioembolic strokes can be observed in patients with COVID-19 due to endothelial effects secondary to inflammation, direct vascular damage, and cardiac damage due to autoimmune causes. It has been reported that an increase in cytokines may also increase susceptibility to thrombosis. In addition, as a result of damage to the coagulation system, abnormalities in D-dimer and platelet levels can be observed and the risk of obstructive or bleeding stroke increases (54).

Neurologic Signs and Symptoms

Neurologic symptoms are observed in patients with COVID-19 (59,60,61). Researchers have also detected the SARS coronavirus nucleic acid component in the cerebrospinal fluid (CSF) of patients and in brain tissue in autopsies (62). Neurologic involvement has also been supported by case reports in the literature. Various neurologic symptoms, including central nervous system (CNS) involvement, peripheral nervous system (PSS) involvement, and skeletal muscle damage have been reported in more than one-third of patients (60).

As **symptoms and diseases indicating CNS involvement,** dizziness, vertigo, sleep disturbance, headache, loss of consciousness, ataxia, seizure, acute cerebrovascular disease, meningitis, and encephalitis have been reported (54,59,60,63,64,65). **Symptoms suggesting PNS involvement** have been reported as taste and smell disturbances, visual impairment, and neuralgia (66). The most common symptoms in patients with PNS symptoms are taste and smell disorders (60). Hyposmia reported in these patients shows the neurotropic potential of the virus. The virus is thought to invade the olfactory nerve and bulbus, or alternatively the sensory fibers of the vagus nerve, which innervate different organs such as the larynx, trachea, and lungs in the respiratory tract. It is recommended that patients with early smell loss, ataxia, and convulsions undergo further investigation in terms of CNS involvement of SARS-CoV-2. Patients with COVID-19 presenting with Guillain Barré syndrome (GBS) reported from clinics in various countries are also observed in the literature (67,68,69,70). Gutiérrez-Ortiz et al. (71) reported two patients aged 50 and 39 years with COVID-19 and Miller-Fisher syndrome and multiple cranial neuropathy (71). Zhao et al. (72) described post-infectious myelitis in a 66-year-old male patient diagnosed as having COVID-19. Wei et al. (73) reported a 62-year-old patient with COVID-19 and oculomotor nerve palsy.

Symptoms indicating skeletal muscle damage have been reported as fatigue in muscles and pain in the extremities. Although there are mild elevations in creatine kinase (CK) levels, muscle damage is defined when there is muscle pain and serum CK level is significantly high (60). Cases of rhabdomyolysis (CK levels: 525-12216 U/l) accompanied by additional organ injuries have been reported (60). SARS coronavirus is also known to play a role in myocardial inflammation.

Laboratory Findings and Prognosis

The course of the infection is mild or asymptomatic in 80-90% of patients. The course is severe in approximately 10% of patients who present with dyspnea, hypoxemia, and radiologically widespread lung parenchymal involvement.

In 5% of patients, respiratory failure, pneumonia, shock and multiple organ failure are seen, and death may develop in very severe patients secondary to ARDS and multiple organ failure (74). It has also been reported that respiratory failure can develop without any signs of subjective dyspnea (75). It is also reported that compensatory hyperventilation causes hypocapnia in these patients. Mortality rates vary between studies, but range between 2% and 5%. It is suggested that the reason for this may be the patient characteristics and/or infection prevalence rates affected by test results applied to symptomatic patients (74). There is a possibility that suddenly developing crowding in intensive care units (ICUs) may also affect mortality rates. In severe patients, the course is as follows: flu-like symptoms, apparent dyspnea occurring after 6 days, hospitalization after 8 days, and endotracheal intubation approximately 10 days after hospitalization (74). The mortality rate of COVID-19 (about 3-7%) is lower compared with SARS-CoV (10%) and MERS-CoV (35%) (76). It is currently thought to be too early to determine the current mortality rates of the disease. There is evidence that advanced age, male sex, ischemic heart disease, hypertension, diabetes mellitus (DM), and chronic lung diseases are the main risk factors for poor prognosis (76,77).

Considering vital follow-ups, most patients with COVID-19 have subfebrile fever and rarely high fever. It is stated that some patients have difficulty in breathing. Although some patients have serious injury due to infection in lung CT, their body temperatures are within normal limits. In these patients, malaise occurs as the main complaint. A group of patients with pneumonia who progressed despite decreasing fever was reported (7).

When vital signs were evaluated, it was found that tachycardia (heart rate >91/min) and/or tachypnea (respiratory rate >20/min) were more frequent in patients with poor prognosis, and their oxygen saturation was 93% or less. These findings suggest that patients with poor prognosis are clinically poor at admission. It is thought that physicians can predict the prognosis of patients with these vital signs (77). It has been reported that high fever, cough, weakness, loss of appetite, symptoms of myalgia, and diarrhea have not predicted prognosis. It has been reported that there is a relationship between respiratory, cardiac, and neurologic complications and poor prognosis. Rapid clinical deterioration may be due to a neurologic event such as stroke, which can lead to high mortality rates (54). It is thought that the respiratory center in the brain stem is affected by the virus, which may cause respiratory failure, disrupt some reflex mechanisms and increase hypoxia (78). Li et al. (79) advocated the hypothesis that the entry of SARS-CoV-2 into the CNS might have partially contributed to respiratory failure in some patients.

The most common laboratory abnormalities in patients admitted to hospital with pneumonia at the time of admission are leukopenia (9-25%) or leukocytosis (24-30%), lymphopenia (63%), and increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (37%) (80). In a study with 1099 patients with COVID-19, lymphocytopenia was found in 83% of patients, thrombocytopenia in 36%, and leukopenia in 34% (53). Also, mild thrombocytopenia, transaminase elevation, and lactate dehydrogenase (LDH) elevation were reported (81). Increased blood urea nitrogen, creatinine, potassium, triglyceride, CK, LDH, hypersensitive cardiac troponin I, N-terminal pro-brain natriuretic peptide (Pro-BNP), D-dimer, ferritin, procalcitonin (≥0.5 ng/ml), and erythrocyte sedimentation rate, and prolongation in activated partial thromboplastin time (aPTT) have been reported more commonly in patients with poor prognosis. Troponin is thought to be a strong parameter in demonstrating mortality. It has also been reported that increased C-reactive protein (CRP) among increased inflammatory markers may be correlated with disease severity (51).

Typical thoracic CT findings are ground-glass opacities, especially in the peripheral and lower lobes, and consolidation in bilateral multiple lobular and subsegmental areas are seen especially in patients in ICUs. The number of lung lobes affected is related to the severity of the disease. As the disease progresses, opacities tend to coalesce and thicken. Non-typical CT findings are pleural effusion (about 5%), masses, cavitations, and lymphadenopathies. In the presence of these findings, alternative diagnoses should be investigated. It has been reported that lung CTs may be normal within 2 days after the onset of symptoms. The sensitivity of CT was found higher in patients with positive RT-PCR (86-97% in various studies) and lower in patients without respiratory symptoms (82,83).

Low complement-3 and 4 values, increased levels of interleukin (IL)-2 receptor, IL-6, IL-8, IL-10 and tumor necrosis factor alpha (TNF-α), and undetectable levels of IL-1β have been reported more frequently in patients with a poor clinical condition (77).

Patients with pH values below 7.35 or above 7.45 in arterial blood gas evaluations have been reported. Partial oxygen pressure, actual bicarbonate values, and total carbon dioxide levels have been found to be lower in patients with worse clinical condition (77).

Respiratory and cardiac complications due to progression of the disease have been reported in patients with COVID-19. Among the most common, ARDS, type 1 respiratory insufficiency, sepsis, acute cardiac damage, heart failure, shock, alkalosis, hyperkalemia, acute kidney failure, and hypoxic encephalopathy have been reported. Rarely, acidosis, disseminated intravascular coagulation (DIC), and acute liver failure can be seen. Gastrointestinal bleeding has also been reported in the literature. Those with cardiovascular comorbidities are more likely to develop acute cardiac damage and heart failure. Cardiac complications, with or without a history of cardiovascular disease, have been reported more frequently in patients known to have chronic hypertension (77).

As a result, the true extent of COVID-19 infection is still in the process of being understood, because it has only been a few months since its first appearance. It is hoped that a clearer clinical picture will be revealed in the coming months.

COVID-19 and Pulmonary Involvement

The COVID-19 pandemic is a viral pneumonia pandemic. Person-to-person transmission occurs primarily through direct contact or by droplets that spread from an infected person by coughing or sneezing. In patients confirmed to be infected with SARS-CoV-2, the most common initial symptoms are fever, cough,

and fatigue. Other symptoms and signs are sputum, headache, hemoptysis, diarrhea, dyspnea, and lymphopenia (84).

The clinical severity of SARS-CoV-2 infections is classified into four main groups according to the Chinese National COVID-19 Guideline (85):

1- Mild type: Clinical symptoms are mild and there are no abnormal radiologic findings.

2- Moderate type: This manifests with pneumonia in thorax CT, fever, cough, and other symptoms.

3- Severe type:

(1) Respiratory distress, respiratory rate ≥30/min;

(2) Oxygen saturation in room air ≤93%;

(3) Patients with partial oxygen pressure in arterial blood/fraction of inspired oxygen ≤300 mm Hg.

4- Critical type:

(1) Respiratory failure occurs and mechanical ventilation is required;

(2) Shock occurs;

(3) Other organ dysfunction that needs monitoring treatment in ICU.

Hypoxemic respiratory failure is frequently observed with pulmonary involvement of coronavirus. Hypercapnic respiratory failure can be seen due to mucus plugs. According to available data, in severe cases, the male/female ratio is 2/1. In severe cases, older age has been identified as a risk factor, especially over 65 years. The most common comorbid conditions are hypertension, DM, and cerebrovascular and cardiovascular diseases (61,86,87).

Approach to Pulmonary Disease

Nasal and oropharyngeal swabs are taken from patients presenting with the listed symptoms. As an imaging method, chest radiography is performed and evaluated and lung CT is performed with the appropriate technique in the following defined situations. Clinical decisions are made according to the history and examination findings in pregnant patients who cannot undergo CT.

Fever + no cough, and normal chest radiography: Low-dose CT without contrast

Fever + no cough, and chest X-ray is diagnostic/non-diagnostic: Low-dose CT without contrast

Fever + cough, comorbid disease, or advanced age (≥50 years) and non-diagnostic chest radiography: Full-dose CT without contrast

If there is an indication for another disease, contrast-enhanced CT is performed.

CT should be avoided in young women aged under 20 years.

Bilateral lobular type, peripherally located, diffuse patched ground-glass opacities, paving stone appearance, and diffuse consolidations are characteristic CT findings of COVID-19 pneumonia (Figure 3) (88).

The radiologic findings of the lung become evident on the 5th and 7th days, especially after the onset of symptoms. In a series of 21 hospitalized patients with COVID-19 pneumonia, CT findings were classified in four stages according to their radiologic course:

1- Early period (0-4 days): Ground-glass opacities, lower lobe or often bilateral involvement

2- Progression period (5-8 days): Rapid progression, bilateral multilobar ground-glass opacities

3- Peak stage (9-13 days): Intense consolidations with slow progression in areas showing involvement

4- Resolution phase (after the 14th day): The regression of radiologic densities, which can extend until the 26th day by controlling the infection.

In the study conducted by Fan et al. (89), single intrapulmonary lesions were found in 32% of patients, multiple intrapulmonary lesions in 22%, diffuse intrapulmonary lesions in 44%, subpleural lesions in 44%, and localized lesions along bronchovascular bundles in 16%. In 12% of patients, <10 mm ground-glass nodules were found. Pieced ground-glass opacities with or without consolidation were found in 82% and pleural effusion in 4%.

In laboratory findings, CRP, procalcitonin, leukocyte, and neutrophil values were high and lymphocyte values were low. Troponin I, myoglobin, and BNP were significantly higher (85).

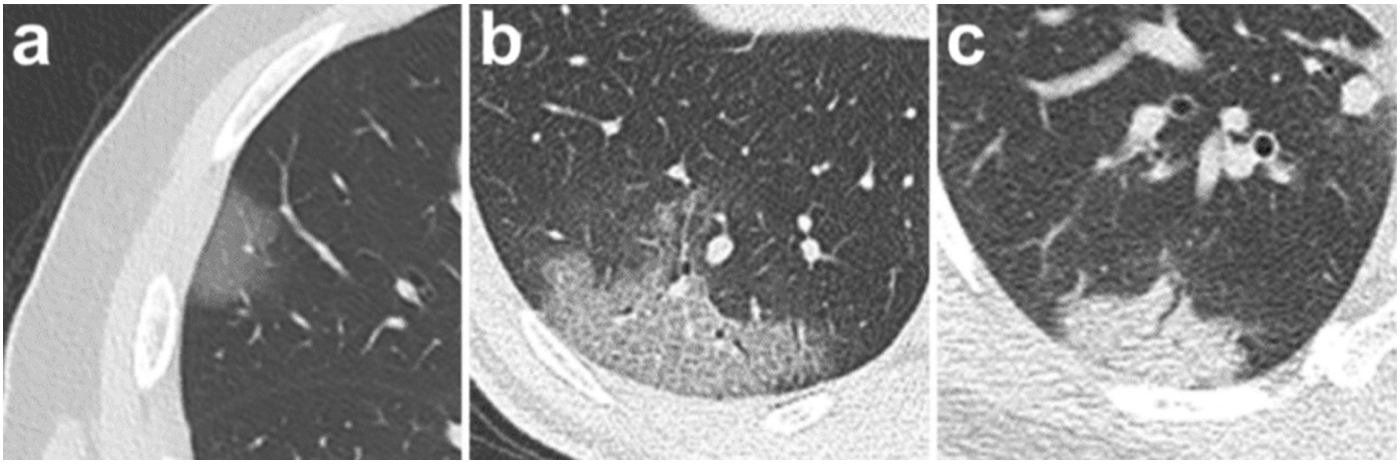

Figure 3. Thorax CT findings of COVID-19 pneumonia
a) Ground-glass appearance, b) Septal thickening and ground-glass appearance c) Consolidation
CT: Computed tomography, COVID-19: New Coronavirus Disease

Treatment for Pulmonary Disease

Patient management with uncomplicated pneumonia:

a. Those with symptoms such as fever, muscle/joint pain, cough, sore throat and nasal congestion, with a respiratory rate <30/minute, with SpO_2 level in the room air above 90%,

b. Those under the age of 50 years who do not have underlying comorbid diseases (cardiovascular diseases, DM, HT, cancer, chronic lung diseases, other immunosuppressive conditions),

c. Those with no poor prognostic criteria (e.g. blood lymphocyte count of 40 mg/l or ferritin >500 ng/ml or D-dimer >1000 ng/ml) in the blood tests performed at admission,

d. Those with mild pneumonia findings on chest radiography or tomography are evaluated as having mild pneumonia (without severe pneumonia finding) and the staff in charge is recommended to take the respiratory tract sample for PCR test using PPE (gowns, N95 mask, goggles/face shield, gloves) to protect against COVID-19 infection. Patients with possible infection are sent to home or to related isolation areas with the recommendation of isolation outside the hospital after empirical treatment is started. In empirical treatment, **hydroxychloroquine sulfate** should be preferred and should be given orally at a dose of 2x200 mg/day for 5 days. Considering the season and other factors, oseltamivir can be added to the treatment in patients in whom influenza cannot be excluded. The patient is informed about coming back to the hospital while wearing a mask in case their general condition worsens and monitoring is performed outside the hospital. Those whose symptoms and findings improve after the test result is positive for COVID-19 complete the recommended treatment period and are isolated at home until the 14th day following the improvement of symptoms. Patients whose symptoms and findings persist or whose clinical condition worsens are evaluated in terms of hospitalization, and monitoring at home or in hospital is decided according to the clinical status. Those whose symptoms and signs improve after a negative test result are isolated at home until the 14th day following the improvement of symptoms. Patients whose symptoms and findings persist, those who have not had a fever but who now have a fever, those who have an increase in coughing or develop shortness of breath are taken to the hospital while wearing a mask to evaluate a second sample, be hospitalized or investigated for other possible causes (90,91).

Management of patients with signs of severe pneumonia:

a. Those with symptoms such as fever, muscle/joint pain, cough, sore throat and nasal congestion, with a respiratory rate ≥30/minute, with SpO_2 level in the room air below 90%,

b. Those with poor prognostic criteria (e.g. blood lymphocyte count of 40 mg/l or ferritin >500 ng/ml or D-dimer >1000 ng/ml) in the blood tests performed at admission,

c. ICU consultation is requested for patients with bilateral widespread pneumonia findings on chest X-ray or tomography for potential admission to the ICU unit in accordance with the criteria above. The hospitalization of the patients is decided together with the physician responsible for intensive care. Empirical treatment is started in accordance with the treatment algorithm without waiting for the test result. In empirical treatment, hydroxychloroquine sulfate (2x400 mg loading, 2x200 mg/day maintenance) and/or **favipiravir** (2x1600 mg loading, 2x600 mg/day maintenance) are started. Azithromycin (500 mg on the first day and 1x250 mg/day for other 4 days) can be added to the treatment. Patients should be evaluated in terms of QT prolongation risk. Considering the season and other factors, oseltamivir may be added to the treatment in patients in whom influenza cannot be excluded. Oseltamivir should not be given or discontinued if favipiravir is started or added. Empirical antibiotic therapy can be started to these patients if findings that support pneumonia are detected with imaging methods. Patients with positive results whose symptoms and findings improve complete the recommended treatment period. Patients who are decided to be discharged continue their isolation at home for 14 days after discharge. Patients whose symptoms and findings persist or whose clinical condition deteriorates are evaluated with intensive care treatment recommendations in terms of other treatment options, and a PCR sample is taken 24 hours after the test results are found negative. If the second PCR test is negative, alternative diagnoses are considered. Those who are found positive in the second PCR test continue the COVID-19 treatment. In pregnant women, hydroxychloroquine sulfate is used for 5 days with a dosage of 2x200 mg/day or **lopinavir** 200 mg + **ritonavir** 50 mg is used for 10-14 days with a dose of 2x2 tablets/day (90,91).

Acute Respiratory Distress Syndrome

ARDS is defined as respiratory distress that occurs or worsens in the past week. Radiologically, pleural effusion, collapse or nodular bilateral opacities are detected. It is a respiratory failure that cannot be explained by heart failure or excessive volume (90,91).

There are 3 types:

Mild ARDS: 200< PaO_2/FiO_2 ≤300 [positive end-expiratory pressure (PEEP) ≥5 cm H_2O]

Medium ARDS: 100< PaO_2/FiO_2 ≤200 (PEEP ≥5 cm H_2O)

Severe ARDS: PaO_2/FiO_2 ≤100 (PEEP ≥5 cm H_2O)

Oxygen therapy may be sufficient in most patients under close monitoring. Oxygen therapy can be performed using conventional low flow (<15 l/min) methods or high-flow nasal oxygen (HFNO) cannulae. The aim is to keep oxygen saturation >92%. Up to 6 l/min oxygen can be given with the nasal cannula and the FiO_2 reached does not exceed 45%. Therefore, oxygen should be given with a simple face mask and a non-breathing (valve) reservoir (bagged) mask, respectively, in patients requiring oxygen above 6 l/min. With a simple face mask, 5 l/min oxygen is started and it can be increased up to 8 l/min. The FiO_2 reached is at most 60%. With re-breathing (valve) reservoir (bagged) mask, >85% FiO_2 is obtained with a flow rate of 10-15 l/min. However, it should be remembered that administration >6 hours and FiO_2 >60% may also lead to oxygen toxicity. In patients in whom oxygenation cannot be corrected with these methods, oxygen is given with the HFNO cannula system, if possible, by increasing the flow (maximum 60 l/min) to ensure FiO_2 is <60%. Due to the high risk of aerosol generation of high-current oxygen application, it is necessary to apply it with maximum PPE in negative pressure rooms if possible, or if not possible, in single rooms.

The positive effects of the prone position administration on hypoxia have been demonstrated in non-intubated patients with lung involvement. Patients should be placed in the prone position

for long periods of time, even if they are not intubated. If the patient does not need intubation immediately, NIMV can be tried. Patients receiving oxygen therapy should be monitored with SpO_2 as well as respiratory rate, dyspnea, use of additional respiratory muscles, depth of breathing and arterial blood gas as needed. In situations including increased respiratory workload (dyspnea, tachypnea ≥30/min), use of additional respiratory muscles, paradoxical respiration and respiratory alkalosis; mechanical ventilation by intubation should be considered (91).

COVID-19: Non-pulmonary Systemic Effects

The typical clinical and radiologic features of the infection are ground-glass opacities, fever, dry cough, dyspnea, myalgia, and radiologically atypical pneumonia, which are similar to SARS (61). Data indicate that COVID-19 can also affect many systems including cardiovascular, gastrointestinal, neurological, hematopoietic, and immune systems, and can manifest with extrapulmonary involvement in people with immunodeficiency (92). Extrapulmonary involvement is of clinical importance in terms of transmission dynamics and the course of the disease. This section discusses the effects of COVID-19 on gastrointestinal and hematologic systems.

In the SARS outbreak in 2002-2003, diarrhea was reported in 16-73% of patients, usually in the first week of the disease. In the MERS outbreak in 2012, approximately one in four patients had diarrhea or abdominal pain at the time of admission. Some patients with COVID-19 also have gastrointestinal system (GIS) symptoms such as diarrhea, vomiting, and abdominal pain. Of the first reported patients from Wuhan, 2-10% had gastrointestinal symptoms such as diarrhea, abdominal pain, and vomiting (61,93). In one study, gastrointestinal symptoms were reported in approximately 40% of hospitalized patients. Abdominal pain was detected more frequently in patients who were hospitalized in ICUs than in patients who did not need ICU hospitalization. In some patients, diarrhea and nausea started 1-2 days before fever and respiratory symptoms (61).

Two major studies in China focused on the GIS symptoms of COVID-19 and the detection of the virus in feces (94). Jin et al. (94) reported that 28% of 74 patients with COVID-19 with GIS symptoms had no respiratory symptoms. Compared with patients without GIS symptoms, these patients were reported to have a more severe disease course, higher fever, and elevated liver enzymes. In addition, it was observed that the tendency of the disease to cluster in the family was high in these patients. Lin et al. (95) reported that 61% of all patients had symptoms of the GIS such as diarrhea, nausea, and vomiting. They performed endoscopic examination in six patients and detected the virus in many points of the GIS. In more than half of the patients, viruses were detected in fecal samples. Xiao et al. (96) detected the virus in feces in 53.4% of patients between the 1st and 12th days of the disease. They showed the presence of a fecal virus even when the virus in the respiratory tract became undetectable in 20% of those patients. In a study from Singapore, virus was detected in feces in nearly half of the patients with COVID-19 and almost half of these patients had no GIS symptoms such as diarrhea (97).

It has been determined that the viral receptor ACE-2 for SARS-CoV-2 is found in high rates in lung cells and in esophageal, ileum, and colon epithelial cells. Thus, it is thought that SARS-CoV-2 can infect and replicate in the GIS (98). Enteric symptoms such as diarrhea occur due to increasing GIS permeability to foreign pathogens leading to malabsorption of enterocytes (99).

Detection of SARS-CoV-2 RNA in feces brings with it fecal-oral transmission concerns, particularly in areas with poor sanitation conditions (100). Both prolonged virus positivity in feces and associated GIS symptoms in GIS infection of SARS-CoV-2 have important effects on patient care and infection control. Fecal-oral and aerosol transmissions of the virus need to be determined. Physicians should be careful that COVID-19 may start with GIS symptoms, especially before fever and respiratory symptoms begin.

In addition to GIS symptoms, there may also be liver damage and elevated liver enzymes in patients with COVID-19. The available data show that 14.8-53.1% of patients with COVID-19 had elevated ALT and AST values during the disease, with a slight increase in serum bilirubin levels (93,101). Epidemiologic data indicate that male sex, advanced age, and possibly high viral load are risk factors for liver dysfunction associated with COVID-19 (102).

The mechanism of COVID-19-associated liver injury/dysfunction is not fully understood; liver damage may develop as a result of direct viral infection, and may be secondary to systemic inflammatory response, ARDS-associated hypoxia and reperfusion dysfunction, multiple organ failure, or hepatotoxic effects of medications used in therapy. Although the epithelial cells in the biliary tract produce 20 times more ACE-2 receptors than hepatocytes, and it has been suggested that SARS-CoV-2 infection may cause damage to epithelial cells in the biliary tract, it is suggested that there is no direct damage caused by the virus due to the fact that elevated levels of alkaline phosphatase, bilirubin, and gamma glutamyl transferase have rarely been reported and that no significant damage has been detected in hepatocytes and biliary tract cells in histopathologic investigations (100,103). In addition, another possible mechanism is that an "inflammatory storm" or "Systemic Inflammatory Response syndrome" (SIRS) triggered by COVID-19 causes increased cytokine release and damage to the liver cells and necrosis. The shock and hypoxia caused by the COVID-19-associated ARDS table can also lead to the release of reactive oxygen species and peroxidation products, causing secondary liver damage. Finally, although antipyretics such as acetaminophen used in treatment have not been found to be effective in hepatotoxicity, it is thought that antiviral drugs such as oseltamivir, abidol, and lopinavir may also cause or contribute to hepatotoxicity (102).

In patients with mild COVID-19 infections, liver damage is usually temporary and can return to normal without any special treatment. However, when severe liver failure develops, additional treatments are required. Physicians should also consider liver function test results in patients with COVID-19, especially in patients with prior liver disease and older age, and focus on the cause of liver dysfunction in each patient.

There is growing evidence that the so-called "Cytokine Release syndrome" or "cytokine storm" characterized by an increased release of proinflammatory cytokines and chemokines by the

immune system has an important role in patients with severe COVID-19. Cytokine storm develops within 7 to 14 days after the onset of symptoms following viremia, there may be a relationship between cytokine storm and atrophy of the lymphoid organs, and cytokine storm further disrupts the lymphocyte cycle (57).

It was shown that inflammatory cytokines such as IL-6, IL-1β, IL-2, IL-7, and IL-10, granulocyte colony-stimulating factor, monocyte chemoattractant protein-1, TNF-α, and chemokines were significantly increased in patients with COVID-19, especially in those with critical disease (81). Tissue necrosis, interstitial macrophages, and monocyte infiltration were detected in the lungs, heart, and gastrointestinal mucosa of patients with COVID-19, with high levels of inflammatory cytokines in postmortem pathologic examinations (103). In critical patients, hyperactive proinflammatory T-cells with severe lymphopenia and decreased regulator T-cells also support dysregulated immune response (101,104). Studies on the treatment of increased and harmful immune response in patients with COVID-19 are ongoing.

Data from various regions of China identified an increase in CRP in 60.7%, procalcitonin in 5.5%, and LDH in 41% of patients with COVID-19 (53). Increased LDH and CRP values have been associated with ARDS development and mortality and high procalcitonin values have been associated with a much higher risk of infection (105). In a retrospective study, it was stated that approximately half of the patients who had COVID-19 infection had higher D-dimer value, and this value increased even more in those who had more severe infection. The dynamic effect of D-dimer may correlate with the severity of the disease and has been associated with negative results in patients with community-acquired pneumonia (106). In an analysis, patients presenting with cardiac involvement due to COVID-19 infection were more prone to coagulation disorders than those without cardiac involvement. In patients with high troponin levels, prothrombin time (PT) and aPTT were more likely to prolong (107). Prolonged PT in patients with COVID-19 pneumonia were associated with an increased risk of ARDS, and increased D-dimer levels were associated with an increase in both ARDS and mortality. In addition, the difference between the mean D-dimer levels between survivors and those who died was found to be greater than the difference between groups with and without ARDS, and it was stated that DIC-related complications could lead to death, independent of ARDS (81,105). The likelihood of DIC was shown to increase in the event of PT and aPTT prolongation, increased fibrin destruction products, and severe thrombocytopenia (106).

There are data indicating that coagulation profiles of patients with COVID-19 support severe hypercoagulability rather than DIC (108). Fibrinogen and excessive fibrin polymerization can cause massive fibrin formation and deposition. In addition to microcirculation thrombosis, fibrin deposition in the alveolar and interstitial lung tissue adversely affects the prognosis by exacerbating respiratory failure. Venous thromboembolism (VTE) is another important issue for patients receiving treatment for COVID-19. Dehydration, acute inflammation, the presence of other cardiovascular risk factors, prolonged immobilization and having a classic genetic thrombophilia such as heterozygous factor V Leiden mutation are common comorbidities that potentially increase the risk of VTE in hospitalized patients with COVID-19. The possibility of endothelial cell activation/damage due to the binding of the virus to the ACE-2 receptor may further increase the risk of VTE. The release of large amounts of inflammatory markers and administration of hormones and immunoglobulins to critically ill patients can lead to increased blood viscosity. Also, mechanical ventilation and catheterization procedures can cause vascular endothelial damage. The combination of all the above factors can lead to the formation of deep vein thrombosis (DVT) and even the development of lethal pulmonary thromboembolism (PTE) due to thrombus migration. PTE should be kept in mind, especially in patients with typical DVT symptoms, who develop hypoxemia or right ventricular dysfunction unrelated to known respiratory pathology. Therefore, pharmacologic thrombophylaxis should be performed in patients hospitalized due to COVID-19 when they have a risk of developing VTE.

One of the hematologic abnormalities reported in patients with COVID-19 was thrombocytopenia. Thrombocytopenia, which is thought to occur as a result of multifactorial etiology, is associated with critical disease and mortality (109).

Treatment of COVID-19: Specific Treatments

Currently, there is no specific treatment for COVID-19 that has been proven to be safe and effective. In this section, some treatment agents, mechanisms of action, and scientific study results that are likely to have potential efficacy against SARS-CoV-2 are summarized.

A) Antiviral Treatments

1) Hydroxychloroquine/Chloroquine: Hydroxychloroquine, which has a chemical structure very similar to chloroquine, is used in the treatment of malaria and rheumatic diseases. It has been shown in cell cultures and animal studies that it has strong antiviral activity against SARS-CoV (110). In China, multicenter clinical studies reported that chloroquine phosphate had significant efficacy and acceptable safety in COVID-19-associated pneumonia. The drug shows its antiviral effect by inhibiting lysosomal activity by increasing endosomal pH in cells that present antigen and preventing auto-antigen presentation to T-cells. In addition, hydroxychloroquine and chloroquine inhibit virus fusion with the host cell by disrupting the cellular receptor of SARS-CoV, ACE-2. Hydroxychloroquine dosage and duration of use differ from country to country. Routine ECG for QT prolongation and routine hemogram, electrolytes, and kidney and liver function tests are recommended during patient follow-up during hydroxychloroquine use. Although the use of chloroquine could be supported by expert opinion, the recommendations of the "clinical management of severe acute respiratory infection when the new coronavirus (2019-nCoV) infection is suspected", which was published by the WHO, considered chloroquine use in COVID-19 as experimental. In a study without a control group evaluating 36 patients with COVID-19 from France, hydroxychloroquine treatment was found to be significantly associated with reduction/loss in viral load (114). In contrast, a recently published study in the USA retrospectively compared hospitalized patients who were treated with hydroxychloroquine (n=97), hydroxychloroquine/azithromycin (n=113), and patients who were not treated with hydroxychloroquine (n=158). It was

shown that exposure to hydroxychloroquine increased mortality at the end of the comparison (28%, 22%, and 11%, respectively). In corrected analyses, those who used hydroxychloroquine alone had a 2.6-fold increase in mortality (p=0.03) compared with those who did not, and the difference between those who used monotherapy and combined therapy did not reach statistical significance. In addition, no significant difference was observed between the groups in terms of the need for mechanical ventilation (13%, 7%, and 14%) (133). In another study in which two different doses of chloroquine were examined, QT prolongation was at the forefront in the high-dose group during the interim analysis phase. The study was stopped due to the observation of toxic effects (134). The COVID-19 sepsis guide also reports that there is insufficient evidence to recommend the use of chloroquine and hydroxychloroquine. In the "COVID-19 SARS-CoV-2 Infection Guide" prepared by the Ministry of Health and updated according to scientific developments, it is emphasized that starting antiviral therapy early is more beneficial. Therefore, it is recommended that hydroxychloroquine treatment should be started immediately in patients who are symptomatic and are considered to have the possibility of COVID-19. Hydroxychloroquine tablets 2x200 mg/day for 5 days are recommended in asymptomatic patients diagnosed as having definitive COVID-19 to be followed up without hospitalization, in patients diagnosed as having possible/definitive COVID-19 with uncomplicated or mild pneumonia, and in patients with uncomplicated/definitive COVID-19 with the indication of hospitalization. Hydroxychloroquine is recommended for 5 days with 2x200 mg/day follow-up dose after a hydroxychloroquine loading dose of 2x400 mg in patients with possible/definitive COVID-19 with mild or severe pneumonia (1).

2) Azithromycin: This is a macrolide group antibiotic used in the treatment of Gram-positive cocci. *In vitro* and preliminary clinical studies have shown that hydroxychloroquine alone or in combination with azithromycin (hydroxychloroquine + azithromycin) can be effective in the treatment of COVID-19 (114). However, further studies are needed to show the effectiveness of this combination. It should be remembered that if these two drugs are used together, serious QT prolongation may occur. According to the physician's decision, azithromycin can be used in the treatment of adult patients with possible/definitive COVID-19 pneumonia (1).

3) Favipiravir: This is an antiviral agent that is a guanine analogue and inhibits RNA-dependent RNA polymerase. It is mainly used in the treatment of influenza virus. *In vitro* studies have shown that favipiravir inhibits SARS-CoV-2, which is an RNA virus (115). Clinical studies have been initiated for the treatment of COVID-19. In a study of 80 patients in China, patients receiving favipiravir and lopinavir/ritonavir were compared. According to this, favipiravir was reported to show stronger antiviral efficacy, but less adverse effects. In the Ministry of Health COVID-19 adult patient treatment guide, it is recommended to use favipiravir with a dosage of 600 mg twice a day for 5 days after loading 1600 mg twice per day in patients with severe course who do not respond to the first treatment (1).

4) Remdesivir (GS-5734): This is a broad-spectrum antiviral that is an adenosine nucleotide analogue and inhibits RNA polymerase. The use of remdesivir in COVID-19 has been reported in several case series (100-116). Randomized, controlled efficacy studies on remdesivir are ongoing (117). Contradictory results have been reported in studies performed to date.

5) Lopinavir (200 mg)/Ritonavir (50 mg): These are aspartate protease inhibitors used in the treatment of HIV infection. In a randomized controlled trial, no benefit beyond standard care was observed in adult hospitalized patients with severe COVID-19 treated with lopinavir/ritonavir (118). It was shown that concomitant use of lopinavir/ritonavir with other antivirals (Ribavirin) in SARS-CoV infection was more effective than ribavirin treatment alone in terms of ARDS development and mortality. The WHO also reported that lopinavir/ritonavir therapy might be of benefit in COVID-19 infection when used with antivirals such as interferon beta, oseltamivir or ribavirin (119). The Ministry of Health's COVID-19 adult patient treatment guide states that the lopinavir/ritonavir combination can be used as an alternative drug when other medicines cannot be used for different reasons (1). The WHO started a study to evaluate effectiveness of remdesivir, hydroxychloroquine/chloroquine, and lopinavir/ritonavirin when used with or without interferon beta on COVID-19.

B) Convalescent Plasma (CP) Therapy

This is the transfusion of plasma from patients who have recovered from coronavirus infection and who are thought to have acquired virus-specific immunity. The goal is to neutralize the virus. CP has been tried in the SARS-Cov-1, ebola, and MERS-CoV outbreaks and successful results have been obtained. The United States Food and Drug Administration (FDA) has approved the use of CP for certain conditions in patients with COVID-19. It is not recommended to use this treatment method after the onset of symptoms where cytokine storm comes to the fore. The Ministry of Health has set the conditions for the implementation of this treatment in the "The guideline for the provision and clinical use of immune CP in COVID-19". This method of treatment should be used in addition to the medication and supportive treatment that the patient is receiving. It should be documented that the serum IgA level is normal in patients who are planned to have CP treatment, and this treatment should not be administered to patients with IgA deficiency (120).

C) Vaccine Development Studies

Numerous vaccine studies have been initiated to prevent coronavirus infection. The coronavirus spike protein, a characteristic structural component of the viral envelope, determines the tropism of the virus and its entry into host cells. The virus binds to the ACE-2 receptor in humans and enters the cell. In animal studies, the protective effect of antibodies against the S1 region of the spike protein of the virus in live coronaviruses has been proven. In a study performed in mice, specific IgG formation was observed in all groups 2 weeks after vaccination. The first human vaccination study was initiated in the USA and a messenger RNA platform that provided the expression of the spike protein of the virus was used to induce the immune response (121).

The importance of immunization with BCG vaccine is also mentioned in preventing coronavirus infection. It is suggested that BCG immunization induces a nonspecific immune response

in viral infections (122). A clinical study has also been initiated among healthcare professionals to evaluate the effect of BCG immunization on infection. Again, there are studies showing that the BCG vaccine reduces COVID-19 related mortality and the earlier the BCG vaccination policy in a country, the more the mortality rate per million population associated with COVID-19 has decreased (123). The WHO suggests that it should not be used to reduce the severity of COVID-19 and that more data are required.

Treatment of COVID-19: Severe Patients and Intensive Care

It is difficult to determine the true incidence of critical diseases associated with COVID-19 due to differences in available resources for diagnostic testing, contact tracking, and surveillance. In a study evaluating 55.924 patients with laboratory-confirmed COVID-19, the critical disease rate including respiratory failure, shock, and multiple organ failure was found as 6%. Acute hypoxemic respiratory failure containing ARDS (60-70%), shock (30%), myocardial dysfunction (20-30%), and acute kidney damage (0-30%) were the most common complications. Hypoxemia without respiratory distress could develop in older patients (124).

The mortality rate increases from 0.5-4% in all infected patients to 22-62% in critically ill patients (125). Advanced age, comorbidities, respiratory failure, high SOFA score at hospitalization, high D-dimer (>1 μg/ml), CRP elevation, lymphopenia and secondary infections have been found to be associated with hospital mortality. From the onset of symptoms, the course of the disease is difficult to predict and prognostic biomarkers are needed (124).

Lower respiratory tract samples are recommended for diagnosis in patients with suspected COVID-19 in mechanical ventilator. Endotracheal aspirate should be preferred for samples of the lower respiratory tract (126). It should be kept in mind that RT-PCR results may be false-negative, even in patients with a contact history or typical signs and symptoms. In a study evaluating 1014 patients with COVID-19, thorax CT findings and RT-PCR tests obtained from throat swabs were compared. RT-PCR was found as 59% positive, whereas thorax CT findings were diagnostic in 88% of patients (127). Serologic detection of IgM and IgG antibodies against coronavirus may be an alternative or complementary test method; however, there are question marks about the sensitivity of the kits used in antibody determination (128).

Bilateral lobular type, peripherally located, widespread patched ground-glass opacities are characteristic thorax CT findings of COVID-19 pneumonia (127,129) If CT cannot be performed in the ICU due to cardiovascular instability, lung ultrasonography may be an alternative diagnostic method. Lung ultrasonography can be used for triage (not pneumonia or pneumonia), clinical awareness, assessment of prognosis, ventilation and weaning decisions, and treatment response. In early viral pneumonia, pneumogenic vertical artifacts or small areas of white lung can be detected. In severe COVID-19 pneumonia, significant consolidations and widespread patchy changes may occur, especially in the posterobasal areas (130).

The most important point to be considered in the treatment and care strategies associated with COVID-19 in the ICU is the maximum protection of medical personnel. PPE including N95/FFP2 or equivalent respirators should be used in processes producing aerosols. Among the procedures that produce droplets in the ICU are endotracheal intubation, bronchoscopy, open aspiration, application of nebulizer therapy, balloon-mask ventilation before intubation, placement in the prone position, separation of the patient from the ventilator, NIMV, tracheostomy, and cardiopulmonary resuscitation. It is recommended that these procedures be performed in negative-pressure chambers (126). Some patients may progress rapidly to ARDS, DIC, septic shock, and ultimately to multiple organ failure. Therefore, early diagnosis and timely treatment of critical patients are very important. However, there is currently no specific treatment for COVID-19 that has been proven to be safe and effective (126).

As mentioned above, there is currently no antiviral therapy with efficacy confirmed for COVID-19. Available drug options that come from clinical experience in the treatment of SARS, MERS, and other previous influenza viruses are used for the treatment of patients with COVID-19. Although these antiviral drugs are promising in the treatment of COVID-19: 1) Adverse effects of the drugs should be monitored in the clinic; 2) the effects of these drugs on critical patients should be clarified; 3) it should be borne in mind that potential mutations of the coronavirus could lead to drug resistance (131).

In our country, according to the guidelines published by the Ministry of Health Science Board, it is recommended to start hydroxychloroquine (2x400 mg loading, 2x200 mg/day maintenance) and favipiravir (2x1600 mg loading, 2x600 mg/day maintenance) in patients diagnosed as having possible or definitive COVID-19 pneumonia (1). Although it is stated in the same guideline that the lopinavir/ritonavir combination can be used when necessary (1), routine use of lopinavir-ritonavir is not recommended in the COVID-19 sepsis guideline (126).

In patients with severe viral pneumonia, coinfection or cross-infection with bacterial pathogens, including *Staphylococcus aureus*, may develop during medical treatment in the hospital. Empirical antibacterial therapy should be planned for these patients in the presence of signs of severe disease (severe pneumonia, respiratory failure, hypotension and fever) or clinical worsening (131).

In patients with severe COVID-19, the cause of rapid progression to ARDS is thought to be the overproduction of immune cells and cytokines, called "Cytokine Release syndrome" or "cytokine storm" (132). The cytokine increase in COVID-19 resembles secondary hemophagocytic lymphohystiocytosis. For this reason, some authors recommend evaluating H scores in cases of critical illness due to COVID-19. It has been stated that immunosuppressive agents can reduce mortality if the score is high. Treatment options include steroids, intravenous immunoglobulin (IVIG), and selective cytokine blockers (for example, anakinra or tocilizumab) (136). However, more evidence is needed to advise on cytokine storm treatment (126).

There are no controlled clinical studies on the use of corticosteroids in patients with coronavirus infection. In a study evaluating 26 patients with severe COVID-19 pneumonia, the use of 1-2 mg/kg/day methylprednisolone for 5-7 days was shown to be associated with improvement in radiographic findings (137). In a retrospective study evaluating 84 patients with ARDS

associated with COVID-19, lower mortality was found in patients treated with methylprednisolone (105). Corticosteroids also have a number of negative effects, including avascular necrosis, psychosis, diabetes, and delayed viral clearance (124). It is recommended that methylprednisolone (1-2 mg/kg/day) be given for 5-7 days only in patients with ARDS who are on mechanical ventilation (1,126).

Tocilizumab is a recombinant monoclonal antibody that binds to the IL-6 receptor and inhibits signal transmission. It is used in the treatment of rheumatoid arthritis. Inhibition of IL-6 can help weaken the cytokine storm due to COVID-19. In the COVID-19 sepsis guideline, there is insufficient evidence to suggest the use of tosilizumab (126). According to the guideline published by the Ministry of Health in our country, it is stated that tocilizumab can be used at a dose of 8 mg/kg (maximum 800 mg) in patients with macrophage activation syndrome characterized by cytokine storm. It has been noted that depending on the severity of the findings, 400 mg or 800 mg can be administered once, and if the first dose is 400 mg, a dose of 200 or 400 mg can be repeated within 12-24 hours, taking into account changes in clinical and laboratory findings (1).

IVIG is considered the safest immunomodulating drug for the treatment of severe infection and sepsis. It has high-titers neutralizing antibody against viruses, bacteria and other pathogens, and can modulate the host immune response. However, in a large-scale multi-center randomized placebo-controlled study, IVIG was not shown to improve survival in severe sepsis (138).

According to the guide published by the Ministry of Health Science Board in our country, alternative treatments such as stem cells for patients diagnosed with COVID-19 can be tried with the permission of the relevant boards of the Ministry of Health (1).

Plasma from patients recovering from coronavirus infection can be a potential candidate for treatment by providing passive immunity. There are reports of patients undergoing CP treatment who had clinical improvement, but this is limited to case series. Its effectiveness and safety are limited. Adequate levels of neutralizing antibody titer target against 2019-nCoV are unknown. According to the guide published by the Ministry of Health in our country, it is stated that the application of immune plasma in patients with COVID-19 with ARDS with clinical symptoms can be performed with the permission of the relevant boards of the Ministry of Health (1). The criteria to use CP in COVID-19 according to "The guideline for provision and clinical use of immune CP in COVID-19" are as follows:

1. Presence of bilateral diffuse involvement in CT that is compatible with COVID-19
2. Respiratory rate >30/min
3. PaO_2/FiO_2 <300 mm Hg
4. Oxygen saturation <90% or partial oxygen pressure <70 mm Hg despite nasal oxygen supply of 5 l or more per minute
5. The need for mechanical ventilation
6. Increase in SOFA score
7. Need of a vasopressor
8. Poor prognostic parameters (lymphopenia and increased CRP, erythrocyte sedimentation rate, ferritin, LDH, and D-dimer levels). The recommended dose is a minimum dose of 200 milliliters of COVID-19 immune plasma unit, one per day, and a maximum of 3 doses (600 ml) at 48-hour intervals if necessary.

As a result, a 3 stage staging system is recommended for diagnosis and treatment management in patients with COVID-19. In all stages of the disease, pathophysiologic mechanisms are different. In the early stage (Stage 1) and in the first part of the middle stage (Stage 2a), the increase in viral replication is at the forefront. In the second part of the middle stage (Stage 2b) and in the severe stage (Stage 3), hyperinflammation has been reported. It is thought that antiviral treatments that have been shown to be effective can accelerate recovery, reduce infectiousness, and prevent disease progression in patients with Stage 1 disease. Appropriate antiviral treatments can be used in Stage 2. In Stage 2b where hypoxia develops, it is stated that corticosteroids can be used if it is predicted that mechanical ventilation may be needed. In Stage 3, immunomodulating agents can be applied to suppress systemic inflammation.

The critical factor in the ICU is respiratory support. The prevailing condition in the new type of coronavirus-associated pneumonia is hypoxemic respiratory failure and hypercapnic respiratory failure is also observed less often. Approximately 14% of patients were found to need oxygen therapy, and in 5% mechanical ventilation and hospitalization in the ICU were required (74). Oxygen therapy and NIMV could reduce the need for endotracheal intubation. Oxygen therapy can be applied by conventional low-flow (<15 l/min) or HFNO methods. Low-flow oxygen can be given with a nasal cannula (FiO_2 24-45% with 1-6 l/min O_2), simple face mask (FiO_2 at most 60% with 5-8 l/min O_2), and a non-rebreather (valve) reservoir (bagged) mask (>85% FiO_2 with a flow rate of 10-15 l/min) flow rate). HFNO oxygen can be provided with a nasal cannula up to 60 l/min (129). NIMV can be applied early in selected patients with hypoxemic respiratory failure, in whom oxygenation cannot be corrected with these methods. However, NIMV can cause healthcare workers to become infected due to the risk of producing infected aerosols. Parameters such as respiratory status and oxygen index (PO_2/FiO_2) should be closely monitored and mechanical ventilation should be initiated if necessary. HFNO support has emerged as an alternative to NIMV in preventing intubation in acute hypoxemic respiratory failure (131). However, it should not be forgotten that there is a high risk of aerosol formation during HFNO support. Diffusion of exhaled air increases when HFNO is administered or when the patient coughs. When the patient is wearing a mask, this diffusion distance is significantly reduced. In a meta-analysis comparing HFNO and NIMV, HFNO was found to reduce the need for intubation but did not affect mortality and stay in ICU (139). The risk of intubation is lower with HFNO and NIMV poses a higher risk of virus transmission for healthcare workers. HFNO is stated to be superior to NIMV in the current COVID-19 guidelines. However, NIMV may be useful in the event of other forms of respiratory failure, such as hypercapnic respiratory failure and if respiratory failure is caused by pulmonary edema (126). NIMV and HFNO should be administered in single and negative pressure rooms, if possible. During NIMV, a closed mask with a heat and moisture balancing virus filter or a two-way ventilator with a filter should be used. The mask should be placed tightly on the face and air leaks should be prevented. The ventilator must be in standby mode when wearing or removing the mask (140). NIMV can be applied with an oro-nasal, full-

face or helmet mask. It is an important advantage that a helmet with NIMV reduces exhaled air emission, and therefore there are opinions indicating that it may be more advantageous in terms of aerosolization risk. However, in the current COVID-19 related guidelines, there is no suggestion regarding the use of helmets instead of face masks in NIMV (126).

Patients should be closely monitored for clinical worsening during the use of NIMV and HFNO. If no positive response is obtained in the first few hours (refractory hypoxemia, tachypnea, tidal volume >9 ml/ideal kg), patients should be evaluated for invasive mechanical ventilation (129). Patients who are preoxygenated with HFNO are found to have a shorter intubation time and less risk of hypoxia during intubation. In addition, it is thought to carry a lower risk of contamination compared with manual balloon-mask preoxygenation (141). In cases of preoxygenation with balloon-mask, a filter should be used. Endotracheal intubation should be performed by trained and experienced staff with a rapid sequential intubation protocol. Video-laryngoscope should be used if possible for intubation. Intubation can be performed with flexible bronchoscopy in patients who are thought to have a difficult airway for intubation. However, bronchoscopy carries a high risk for creating aerosols. Neuromuscular blocking agents can be used to suppress cough before intubation. Positive pressure ventilation should not be initiated without inflating the endotracheal cuff. A heat-moisture exchanger filter can be used, but active humidification should be preferred in cases of intense plug and increase in dead space (129). Coughing, insufficient sedation, direct laryngoscopy, and manual ventilation during intubation increase the risk of contamination by causing the formation of aerosols (141). As a method of aspiration, a closed system should be used. A virus filter should be placed on the inspiratory and expiratory tips in the mechanical ventilator (140).

If the oxygen requirement is decreased (FiO_2 <40%, PEEP <8 cm H_2O) in patients with very low sedation or not receiving sedation, in whom hemodynamic stability and a sufficient level of consciousness are achieved, and the gag and cough reflexes are preserved, the patient should be evaluated for weaning from the mechanical ventilator. Rapid shallow breathing index (respiration rate/tidal volume) should be calculated. If this value is <100, it is an important indicator for successful weaning (129). Pressure support ventilation mode should be preferred in the ventilator for testing for spontaneous breathing. Compared with the T-tube method, contaminated particles are less likely to get into the air with this method (140).

In patients with suspected or confirmed COVID-19, bronchoscopy should only be performed if there is an alternative diagnosis possibility and life-saving intervention requirement that will change patient management (142).

In severe ARDS, lung protective strategies should be applied to minimize mechanical ventilation-related lung damage and increase survival. Lung-sparing strategies are: low tidal volume ventilation (4-8 ml/ideal kg), low plateau pressure (<30 cm H_2O) and reduction of inspired oxygen concentration to reduce oxygen toxicity (131). Additionally, driver pressure (plateau pressure-PEEP) should be evaluated in these patients and it should be kept lower than 14 cm H_2O. In cases of hypercapnia and pH <7.15, tidal volumes can be increased to 8 ml/kg. Otherwise permissive hypercapnia may be allowed (129).

In ARDS, extrinsic PEEP is used to prevent repeated opening and closing of the alveoli and ventilator-associated lung damage. PEEP increases alveolar recruitment, improves oxygenation, and reduces oxygen demand. The data regarding the effect of PEEP in ARDS are based on meta-analyses before COVID-19. High PEEP strategy in ARDS has been shown to reduce mortality in the ICU and cause a positive oxygenation response. In light of this information, it is stated that high PEEP is superior to low PEEP in patients diagnosed as having COVID-19 with moderate-severe ARDS who are on a mechanical ventilator. However, it should be remembered that patients who undergo high PEEP (PEEP >10 cm H_2O) should be followed in terms of barotrauma (126).

Neuromuscular blocking agents can be used in the first 24-48 hours in cases of resistant hypoxemia and hypercapnia despite sedation in moderate-severe ARDS, accompanied by ventilator incompatibility (129). Also, suitable recruitment maneuvers should be tried in patients with moderate-severe ARDS and the prone position should be used for at least 12 hours. The prone position is a technique that increases oxygenation in ARDS, possibly through ventilation-perfusion coupling and improvements in gravity-related atelectasis (131). In a study examining the clinical course of COVID-19 in the ICU, the prone position was used in 12% of patients. However, there were no data on the clinical course of these patients. Healthcare professionals should be alert for complications such as pressure ulcers, the removal of vascular access or the endotracheal tubes, facial edema, temporary hemodynamic instability, corneal abrasion, brachial plexus injury, and pressure-related low flow in the vascular access in hemodialysis. Physicians should be knowledgeable about unstable spinal cord, open abdomen, thoracic surgery, or trauma, which are absolute contraindications for prone ventilation. Enteral feeding from the nasogastric or nasoduodenal tube can be continued in the prone position (126). The positive effects of prone positioning on hypoxia have been noted in patients with COVID-19 pneumonia who have not been intubated. However, information about these patients has not been presented to the literature. High PEEP practice, prone position, and recruitment maneuvers are classic knowledge in ARDS management. However, Gattinoni et al. (143) recently pointed out that a classic ARDS treatment approach might not always be useful or even impair lung physiology in patients with COVID-19 with respiratory failure (145). According to this view, there are two different lung involvement phenotypes in the COVID-19 process. The phenotype, characterized by low elastance (high compliance) called "Type L", has a low ventilator perfusion rate and low recruitability. This phenotype is associated with a low lung weight, and thorax CT shows ground-glass opacities primarily in the subpleural area and lung fissures. "Type H" is characterized by high elastance (low compliance), high right-to-left shunt, high lung weight and high recruitability. Quantitative analysis of CT scans in this phenotype shows a marked increase in lung weight (>1.5 kg) (144,145). Severe hypoxemia in high compliance lungs is due to disturbance in lung perfusion and loss of hypoxic vasoconstriction. Instead of high PEEP application in the classic ARDS approach, it is recommended to increase FiO_2 liberally as a solution of hypoxemia in "Type L" patients without dyspnea. It has been stated that early intubation may even cause a transition to the "H Type" phenotype in these patients.

High PEEP administration in these patients may also cause hemodynamic impairment. The H-type phenotype is similar to the usual severe ARDS. Therefore, higher PEEP, prone position, and extracorporeal support are classic therapeutic choices (144).

In the absence of evidence of tissue hypoperfusion, conservative fluid therapy should be preferred to liberal fluid therapy in patients with ARDS undergoing mechanical ventilation due to COVID-19 (126). Aggressive fluid administration may worsen oxygenation and ventricular function (131). Given the close relationship between 2019-nCoV and acute myocardial damage, this worsening may be more severe (146). If refractory hypoxemia in COVID-19-induced ARDS continues despite optimal ventilation, recovery treatments, and prone positioning, it is recommended to use venovenous ECMO (126).

Sepsis is defined as organ failure caused by irregular host response accompanied by a suspected or documented infection. Organ failure means symptoms and signs including changes in consciousness, difficulty in breathing, low oxygen saturation, decreased urine output, increased creatinine, increased heart rate, weak pulse, cold extremities or low blood pressure, signs of coagulopathy, thrombocytopenia, acidosis, increased lactate level, or hyperbilirubinemia. Septic shock should be considered in cases of fluid therapy-resistant hypotension, vasopressor requirement in order to maintain the mean arterial pressure of ≥65 mm Hg and lactate level >2 mmol/l. It should be remembered that patients with COVID-19 may experience myocarditis and associated arrhythmia and cardiogenic shock (129).

Dynamic parameters such as skin temperature, capillary filling time and/or serum lactate measurement should be used to evaluate fluid response in patients with COVID-19 and shock. Balanced crystalloids and conservative fluid strategy should be applied for hemodynamic support. Noradrenaline should be used as the first agent in case of the need of vasoactive agents. If the target mean arterial pressure cannot be reached with noradrenaline, vasopressin or epinephrine should be used as a second-line agent. For patients with shock and COVID-19 who have evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and noradrenaline, dobutamine should be added instead of increasing the dose of noradrenaline. Low-dose corticosteroid therapy (200 mg/day hydrocortisone) can be used in patients with COVID-19 and refractory shock (126).

Due to excessive inflammation, hypoxia, immobilization and DIC, there may be a predisposition to both venous and arterial thromboembolic disorders in patients with COVID-19. In a study evaluating the incidence of venous and arterial thromboembolic complications in patients with COVID-19 who were followed up in the ICU, the incidence of complications was 31%. In that study, diagnostic tests for thrombotic complications were performed only in case of clinical suspicion, and the incidence was reported to be even higher if they were used for screening (107). Early anticoagulation can prevent clot formation and reduce microthrombus, thereby reducing the risk of major organ damage. According to the guidelines published by the Ministry of Health Science Board in our country, it is recommended to apply enoxaparin at a dose of 0.5 mg/kg every 12 hours for thrombosis prophylaxis in patients with D-dimer >1000 ng/ml. In patients with creatinine clearance below 30 ml/min, the dose of enoxaparin should be reduced (1).

In the event of cardiac arrest, all members of the team must wear PPE before cardiopulmonary resuscitation. There should be at least two physicians during balloon-mask ventilation and tracheal intubation. Intubation should be performed with the help of a video-laryngoscope. Recognizing shocking rhythms as soon as possible and performing appropriate interventions can maintain circulation and prevent the need for more respiratory support, such as intubation (129).

Nutrition in The Pandemic and Nutrition in Patients with COVID-19

One of the most important factors in maintaining health is ensuring adequate and balanced nutrition. Pandemic period

Table 3. The WHO's healthy diet recommendations

Fruits, vegetables, legumes, nuts, whole grain foods, meat and dairy products should be consumed daily and regularly
2 servings of fruit
3 servings of vegetables (avoid overcooking to prevent loss of nutritional values)
180 g cereal
160 g meat or legume (1-2 times a week red meat, 2-3 times a week poultry)
Adequate amount of water should be consumed
8-10 glasses of water a day
Avoid excessive caffeine consumption and sugary drinks
A reasonable amount of oil should be consumed
Unsaturated fats should be preferred (fish, avocado, nuts, olive oil, soy, canola, sunflower and corn oils)
Saturated fats should be avoided (fatty meats, butter, tallow, margarine, cream, palm and coconut oil)
Poultry and fish should be preferred over red meat
Less salt and sugar should be consumed
Daily salt consumption should be limited to 5 g (about 1 teaspoon) of iodized salt
Sugary drinks and salty sauces (soy sauce, fish sauce) should be avoided
Fresh vegetables and fruits should be preferred as a snack

WHO: World Health Organization

and COVID-19 infection have brought with it many unique nutritional problems. Problems in accessing healthy and fresh food, changes in dietary habits, and exercise possibilities caused by constant home stay and quarantine conditions are critical problems both in terms of disease process and in the long term for health protection (147,148,149). The unconscious and unjustified use of some preparations and vitamin-mineral supplements can also bring harm rather than benefit. Although the title of this section is nutrition in patients with COVID-19, there is not much disease-specific diet information different from previous diseases in the literature so far. This issue is also highlighted in the most current ESPEN guide (150).

It is clear that the immune system plays a complex role in COVID-19 infection. In previous influenza outbreaks, malnutrition has been shown to be an important predictor of mortality (151). Malnutrition, especially protein-energy malnutrition, has been reported to cause changes in many different parts of the immune system, most notably cell-mediated immunity and increase mortality due to infection (152). Lack of micronutrients such as zinc and selenium, which are critical for proper functioning of immune system, can also lead to disruption in various stages of immunity. On the other hand, obesity is also reported to disrupt immune system functions, and adipose tissue can become a pathologic immune activation site, leading to a chronic systemic inflammatory response. In this context, proper nutrition is extremely important both for patients diagnosed as having COVID-19 and for healthy people. The WHO's recommendations for healthy people are summarized in Table 3 (153).

Risky patients and patients with mild disease followed up at home should be evaluated in terms of malnutrition and appropriateness of feeding. Normal or high body mass index of patients does not prove that they are fed adequately and balanced, and therefore, patients with obesity should be questioned in this regard and should be educated accordingly. It should be kept in mind that especially elderly and/or people with chronic diseases will be at greater risk in terms of malnutrition. In addition to anamnesis, scales such as Malnutrition Universal Screening Tool can be used in the evaluation of patients (150). Patients who are found to be at risk in this way should be treated with the support of dietitians.

Daily energy and macronutrient needs should be calculated considering the patients' ages, nutritional status, activity levels, concomitant diseases, and tolerance levels. A diet program providing approximately 25-30 kcal/kg/day of energy, containing 1 g/kg/day of protein, with a fat/carbohydrate ratio of 30/70 as an energy source will be suitable for these individuals (150). It may be considered to replace the missing vitamins and minerals in people with malnutrition and to prescribe oral nutritional supplements and enteral solutions if needed. One of the important points to consider is the patient's hydration status. It is critical to enlighten patients about the importance of water consumption and prevent dehydration because diarrhea is seen in the disease process.

The importance of maintaining regular physical activities in the quarantine period should also be conveyed to individuals. It should be kept in mind that yoga and meditation will be beneficial for both physical and mental health, and patients should be advised in this direction.

The NRS-2002 (nutritional risk score) criteria can be used in the evaluation of malnutrition in patients followed up in the hospital (150). If the nutritional needs of patients who are followed up in the ward but do not need hospitalization in the ICU cannot be met with normal nutrition programs (for example, in cases of no food intake for 3 days or in cases of providing less than 50% of targeted nutrients for a week), enteral nutrition should be considered (154). Enteral nutrition is a safer alternative to parenteral nutrition, which has high complication rates. If possible, a nasogastric catheter can be placed or percutaneous endoscopic gastrostomy can be opened in patients who are not expected to tolerate long-term oral intake.

Before deciding on enteral nutrition, it is necessary to answer honestly why the patient's oral nutritional needs cannot be met. When one listens to the experiences of patients discharged from the pandemic wad, one will see that three meals are provided, but the disease creates a tremendous reduction in taste and the food cannot be eaten due to the lack of flavor. Patients can become hungry at times when there is no food, and there is difficulty in food supply due to fear of contamination. It should never be forgotten that good sleep, moral motivation, and healthy and sufficient food consumption are required to overcome the disease. It should be borne in mind that patients who are under absolute quarantine during the pandemic are not able to obtain meals from outside when they do not like the standard provided meals. It may be reasonable to organize the PPE-wearing staff to provide food in a wider time period and to have a variety of snacks always available in the patient rooms. For snacks to be kept in patient rooms, high nutritional, healthy, and easily consumable/digestible foods should be preferred. For example, nuts, dried and fresh fruits, cheeses, dairy desserts, and whole grain snacks may be suitable choices (155). Fluid intake is also an important consideration. First of all, it should be tried to provide sufficient fluid intake orally, and if necessary, the patient's dehydration should be prevented with intravenous fluid supplements.

In patients who are followed up in the ICU but not intubated, it should be aimed to provide adequate nutrition with oral intake and oral nutritional supplements. It is reported that a significant proportion of patients receiving NIMV support, especially oral nutrition and protein-energy intake are inadequate, and this is associated with prolonged hospital stay and prolonged NIMV use (156). However, nasogastric tube placement in these patients for the purpose of enteral nutrition can also reduce the efficacy of NIMV and extend the duration of stay by causing air leakage in NIMV and gastric dilation, all of which disrupt diaphragm function (157). Therefore, peripheral parenteral nutrition option should also be considered in these patients (150). The protein-energy needs of most patients receiving oxygenation via nasal cannulae can be provided by oral nutrition. However, it is critical to evaluate patients in this regard and to provide oral supplements or switch to enteral nutrition if needed.

In patients who are followed up on mechanical ventilation, enteral feeding through a nasogastric catheter is appropriate. Continuous administration of enteral nutrition should be preferred to administration with boluses (158). The prone position does not constitute a contraindication for enteral nutrition. The use of the post-pyloric route may be considered in patients with gastric intolerance and a residual exceeding 500 ml despite prokinetic treatments such as intravenous erythromycin or metoclopramide and in patients with risk of aspiration (158).

The energy requirement in these patients should be calculated using an indirect calorimeter, if available, or VO_2 measured from the pulmonary artery catheter, or VCO_2 obtained from the ventilator. In the first days of acute illness, hypocaloric nutrition (not to exceed 70%) should be provided, and on the 3rd day, 80-100% of the total energy need should be targeted. If a formula-based calculation is used instead of the methods described above, it is appropriate to provide a hypocaloric (less than 70% of the estimated value) regimen in the first week because these formulas calculate the energy needs of patients more than they actually need. In emergencies, it is aimed to reach 50-70% of the energy need calculated on the 20 kcal/kg/day formula and 80-100% on the 4th day. Protein need should be calculated as 1.3 g/kg/day and the protein target should be achieved in 3-5 days. In patients with obesity, it is appropriate to give protein according to the corrected body weight instead of the actual body weight. In addition to adequate protein support, controlled physical activity and mobilization will also help in maintaining muscle mass (150).

If the patient is in uncontrolled shock, hemodynamic targets in terms of tissue perfusion are not achieved and there is life-threatening hypoxemia, hypercapnia, and acidosis; enteral nutrition should be postponed. When the clinical condition stabilizes and the shock is brought under control, low-dose enteral nutrition may be started with close follow-up in terms of intestinal ischemia findings. Despite all interventions and supportive treatments, it is possible to consider parenteral nutrition in patients who cannot get adequate nutrition with enteral nutrition for 1 week. The infusion rate of carbohydrates in enteral nutrition and glucose in parenteral nutrition should not exceed 5 mg/kg/min (158). In total parenteral nutrition, daily lipid amount should be adjusted according to the patient and kept below 1.5 g/kg/day (158). Trace elements should be provided, and vitamin deficiencies should be detected and treated. In the follow-up of patients, it is recommended to use blood glucose (target 106-145 mg/dl or 6-8 mmol/l), as well as triglyceride levels and electrolyte panels including phosphate, potassium, and magnesium (150).

Swallowing problems are common in the period after mechanical ventilation. In cases where adequate nutrient intake cannot be achieved with measures such as thickeners, it may be considered to support the patient with enteral nutrition or temporary parenteral nutrition until nutritional rehabilitation is achieved. Consequently, it should be kept in mind that nutrition is an indispensable part of the treatment in these patients, and all patients including people at risk and those who are followed up in the ICU should be evaluated in this regard.

COVID-19 AND NEUROLOGY

Neurologic Examinations in Patients with COVID-19

Different neurologic involvements due to SARS-CoV-2 have been demonstrated (60-70,159-163). In order to understand the neurologic changes that may develop in patients, accurate and sufficient neurologic evaluations are required.

The content and order of the neurologic examination (NE) may vary depending on the characteristics of the patient and the habits of the examining physician. However, regardless of the order followed, there must be a certain algorithm. NEs should basically be made "from head to toe". Classic "NE Guide" steps are followed. A classic NE includes examination of mental state, cranial nerves, motor and sensory system, reflexes, and cerebellar examination and examination of walking. Neurologic evaluations of patients diagnosed as having COVID-19 are made by following roughly the same paths. However, there is a very important

Table 4. Points to be considered during neurologic examinations of patients with COVID-19

Algorithm in the neurologic examination guide requires modification 1- The examination including the head and neck region can be left to the end according to the patient's current COVID-19 diagnostic classification, 2- "Close contact" and "high risk" rules must be taken into consideration in the aerosolization area.
Basic personal protective equipment must be used during the neurological examination. 1- Gloves 2- Gowns (non-sterile, preferably liquid impermeable and long sleeves), 3- Medical mask (surgical mask; containing three polyprolene materials, produced with melt blowing technique), 4- Face protector, 5- Glasses, 6- Liquid soap, 7- Alcohol-based hand antiseptic should be used
If neurological examination is absolutely necessary at the patient's aerosolization site 1- At least N95/FFP2 mask (should be planned at the beginning), 2- Wide face shield rather than glasses, 3- Two layers of gloves should be used
Devices to be used during neurologic examination should be cleaned according to the manufacturer's recommendation 1- If there is no special recommendation, it should be disinfected with 70% ethyl alcohol and left to dry on its own
Gloves should be changed after each patient, effective hand washing should be done for 20 seconds

COVID-19: New Coronavirus Disease

point here. Every patient should be considered as a "patient with definitive COVID-19". For this reason, basic PPE should be used during NEs requiring close contact with the patient such as neck stiffness, meningeal irritation findings, pupil examinations, and evaluation of the head pairs should be abandoned, and further protection measures should be taken during these examinations (Table 4).

The patient must be examined while wearing a surgical mask both in the outpatient clinic and in the ward. Surgical masks must be worn and social distancing must be maintained during meetings with relatives who are in contact with the patient. Especially, if the patient will be evaluated by a large number of physicians for training and consultation, the distance between the examination table, patient bed, and other physicians should be maintained.

If the surgical mask is to be removed after the NE, the mask must be left on a clean A4 paper after the total removal from the part on the ears with both hands. The mask should be changed as soon as it shows signs of moisture. The habit of touching the root of the nose should be minimized. Frequent use of hand disinfectants, effective hand washing, and changing gloves after contact with each patient are important.

Equipment used during NEs (e.g. stethoscope, reflex hammer, diaposone, ophthalmoscope, vision cards) should be disinfected with 70% ethyl alcohol and left to dry. This process is also valid for protective materials such as glasses and face shields. If the patient is to undergo a neurologic procedure or an intervention along with NE, personal protection rules are sufficient outside the aerosolization zone. Otherwise, it should be treated as a high-risk transaction.

Electroencephalography (EEG) in the Pandemic

It is recommended that routine EEG recording should not be performed if it is not an emergency during the pandemic. The main reason for this is to reduce the risk of COVID-19 exposure of patients and hospital staff. In addition, with the increasing number of asymptomatic patients, it is recommended that all patients who are consulted and examined are considered to be patients with confirmed or suspected COVID and similar measures should be taken for EEG recording in each patient.

In patients with coronavirus, the balance between the necessity of EEG recording and the risk of contamination should be questioned, and whether EEG would be performed should be decided. Although EEG recording is indicated in clinical patients with encephalitis and encephalopathy, high risk of transmission to the environment or healthcare personnel during the transportation of the patient will be effective in this decision process. If it is thought that the EEG result may cause changes in the treatment plan, additional measures must be taken before and after the EEG recording (166,167).

Long-term EEG monitorization (video-EEG or continuous EEG) other than routine-emergency EEG recording is not recommended during the pandemic. It is recommended that long-term video-EEG monitorization (VEM) that is included in examinations, especially for epilepsy surgery, and can also be used for differential diagnosis, are delayed for at least 6-8 weeks during the pandemic. However, if VEM is planned for the diagnosis and follow-up of subclinical seizure or no convulsive status epilepticus (NCSE), this should be evaluated selectively because the use of collodium, which is used in long-duration recordings, with oxygen-air contact increases the risk of COVID-19 transmission. In addition, the exposure of the technician increases as there will be a need for frequent gel use. Therefore, if it is considered that VEM is necessary, electrodes in the form of headers should be preferred.

Precautions to be Taken When Electroencephalography Recording is Planned in the Laboratory

As far as possible, an EEG room and device should be reserved for patients with COVID. During the transfer of the patient, one route and one elevator should be used within the hospital within the knowledge of the infectious diseases committee. It must be ensured that the patient wears a mask.

A. What Should be Done by a Technician Before the Patient Arrives at the EEG Laboratory

1. Hand hygiene should be provided, gloves should be worn,
2. Furniture and equipment (such as chair-stretcher) that will not be needed during recording in the EEG room should be removed from the room,
3. The devices that need to stay in the room during recording (EEG device's keyboard-mouse, "head box", photic stimulator, pen to be used for taking notes, stretcher) should be covered with a disposable plastic-paper cover or wrapped with stretch film,
4. First, electrodes, paste-gel, and a wooden tongue depressor should be prepared (disposable electrodes or electrodes in the form of a cap should be used if possible), and containers containing electrodes kept in disinfectant liquid should be in a disposable plastic structure or covered with stretch film,
5. Oxygen mask should be checked,
6. Gloves should be removed and thrown into the medical waste box, hand hygiene should be provided,
7. N95 mask, surgical site over N95 mask, gowns (protective gowns can also be worn before the mask), goggles, cap, face shield and gloves should be worn, respectively (168) (respiratory protection must be provided first).

B. After the Patient is Taken to the EEG Recording Room

1. There should be no hospital staff or relatives of the patient in the room except the EEG technician during the recording,
2. The EEG device should be kept as far as possible to the patient,
3. The door should be kept open, and as much as possible, the room should be ventilated by opening windows and doors,
4. An EEG recording plan should be made with physicians working in the EEG unit. EEG recording should be performed with fewer electrodes and for short a period if necessary (e.g. for 10 minutes, Fp1-F7-T3-T5-O1 and Fp2-F8-T4-T6-O2 recordings recommended in the 10-20 system and Fp1, F7, T7, P7, O1, C3, Fp2, F8, T8, P8, O2, C4, Cz, ECG, Earth-reference) recordings recommended in the 10-10 system (Figure 4) (169).

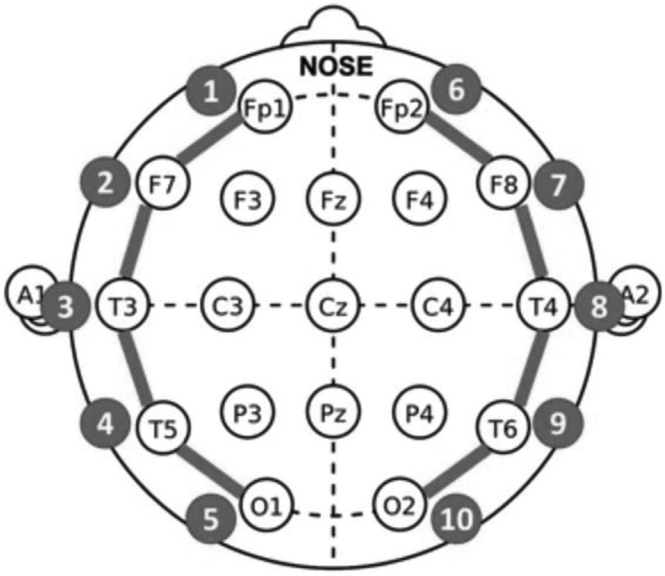

Figure 4. Limited montage recommended according to the 10-20 system

C. During EEG Recording

1. No mobile phone or other computer should be used during recording,

2. Nobody should enter the recording room unless mandatory,

3. In the knowledge of the physician responsible for the EEG, hyperventilation should not be performed to the patient as an activation method, and if necessary, response to the photic stimulus and verbal-tactical stimulus should be evaluated,

4. After recording the response to the necessary stimuli after beginning the recording, the technician should watch the recording at the farthest point where they can follow the recording and the patient,

5. Notes to be taken during recording should be digitally saved on the device as much as possible; additional forms, paper or pencil should not be used.

D. After EEG Recording is Complete

1. Electrodes should be taken into disposable containers containing disinfectant material, if disposable electrodes are used, they should be thrown into the medical waste bin,

2. The corridor should be emptied and the patient should be removed from the room,

3. Technicians and physicians should not leave the room with PPE,

4. After the patient leaves the room, the device/room should be cleaned/disinfected: The plastic/paper sleeve or stretch films on the devices should be removed and thrown into the medical waste bin, and a disposable wooden tongue depressor used for applying paste-gel should be thrown into the medical waste bin. If an oxygen mask is used, it should be thrown into the waste bin,

5. Gloves should be taken off and thrown into the medical waste bin, hand hygiene should be ensured,

6. After wearing new gloves, the devices (keyboard, mouse, photic stimulator, head-box, stretcher and oxygen inlets if used) should be wiped at least twice with a disinfectant wipe/paper towel.

E. After Room-device Cleaning

1. PPE should be removed respectively (gloves, gowns, face shield, glasses and cap should be removed and thrown into the medical waste bin or disinfection bin) and hand hygiene should be provided,

2. The surgical mask and N95 mask should be removed last and hand hygiene should be provided again,

3. The windows should be opened and the room should be ventilated, the air flow should be accelerated by going out of the room,

4. Notification should be given for removal of the medical waste and disinfection bin,

5. Information about the patient's recording should be recorded in the notebook in the reading room with a different pen (if a paper-form was used for technician's notes during recording, it should be thrown in the medical waste bin),

6. Floor cleaning of the room should be provided according to the recommendations of the infectious diseases committee.

When Portable EEG Recording is Planned at the Bedside of the Patient;

1. Before portable EEG recording, device-electrodes should be prepared in accordance with the above information for the EEG laboratory,

2. Before entering the patient room or the room where the EEG recording will be performed, precautions should be taken with PPE and the patient should wear a mask,

3. If a nebulizer is used for the patient before portable EEG recording, recording should be done at least 4 hours later (if conditions are appropriate),

4. If portable EEG recording is to be performed, it should be preferred to make the recording outside the room where the patient is staying.

Electromyography in the Pandemic

Although the AANEM guideline (170) was used in the writing of this section, the text was edited and developed taking into account both the new information that has emerged since March 31st, 2020, and the differences and needs of our country. On the one hand, this text should not be considered as a guideline, but merely a guide for tackling the difficulties faced, and physicians should make their own decisions about their patients.

Clinical neurophysiology or EMG laboratories are some of the busiest departments in hospitals. Due to the large number of patients, the time allocated to each patient is limited. This makes it difficult to carry out a complete, sufficient examination and to protect physicians from accidents. Nevertheless, physicians overcome these difficulties in routine working conditions with their experiences and skills. On the other hand, the COVID-19 pandemic has changed the working order in EMG laboratories, as in all areas of healthcare facilities.

Two critical points stand out in pandemic days. The first is patient triage, and the second is to protect the health worker from contamination.

Indications of EMG During the Pandemic Period

During the pandemic period, it is necessary to make decisions about which patients should be examined and which procedures should be postponed. Due to the high risk of transmission of COVID-19, patients should be carefully selected. Two basic elements are considered for this choice: 1) Any patient with an urgent need for EMG should not be deprived of the examination. 2) The tests of patients other than these should be postponed to minimize the occupation of the laboratory. In fact, this triage, in other words, priority ordering is already done as routine. However, there is benefit in repeating the algorithm.

Basic Conditions for Immediate/Early EMG:

- Electromyography should provide additional information to the physician in guiding the treatment of the patient. For example, EMG may be indicated when seeking an answer to the question of whether an acute progressive tetraplegia is due to neuromuscular junction disease or GBS. As such, EMG can answer whether the clinical condition is due to amyotrophic lateral sclerosis or multifocal motor neuropathy, a chronic axonal polyneuropathy, or chronic inflammatory demyelinating polyneuropathy. In patients in whom the diagnosis can be made without an EMG examination, it is more appropriate not to perform the test. At the time of the pandemic, tests such as the prognostic evaluation of Bell's paralysis have no place.

- An immediate/early treatment change should be able to prevent permanent disability or death. For example, EMG tests should be postponed if they will be performed to differentiate whether arm pain is due to entrapment neuropathy or radiculopathy in the absence of loss of strength. By contrast, if there is a loss of strength leading to functional impairment, the test should be performed immediately. Investigation of a years-long slowly progressive functional disorder can be delayed. EMG is not a test that should be performed immediately to distinguish a very slow multifocal neuropathy from ALS, as in the example given above.

- In patients in whom these two conditions are met, EMG tests should be performed immediately. Undoubtedly, the clinical picture will not always be so easy, and tests that can and cannot be postponed will not be easily distinguishable. The physician should make the decision on a patient-specific basis.

Electromyography

Each patient should be questioned for the symptoms of COVID-19 prior to an EMG examination; patients with symptoms should be sent to the COVID-19 outpatient clinic, and hospitalized patients should be reported to the attending physician.

Even if they are asymptomatic during the pandemic period, all patients undergoing EMG tests should be handled with caution, and all measures to protect physicians and other healthcare workers from contamination should be applied meticulously. Regarding these measures, there are detailed guidelines prepared by Istanbul Faculty of Medicine and Hacettepe Faculty of Medicine (171,172). Throughout the examination, it is necessary to focus on both the diagnosis of the disease and personal protection. There is no additional difficulty in the laboratory test.

EMG in the Intensive Care Unit

If a patient diagnosed as having COVID-19 is an intensive care patient, bringing them to the EMG laboratory is difficult and has serious risks. Transport of the patient is difficult because it is necessary to protect the environment from contamination. The laboratory is not the ideal place for a situation that requires rapid intervention such as intubation and need for aspiration. Finally, the contamination of the EMG laboratory with virus creates a risk of transmission to subsequent patients and workers. For these reasons, it should be preferred to perform EMG tests in the patients' own beds for intensive care patients with COVID-19.

An easily portable device should be available in the health facility to perform EMG in the patient's ward bed. Special work is needed to keep this device clean.

Preparation of the Electromyography Device for Testing in the Intensive Care Unit:

The device should be covered in such a way as to allow use, but to minimize contact with ICU's air. This is most easily achieved using a giant transparent nylon pouch, staple, bundle, scissors, cellophane, and stretch film. First of all, the device's body and recording-stimulator arm and the device's electrical cables are completely packed in the nylon bag using a string and staples. Then, very narrow holes are made with scissors for the stimulator, and recording and electrical cables. If these holes are opened wide, they are narrowed using cellophane. Outside the bag, exposed parts of the device are covered with stretch film. Thus, the only contact point of the device with the ICU environment is the wheels and their vicinity.

All the cables to be used must be covered with stretch film, with the least possible openings at both ends.

When entering the patient's side, a paper tape measure for distance measurement, two pens, one for spare and one for marking the skin (a reversed ballpoint pen is sufficient, no felt-tip pen needed), note paper, a medical patch is wrapped in pencil and is just more than the need, sufficient dry and alcoholic cotton (plenty of alcohol is needed to remove creams used in patient care from the skin), together with the EMG gel drawn into the injector disposable electrodes should be taken.

The EMG device and cables should be tested in the laboratory before going to the ICU to prevent unexpected device or cable failure.

The Difficulties of Working in the Intensive Care Unit:

Physicians must stand during EMG tests in the ICU. Two people are needed, one using the device and the other applying the test.

The examination may take a long time (45-60 minutes) if the patient has difficulty in cooperating, the lack of space due to the large number of devices in the area, the recording artifacts resulting from the same reason, the sweltering of physicians standing and leaning with the PPE (the bed can be raised if possible) and other factors. However, the physician's patience and diligence are needed so they do not have to go through the whole process again.

If the patient is not intubated, the mask may fall towards their chin. The mask of the patient should be checked frequently to ensure it covers the entire airway during the study.

Process After the test is Completed in the Intensive Care Unit:

After disposal of all disposable materials at the end of the test, it is necessary to remove the packaging from the device and cables at the dirty area/clean area boundary of the unit, and then clean the parts of the device that can be cleaned with surface disinfectant.

In fact, in the device and its appendices, the implementation of the recommendations for the disinfection of the coronavirus in line with the information available to date may seem sufficient, and some of the methods described above may be excessive. Nevertheless, new and sometimes contradictory information about the virus's survival and transmission routes necessitates caution.

If possible, it is recommended to keep the EMG device in storage without use for 72 hours (42), which is the duration during that the virus has been shown to remain viable on plastic and metal.

Whether the device is left without working, it may be important to run the device on its own for up to 2 hours in a place where air circulation is good before returning it to the lab. It is possible that the cooling fan of the EMG might work like a negative pressure system and that the dirty air in the ICU could be sucked into the device with the virus accumulating in the device (there are new data indicating that the virus hangs in the air) (173).

As a final note, it is important to know before the test whether patients with COVID-19 in the ICU have received anticoagulant treatment.

During the coronavirus pandemic and no doubt later, physicians and all other healthcare professionals should remember that protecting themselves at every step is the priority.

COVID-19 and Neuroimaging

Perhaps the most serious of the neurologic complications mentioned in the literature were COVID-19-related CNS encephalopathies. The first case of COVID-19-related encephalitis was reported from Beijing. Bilateral pyramidal symptoms with meningeal irritation findings were detected in a patient who presented with seizure and persistent hiccups. In the patient, who was found to have a positive PCR test, the virus was not be measured in CSF, and it was not understood whether this was caused by a comorbidity or as a direct effect of the virus (175). A similar possible association was shown in a patient in which COVID-19 and tuberculosis meningitis were reported together. It is important to investigate all possibilities without linking such situations to COVID-19 (176).

Another serious complication that may be associated with COVID-19 is acute necrotizing hemorrhagic encephalopathy (ANHE). It was reported from the USA (177). The CT angiography and venogram findings of this patient with bilateral hypodensities in medial thalami in non-contrast cranial CT were found normal. In magnetic resonance imaging (MRI), bilateral mesial temporal lobes and thalami showed hyperintense appearance in T2 and fluid-attenuated inversion recovery (FLAIR) sequences, hypointense signal intensity in favor of hemorrhage in SWI images, and peripheral contrast enhancement in post-contrast sequences. Cortisone was not preferred as a treatment to avoid the risk of worsening respiratory system infection. ANHE is a rare situation that can be seen with influenza and other viral causes. It is generally thought to develop due to intracranial cytokine storm (177). ANHE is seen mostly in the pediatric age group but also in adults. Symmetric involvement of the thalami is typical as in this patient, and the brainstem and cerebellum can also be affected (178).

The first case of CNS encephalitis reported by Moriguchi et al. (63) from Japan also included important details. A 24-year-old patient was admitted to the hospital with a progressive headache, fever, fatigue, and sore throat. Initially, blood tests, RT-PCR examination, and lung CT were within the normal range. Typical changes in lung CT were observed after the loss of consciousness and seizure that occurred on the 9th day of his symptoms, and RT-PCR was still negative for COVID-19 RNA in the nasopharyngeal swab, although it was positive in CSF. A hyperintense lesion along the right lateral ventricular lower horn wall in the diffusion-weighted images, hyperintense signal increase in the right mesial temporal lobe and hippocampus, and mild hippocampal atrophy in FLAIR images were observed in the patient's cranial MRI. Dural involvement was observed in contrast-enhanced sequences. With these images, the patient was thought to have right lateral ventriculitis and encephalitis in the right mesial temporal lobe and hippocampus (63).

Cases of acute disseminated encephalomyelitis were identified and reported after SARS and MERS infections. With COVID-19 infection, only one patient has been reported so far (182). In this patient's cranial MRI examination, acute lesions with diffuse and irregular diffusion restrictions in diffusion-weighted images were observed in the basal ganglia, thalamus and bifrontal area, and MRI angiography was found to be normal. It was reported that full recovery was achieved in the clinical condition after IVIG treatment (182).

Many patients diagnosed as having coronavirus disease are older patients. The increase in D-dimer levels that occur during the course of the disease increases the clotting factors and increases the risk of ischemic events. In addition, the risk of cerebral bleeding is increasing, considering that ACE-2 receptor is the gateway into the body for the virus and the risk of hypertension and thrombocytopenia in elderly patients. It has been reported that stroke below the age of 50 years and large vascular involvement have increased since the COVID-19 pandemic (175).

COVID-19 and Headache

In a retrospective observational study involving 214 patients with SARS-CoV-2 with neurologic findings, CNS symptoms were reported in 24.8% of patients, and headache was reported in 13.1%, which was the second most frequent CNS symptom after dizziness (60).

Meta-analyses of coronavirus-related studies were also quickly turned into publications. In a meta-analysis that covered 38 studies involving a total of 3062 patients with COVID-19 from China, headache was expressed as a minor symptom reported by 15.4% of patients (183). In another meta-analysis, in which 60 studies were reviewed, symptoms of 59.254 patients from 11 countries were investigated. Headache was the 5th most common symptom, followed by fever, cough, myalgia, and dyspnea, and headache was reported in 12% of patients (184).

In coronavirus disease, headache is often identified with fever and may be thought to be associated with it. It was reported that some patients who were hospitalized and monitored, were initially admitted with only fever and headache, and were admitted to neurology clinics considering that COVID-19 was excluded by blood tests and thorax CT. However, days later, typical COVID-19 symptoms such as sore throat, cough, lymphopenia, typical findings in thorax CT, and positive nucleic acid tests emerged and they were isolated (60). This situation emphasizes the need to approach headaches with caution during the pandemic period. It is very important to keep in mind the SARS-CoV-2 infection in patients with headache and fever, as well as preventing delay in diagnosis and preventing contagion.

The second important point is that the headache may be a sign of a developing CNS infection. In this case, it is important to closely monitor the patients' state of consciousness. Cranial MRI and CSF examinations are necessary to be performed in suspected patients.

Other than infection-related headaches, the second important issue is how to manage patients with primary headaches, especially migraine, who come to health institutions to be treated for their headache episodes or for regulation of their medications. The annual prevalence of migraine is 12% in our country (18% in women, 6% in men), and is the second most common cause of disability in the world (185).

What needs to be done in these difficult days is to try to keep this large group of patients away from hospitals and emergency services as much as possible. This is important in terms of protecting both patients and healthcare workers from COVID-19 infection and preventing the workload of hospitals from increasing further. The use of telemedicine systems in patients with migraine has been shown to meet patient satisfaction as well as being affordable (168). Thanks to the widespread use of smartphones, it may be possible for patients to reach physicians via Skype, WhatsApp, and Facetime applications.

The pandemic period is a more difficult period for patients with migraine than other individuals. Nutrition, changing sleep habits, and social isolation trigger migraine attacks. In addition, increased anxiety with added depression increase the frequency of attacks as well as prolong attack periods. This often results in the emergence of drug misuse. It is useful to remind patients not to use acute treatment drugs more than twice a week during this period.

Triptans, paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs) are the agents we use in the first step in the treatment of attacks. There is no restrictive situation with the use of triptans and paracetamol. However, information has been shared that NSAIDs, especially ibuprofen, may exacerbate COVID-19 infection (81). It has been stated that ibuprofen can increase symptoms of COVID-19 by changing ACE-2 enzyme function. The WHO also initially supported this information, but later withdrew its recommendation due to the lack of sufficient evidence (186). The FDA suggested that the scientific evidence that NSAIDs such as ibuprofen aggravated COVID-19 symptoms should be investigated on March 19th, 2020 (187). Ibuprofen, naproxen, and diclofenac are known agents for their efficacy in the treatment of migraine, and ibuprofen is a specific drug for some of the trigeminal autonomic cephalalgias. For this reason, NSAIDs are indispensable options for migraine treatment and there is nothing to restrict their use now.

It is known that corticosteroids cause susceptibility to infections due to immunosuppression. However, the efficacy of steroids in decreasing the duration of attack in cluster headache attack periods is known. It has been proposed that corticosteroid use should be limited in patients with COVID-19 to necessity conditions (188). It is recommended to use corticosteroids for shorter periods only in people who are healthy and have no problems with their immune system.

In preventive therapy, ACE inhibitors and angiotensin receptor blockers (ARBs) are used. Candesartan has been shown to be an effective and well-tolerated agent. Lisinopril was also likely to be an effective agent in the 2015 guideline (189). However, after ACE-2 receptors were shown as the site where the SARS-CoV-2 virus entered the cell, controversy arose regarding the use of these agents during the COVID-19 pandemic. In contrast, the American Cardiology Association made a statement saying there was no experimental or clinical evidence that ACE inhibitors or ARBs or other Renin-angiotensin-aldosterone system antagonists were beneficial or harmful during the COVID-19 pandemic and they should continue to be taken. However, the choice of these drugs during the pandemic should not be preferred in the prophylaxis of patients with migraine due to the risk of theoretical infection (191). There is no condition preventing the use of tricyclic antidepressants, central serotonin-noradrenaline reuptake inhibitors or anti-epileptic drugs used in preventive treatment and patients are recommended to continue their current treatment.

Disorders of Consciousness and Delirium in COVID-19

During coronavirus infection, the virus can affect the CNS through various mechanisms (192). The first is that the virus directly causes neural damage. Theoretically, the virus can invade the CNS via the blood circulation or olfactory pathway via retrograde neuronal transport. The second possible mechanism is the development of hypoxia due to lung involvement during infection, and the CNS is affected secondary to hypoxia. Acidosis due to hypoxia in the course of pneumonia can lead to cerebral vasodilation and cerebral edema resulting in increased intracranial pressure. The third mechanism is the development of SIRS depending on the immune system's response and, accordingly, the cytokine storm affects the CNS. Because the virus can invade the CNS, it can theoretically activate the glial cells and cause a proinflammatory state within the CNS. The virus also has the potential to affect the CNS by binding to ACE-2 receptors, causing vascular damage, or inducing apoptosis through cytotoxic T cells.

The delirium and changes in consciousness due to coronavirus infection may be due to the direct effect of viral infection on the CNS, and more frequently, the systemic effects such as ARDS, hypoxia, pain caused by the disease, the adverse effects of the medications used in the treatment, or the cessation of drugs that have been used for a long time by the patient during this period. It may also be due to the drugs that the patient uses, the effects of hospitalization in the ICU such as disruption of the sleep-wake cycle, and iatrogenic causes such as invasive or NIMV. It is not a false

assumption to suggest that delirium and changes in consciousness may occur in mild COVID-19 course because even simple urinary tract infections can trigger delirium in patients with dementia or older patients who are prone to developing delirium.

When we look at the studies that include data on delirium and changes in consciousness in the course of coronavirus infection, it is seen that there are limited data on this issue. In the first 99 patients who were hospitalized due to pneumonia in January 2020, when the disease was first seen in Wuhan (half of the patients had a history of going to the Huanan Seafood Market), nine patients had confusion at the time of admission. In the study, CNS involvement was detected in 53 patients. In 16 patients, corresponding to 7.5% of the total patients and 30% of patients with CNS involvement, changes in consciousness occurred an average of 8 days after hospital admission (60). There was no detailed information about the nature of changes in consciousness in that study. It was reported that all 214 patients in the study had mild or severe pneumonia. In patients with severe pneumonia, confusion was observed more frequently than in patients with mild pneumonia. The neurologic findings should be evaluated as those in the presence of lower respiratory tract involvement because patients who had the infection without pneumonia were not included in this study.

Another study on neurologic findings involving fewer patients was published from France (160). Agitation was observed in 40 patients of 58 patients (mean age: 63 years) who were diagnosed as having COVID-19 within one month and hospitalized. Confusion was demonstrated in 26 of these patients using the Confusion Assessment Method (CAM) in ICU scale. In most patients, this occurred after discontinuation of sedation and neuromuscular blockage treatments. In that study, only seven of 58 patients had a history of epilepsy, cerebrovascular disease, and mild cognitive disorder, and it was understood that they were not patients with dementia. As can be seen, especially in severe cases with pneumonia, changes in consciousness and delirium are very common. There are as yet no available data on how often and how severe changes in consciousness are in patients with mild symptoms or those with previous dementia. We have had two observations on this matter in the past 3 weeks. Although the symptoms of mild COVID-19 including fever and cough completely disappeared on the 5th day, the delirium added on the dementia findings on the 3rd day of the disease and continued for 11 days in a 72-year-old patient with early-stage Alzheimer's disease who was followed up by Istanbul Faculty of Medicine, Department of Neurology. On the other hand, COVID-19 was detected in the hospital where another patient was admitted with fever and cough who had middle-stage Nasu-Hakola syndrome, which was characterized by young-onset dementia. No worsening or added delirium was observed in the patient. COVID-19 symptoms improved within 8 days.

Changes in consciousness associated with coronavirus infection can also be seen iatrogenically. When the adverse effects of drugs that are in the treatment algorithm created by the Ministry of Health are evaluated in terms of causing delirium or changes in consciousness; hydroxychloroquine appears as a safe drug. It is seen that favipiravir is not associated with changes in consciousness when looking at dose finding and efficacy studies in influenza and ebola virus infections. No delirium or changes in consciousness are observed in the adverse effects of tocilizumab. When the adverse effects of azithromycin are evaluated, it can be seen that it may cause somnolence at a frequency between less than 1 in 100 patients and more than 1 in 1000 patients. The same frequency of agitation and insomnia can be seen in patients using azithromycin.

In the investigation of etiology in a patient with a coronavirus infection and developing delirium, systemic, iatrogenic, and drug-related causes are investigated first and the necessary laboratory examinations are performed. In patients without these causes and/or other neurologic signs and symptoms, it will be an appropriate approach to perform brain CT, MRI, EEG, and lumbar puncture if necessary.

The treatment and management of delirium, especially the hyperactive motor form, which is observed in the course of coronavirus infection, creates great difficulty in the pandemic environment, where patient isolation and prevention of contamination are of great importance. Therefore, prevention and early diagnosis of delirium are vital. According to the common best practice guideline of the British Geriatrics Society and the European Delirium Association, screening tools of delirium should be used in the patient's initial assessment and subsequent at certain intervals (193). The CAM-ICU, the standardization of which has been done in Turkey, and the 4AT, the Turkish form of which is present, are tools that can be used for this purpose. Again, early and correct management of the factors that can trigger delirium is valuable. These factors include pain control, follow-up, and treatment of constipation and urinary retention, adequate oxygen, fluid and nutritional support, and periodic reminding of location and time orientation.

Patients' wards should not be changed frequently and patients need to be able to access their auxiliary devices such as glasses and hearing aids for accurate and adequate perception. It is vital to learn the drugs the patients used before and to learn whether they have a history of chronic alcohol use, to prevent the changes in consciousness and delirium that may develop due to drug and alcohol withdrawal. Although the drugs recommended for the treatment of COVID-19 do not have anticholinergic effects, a review of the anticholinergic adverse effects of the drugs used for the treatment of other accompanying diseases is important for the prevention of delirium and other cognitive disorders.

It is recommended to start medical treatment of hyperactive motor symptoms and agitation early. The adverse effect profile of haloperidol and benzodiazepines used for this purpose should be reviewed before and during use. Respiratory depression caused by benzodiazepines and extrapyramidal adverse effects caused by haloperidol, especially in elderly patients and patients with parkinsonism, should be evaluated separately for each patient.

Consequently, changes in consciousness are frequently observed findings in patients with severe COVID-19. Studies are needed to determine whether the frequency of consciousness changes and the frequency of mild infections in non-severe patients or sensitive patient groups. The currently used drugs in COVID-19 treatment are generally safe in terms of adverse effects leading to changes in consciousness. Although general principles in the management of delirium are valid, it is important to perform early and optimum medical treatment of agitation, taking into account the importance of isolation in the pandemic and the risk of contamination caused by agitation to other patients and healthcare professionals concerned with patient treatment.

The Management of Epilepsy in the COVID-19 Pandemic

It has been reported that viral encephalitis, infectious toxic encephalopathy, and acute cerebrovascular disease may develop due to COVID-19 infection. The presence of anomalies in the vascular or neural pathways, hypoxic brain damage, immunologic brain damage, and possibly the ACE-2 pathway are discussed. Information on emerging seizures associated with COVID-19 infection is not yet sufficient. In a reported 24-year-old patient, it was noted that generalized seizure was added to the clinical picture after 9 days that appeared with fever, headache, and fatigue (63). This patient demonstrated the presence of mild mononuclear pleocytosis and positive PCR for SARS-COVID in CSF. There was hyperintense lesion including right hippocampus, temporal lobe and right lateral ventricle consistent with ventriculitis, and encephalitis in cranial MRI. Another 30-year-old patient was reported from Iran. The patient developed five seizures consecutively without any previous signs or symptoms (207). It was stated that the patient's CSF examination and MRI were normal. With this information, it was discussed that encephalitis caused by viral invasion or a toxic effect of inflammatory cytokines might cause seizures. In the childhood group, in the clinical picture caused by coronavirus, which is a member of the enterovirus group, fever-related seizures will not be surprising (208). Related with this, six epileptic seizures that occurred in a 12-month-old baby were recorded (209). A study from China showed that although 27% of 304 patients with COVID-19 had risk factors for seizure development such as cerebrovascular disease or metabolic disorder, acute seizures or SE were not monitored during the short follow-up period (one month) (210). However, in these patients, the presence of a possible subclinical seizure could not be excluded because NCSE was not clinically suspected and routine or long-term EEG was not performed. In addition, long-term follow-up is not yet known.

During the pandemic, it is recommended to postpone routine outpatient clinic controls as much as possible due to the high risk of transmission of COVID-19 in the population. It is emphasized that the plan for changing the routine treatment scheme should not be considered due to the possibility of causing emergency hospital admissions such as SE. However, it is suggested that patient follow-ups, watching video recordings of seizures, and making future plans can be made via e-mail or telephone (166). In this process, it should be ensured that patients with epilepsy continue their routine lives and do not disrupt their drug-sleep patterns. Providing information and confidence that they can contact their physicians by phone or e-mail, if necessary, will reduce the anxiety of patients and their relatives.

On the other hand, regardless of the frequency of seizures or the severity of epilepsy disease, it should be known that the risk of COVID-19 may increase due to other health problems and treatments. Concomitant DM, hypertension, heart and lung diseases, or difficulty in swallowing may cause more severe clinical course in viral infections as well as in COVID-19. In general, antiepileptic drugs do not facilitate the development of COVID-19. However, some of the drugs used for their antiepileptic activity may increase the risk of COVID-19 due to the immune system suppression feature (ACTH, steroid, immunotherapy, everolimus). However, the benefit-harm balance of these treatments should be evaluated individually.

Nevertheless, in patients with epilepsy who have been diagnosed as having COVID-19 and have received treatment for this, using drugs that may cause arrhythmia (such as hydroxychloroquine leading to QT prolongation) with antiepileptic drugs that may cause arrhythmia (especially lacosamide causing to PR prolongation and sodium channel blockers that may rarely cause arrhythmias) should be avoided. In addition, close follow-up is recommended for concomitant use of antiepileptic drugs, which may cause adverse effects similar to antiviral drugs that may cause liver toxicity. The interactions of antiepileptic and antiviral drugs are presented in Table 5.

The COVID-19 and Status Epilepticus

Hypoxia, multiple organ failure, and metabolic and electrolyte disorders can be observed in patients with coronavirus infection and may require multiple drug regimens and therapeutic interventions. Therefore, it is possible to expect clinical or subclinical acute symptomatic seizures and SE to occur in these patients. In patients with severe COVID-19, a change in mental state has been reported (93). When evaluating a patient with a critical medical condition and a change in mental state, NCSE should be considered as part of the clinical picture. The diagnosis of NCSE can often be ignored because patients in critical medical conditions also have other serious problems. In a study involving 70 patients with MERS-CoV infection, mental status changes were reported in 26% of patients and seizures in 9%. Therefore, when evaluated carefully and specifically, neurologic symptoms may be seen more in patients with COVID-19 (211).

EEG examinations in the encephalopathy due to coronavirus infection reveal bilateral slowing and sharp waves in different cerebral areas (212). The question as to whether epilepsy is a risk for COVID-19 or vice versa is still not fully answered. However, epilepsy remains more innocent among those such as drug use, and conditions in which mobility and associated respiratory function are affected (e.g. asthma, DM, hypertension, severe heart disease, immunosuppressive conditions, indulgence). However, rare clinical conditions such as some epileptic syndromes (e.g. Dravet syndrome) and clinical conditions that are accompanied by respiratory problems (e.g. tuberous sclerosis) or general autoimmune disorders may carry an additional burden in terms of possible SE (213).

The treatment of SE is schematized in Figure 5 according to its stages. There may be a decrease or increase in the drug levels due to drug interactions at the pharmacokinetic and pharmacodynamic levels between the drugs used in the treatment of COVID-19 and antiepileptic drugs. For this, dose adjustments of antiepileptic drugs and drugs used to treat COVID-19 may be required. The use or prevention of potentially interacting drugs is based on a careful assessment of the risk/benefit balance individually. As shown in Table 5, it is always necessary to adjust the treatment appropriately by carefully monitoring the clinical response. The drug-drug interaction table for drugs used in the treatment of COVID-19 and antiepileptic drugs was prepared by the University of Liverpool Drug Interactions Group (197). This table was translated into Turkish by the General Directorate

Table 5. Interactions of antiepileptic drugs and drugs used in the treatment of COVID-19									
	ATV	**LPR/r**	**RDV**	**FAVI**	**CLQ**	**HCLQ**	**NITAZ**	**RBV**	**TCZ**
Carbamazepine	↑⇓	↑⇓	⇓	↔	⇓	⇓	↔	↔	↓
Clonazepam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	⇓♥	⇓♥	⇓	↔	⇓	⇓	↔	↔	↔
Ethosuximide	↑		↔	↔	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	↔♥	↔ ♥	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↓ 50%	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔
Perampanel	↑	↑	↔	↔	↔	↔	↔	↔	↔
Phenobarbital	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↓
Phenytoin	⇓	⇓	⇓	↔	⇓	⇓	↑	↔	↓
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	⇓	↓ ⇓	⇓	↔	⇓	⇓	↔	↔	↓
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	⇓	⇓	⇓	↔	⇓	⇓	↔	↔	↔
Sultiam	↑	↑	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproate	↔	⇑ 38%	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↔	↔	↔	↔	↔	↔	↔	↔

ATV: Atazanavir, LPV/r: Lopinavir/ritonavir, RDV: Remdesivir, FAVI: Favipiravir, CLQ: Chloroquine, HCLQ: Hydroxychloroquine, RBV: Ribavirin, TCZ: Tocilizumab, INF-β: Interferon beta. **Black:** Co-administration of these drugs carries a high risk of drug-drug interaction and should not be administered together. **Grey:** Although there is a risk of drug-drug interaction in co-administration of these drugs, close monitoring is recommended for dose adjustment and possible adverse effects if there are indications. **Dark Grey:** There is a risk of poor/rare drug-drug interaction in co-administration of these drugs. No close monitoring is required. **White:** There is no risk of drug-drug interaction in co-administration of these drugs. The symbols in the table are: ↑ increased exposure to experimental treatment medication used together; ↓ reduction in exposure to concomitant therapy medication; ⇑ Increased exposure to COVID-19 experimental treatment drug; ⇓ Decrease in exposure to COVID-19 experimental treatment drug; ↔ There is no significant interaction between the neurological drug and the COVID-19 experimental therapy drug; ♥: It may cause prolongation in the QT/PR interval in the ECG, and ECG monitoring is required when used together

of Public Hospitals, Department of Supply Planning, Stock and Logistics Management, Hospital Pharmacy Management Unit (214).

Causes and Consequences in COVID-19 and Status Epilepticus Association

Enzyme-inducing anti-epileptic drugs and antimalarial drugs: Among enzyme-inducing antiepileptic drugs, carbamazepine, phenytoin, and phenobarbital can reduce the drug levels of chloroquine and hydroxychloroquine, but are not contraindicated. There is no evidence of the effect of antimalarial drugs on antiepileptic drug levels. Chloroquine and hydroxychloroquine can lower the seizure threshold, but this risk can be ignored (111).

Enzyme-inducing anti-epileptic drugs and antiviral drugs: Enzyme-inducing antiepileptic drugs increase the clearance of antiviral drugs. Ritonavir and lopinavir have potent CYP3A4-inhibiting, cobicistat and atazanavir have CYP3A4-inducing, and ritonavir has uridine diphosphate-glucuronosyltransferase -inducing effects (181). Phenytoin reduces serum levels of ritonavir/lopinavir by 30-50%. Up to a 50% dose increase may be required in antiviral drugs to maintain a stable serum concentration. Ritonavir/lopinavir may increase serum concentrations of CYP3A substrates such as carbamazepine, phenytoin, and phenobarbital. Evorolimus can inhibit CYP3A4 and P-glycoprotein. It may be necessary to adjust the dose to ensure stable serum levels of antiepileptics.

Enzyme-inducing anti-epileptic drugs and corticosteroids: Enzyme-inducing antiepileptics induce CYP3A and reduce serum concentrations of steroids (prednisone, prednisolone, methylprednisolone) by 30-50%. It is recommended to increase the dose of steroids 1.5-2 times in patients receiving enzyme-inducing antiepileptic drugs (215).

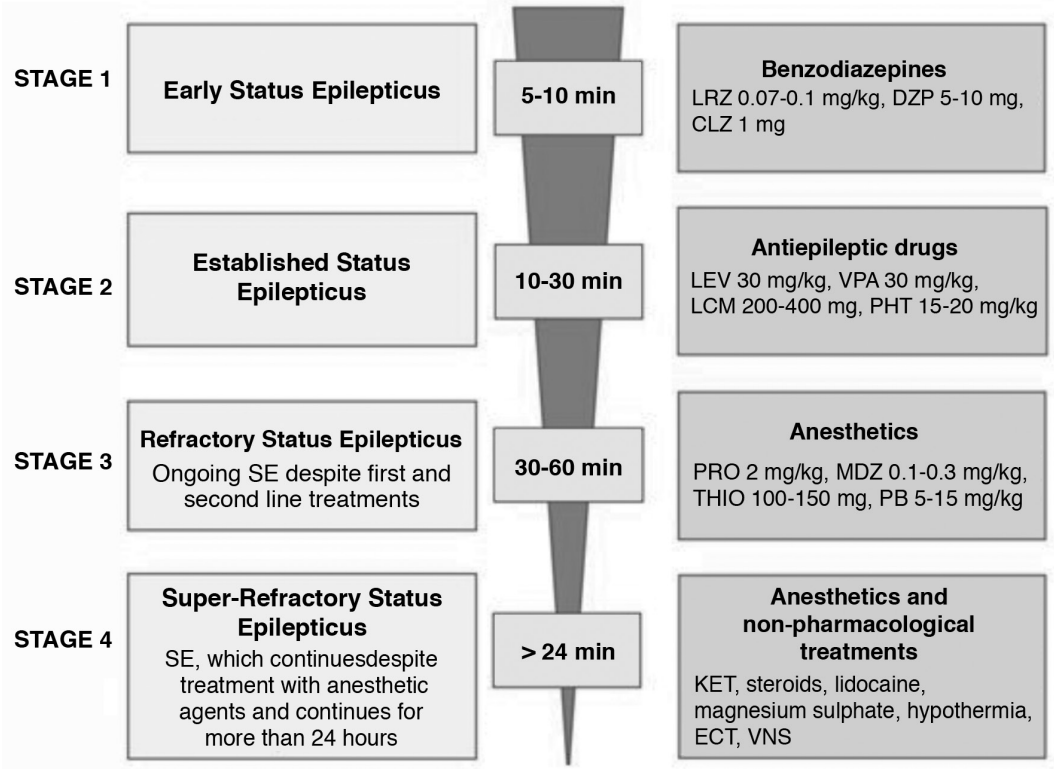

Figure 5. Treatment of SE according to its stages*

SE: Status epilepticus, LRZ: Lorazepam, DZP: Diazepam, CLZ: Clonazepam, LEV: Levetiracetam, VPA: Valproic acid, LCM: Lacosamide, PHT: Phenytoin, PRO: Propofol, MDZ: Midazolam, THIO: Thiopental, PB: Pentobarbital, KET: Ketamine, ECT: Electroconvulsive therapy, VNS: Vagal nerve stimulation

Benzodiazepines and drugs used to treat COVID-19: **Benzodiazepines and drugs used to treat COVID-19:** Diazepam clearance increases with CYP3A enzyme inducers, CYP3A enzyme inhibitors (such as cimetidine, erythromycin, itraconazole, ritonavir), and CYP2C19 enzyme inhibitors (such as fluvoxamine, omeprazole). Lorezepam clearance increases with enzyme inductors and decreases with valproic acid. Midazolam clearance increases with enzyme inductors and decreases with CYP3A enzyme inhibitors (erythromycin, clarithromycin, ketoconazole, diltiazem, verapamil, cimetidine and atazanavir). It may be necessary to increase the dose of atazanavir 4-fold. Clonazepam clearance increases with enzyme-inducing agents.

Cardiac risk of drugs used to treat COVID-19 and antiepileptic drugs: Lopinavir/ritonavir, lacosamide, and eslicarbazepine prolong the PR interval. Atazanavir, chloroquine, hydroxychloroquine, and azithromycin prolong the QT interval in ECG. Combining these drugs may increase the risk of dysrhythmia with prolonged PR/QT interval. Propofol has high pro-dysrhythmic potential. In terms of cardiac rhythm and conduction, caution should be exercised when using these medicines and ECG checks should be performed before and during medication (215).

COVID-19 and Neuromuscular Diseases

Considering the effect of coronavirus pandemic on neurology practice, neuromuscular diseases should also be considered. Publications made to date focus mainly on the effect of the virus on areas such as cerebrovascular diseases and headaches. For the management of neuromuscular diseases under current pandemic conditions, the available data should be carefully evaluated.

In this context, the problems caused by the disease can be addressed under two sub-titles: Neuromuscular diseases that occur with direct or indirect effects of the virus, and the effects of infection and/or treatment of the infection on patients with known neuromuscular disease.

Neuromuscular diseases that occur due to direct or indirect effect of the virus: Considering the prior infection and molecular mimic mechanism, GBS is one of the first diseases that come to mind. Patients with GBS have also been reported with different coronaviruses (216,217). However, the number of patients with GBS reported in relation to COVID-19 to date is less than 10 (68,70,162,218). Published cases have classic GBS features. It is not yet clear whether COVID-19 triggers antibody formation against specific gangliosides. Considering that some of the patients diagnosed as having COVID-19 remain in the ICU for a long time, GBS should also be considered in addition to ICU neuropathy and myopathy in cases of weakness that develop in the ICU.

There are few reports showing the coexistence of coronavirus infection and myopathy. However, it is not possible to reach a definitive judgment in view of the information obtained with these reports. CK levels were found high in 33% of patients who were hospitalized with COVID-19 in Wuhan, where the pandemic started. However, no further investigations for myopathy such as EMG, muscle biopsy or MRI have been made (61). Rhabdomyolysis, myalgia, and CK elevation have been reported with other types of coronavirus. However, it is predicted that patients in ICUs due to general condition worsening may develop critical illness neuropathy and myopathy, as stated above.

Although there are reports of increased frequency of peripheral facial paralysis and trigeminal neuralgia during the pandemic, there is no publication showing a direct association with COVID-19.

Effects of infection and/or infection treatment on patients with existing neuromuscular disease: Infections, independent of COVID-19, may worsen many neuromuscular diseases, or may result in problems and symptoms related to neuromuscular diseases that were previously absent. Cardiac disorder and respiratory function disorders, which can be seen in the course of neuromuscular diseases, can become intolerable with the additional burden of infection. Especially patients with myopathies and ALS with respiratory involvement are at risk in this respect. Apart from this, in some types of myopathy, especially metabolic myopathy, rhabdomyolysis may appear as a result of infection. In this period when the frequency of infection increases, the increase in admissions is also inevitable. One of the important effects of the pandemic is that it can trigger the emergence of autoimmune diseases such as myasthenia gravis (MG). No study examining the course of patients with MG in the pandemic is currently available, but guidelines have been published that address how to manage the disease in this period (98).

Immunosuppressive treatments are used in a significant part of neuromuscular diseases. It is clear that this will pose a risk for COVID-19 infection. Although we do not yet have data on the course of patients with neuromuscular diseases receiving immunosuppressive therapy, there are data in a study conducted in China showing that the risk of COVID-19 infection is increased in patients with cancer receiving this type of treatment (219). However, since discontinuation this type of treatment during this period will exacerbate the underlying disease, discontinuation is generally not recommended (220,221).

The quality of the vaccine, which is planned to be developed in the future, is also of great importance, especially for the group of patients receiving immunosuppressive therapy. In vaccine studies so far, the absence of a live virus vaccine is also an advantage (222). There is also a risk of developing inflammatory neuropathy, especially GBS, with vaccines. Patients who have had seasonal influenza vaccine or swine flu vaccine and have developed inflammatory neuropathy have been reported. However, it is not possible to comment on the risk of developing inflammatory neuropathy in case of COVID-19 vaccine in the light of the available information.

There is currently no definitive treatment for COVID-19. However, although there have been no randomized controlled double-blind trials for some drugs used in different indications, positive effects have been observed in case series. These drugs are also known to have some effects on neuromuscular diseases. For example, ritonavir and remdesivir, previously approved for the treatment of different infections, are also used in the treatment of COVID-19. It has been reported that polyneuropathy and rhabdomyolysis develop with ritonavir used in the treatment of HIV infection (223).

Chloroquine and hydroxychloroquine are also among the agents used in the treatment of COVID-19. Both of these are drugs that have been on the market for a long time and the adverse effect profiles of which are well known. With these medications, neuropathy and myopathy have been observed (224). In addition, patients diagnosed as having MG and patients with myasthenic exacerbation have been reported with the use of both drugs (225).

Azithromycin, an antibiotic from the macrolide group, is one of the drugs used in the treatment of COVID-19. With this antibiotic, myasthenic worsening may develop (226).

As a result, it is not yet possible to say exactly the effect of the COVID-19 pandemic on the practice of neuromuscular diseases in this period. As the accumulation of knowledge increases, the chance of commenting on the course of diseases will increase. In order to improve the knowledge, physicians working in the field of neuromuscular diseases should be vigilant in terms of interpreting the relationship of findings and disorders with COVID-19 during this period. Since it is very difficult for patients to reach risky hospitals during the pandemic period, it is a proper attitude to solve the problems of patients by using electronic communication tools. However, it is necessary to use patient groups and associations effectively to inform patients. Carefully addressing the above-mentioned issues and determining their principles are of great importance in terms of improving the outcomes of the pandemic.

COVID-19 and Neuroimmunologic Diseases

Coronavirus is one of the viruses that mainly targets the human respiratory system, but it also has neuroinvasive abilities and can spread from the respiratory system to the CNS. Neurologic findings may be related to the virus itself or to complications that develop during the process. The virus can enter the CNS, but this is still a speculative point. It is thought that decreases in systemic oxygen levels and cytokine storms cause a number of neurologic findings. Neuroimmunologic symptoms can occur as a result of the interaction of the virus with the immune system. COVID-19, on the other hand, can interact with neuroimmunologic diseases such as multiple sclerosis (MS) and MG, and the treatments used in these diseases may affect the course of COVID-19.

Until now, patients with different neuroimmunologic diseases (e.g. GBS, cranial neuropathy and acute polyneuropathy, ANHE) associated with COVID-19 have been reported (69,70,162,177,212,218,227). There will be an increase in reports of patients with neuroimmunologic diseases associated with COVID-19 in the coming days.

The mechanisms and pathology of acute deterioration in the respiratory reserve are not fully understood. However, a

cytokine storm and activation of type 2 pneumocytes play key roles. In patients severely affected by COVID-19, the cytokine profile is similar to that observed in Secondary Hemophagocytic Lymphohystiocytosis syndrome.

It is known that coronavirus infection causes clinical symptoms by first affecting the lungs and other organs, but immunologic changes defined as "cytokine storm" are observed in patients with poor clinical status despite the loss of viral load; therefore, steroids and drugs that act on the immune system by blocking IL-1 (anakinra) and IL-6 (tocilizumab) are used. In fact, drugs used by neurologists such as interferon beta and fingolimod have been included in the studies in the treatment of COVID-19.

One of the worrying issues for neurologists is the vulnerability of patients with neurologic disease to COVID-19. This is especially true for patients receiving disease-modifying therapies and immunosuppressive drugs. Patients with MS are not at an increased risk due to the immunopathogenesis of the disease in terms of being affected by COVID-19. However, patients with disability may be more susceptible to COVID-19, as well as other infections. The most important issue for patients is the potential of drugs used in treatment, especially immunosuppressive drugs, to affect the risk of COVID-19. High-dose steroids have been clearly identified as a comorbid risk factor because they negatively affect the disease process. Broad-spectrum high-potency immunosuppressants such as cyclophosphamide, alemtuzumab, and anti-CD20 monoclonal antibodies are likely to pose a high risk for infection and poor antiviral response.

Due to concerns about coronavirus infection and the risks of interrupting MS treatment, we recommend that most patients continue treatment. The potential effects of drugs used in the treatment of MS on COVID-19 infection are summarized below. There are no scientific data on this subject to create a consensus, and information based on unpublished articles and opinions of the authors are presented.

Up to now, it has been shared that more than 20 patients with MS in our country and more than 400 patients with MS have had COVID-19 while using immunomodulatory treatments. It is known that there are patients who have had COVID-19 infection and have recovered while receiving fingolimod, natalizumab, ocrelizumab, rituximab, and cladribine, as well as those who are still on treatment. It is known that five patients from Italy have died. The EDSS scores of these patients were over 6.5 and three patients did not receive any treatment. One patient had been on rituximab therapy.

Drugs such as glatiramer acetate, teriflunomide, dimethyl fumarate, and interferon beta have almost no immunosuppressive effects and they do not significantly increase the risk of infection. It will be appropriate for patients who take these drugs to continue their treatment in the same way. On the other hand, there is an opinion that potential antiviral effects of interferon beta group drugs and with less evidence teriflunomide may be beneficial for COVID-19. Clinical research on this subject is also ongoing.

It is thought that there may be an increased risk of infection with natalizumab infusion. However, because it has a low potential to increase other viral infections, it may be considered that its effect on COVID-19 risk will be low. Natalizumab is generally used in patients with active MS disease, and its infusion should continue. However, for patients using natalizumab, postponing the infusion for a few weeks will not be a problem. It is known that some physicians prefer 6-week applications instead of 4-weeks. On the other hand, longer than 2-month intervals between two doses may increase the disease activity and cause rebound activity. For this reason, it is necessary not to take a long break for natalizumab. In order to minimize the risk of contact with those with COVID-19 symptoms, it is very important to perform MS treatment infusions in more isolated and well ventilated units with less patients.

Fingolimod may moderately increase the risk of viral infections, including COVID-19. However, discontinuation of the drug may lead to rebound activity in patients. This can outweigh the risks of the disease that the virus will cause. A feature of COVID-19 is that it decreases the lymphocyte count, and the main effect of fingolimod is to decrease the number of lymphocytes. For this reason, it may be preferable to keep the lymphocyte count above 200-300 and adjust the dose accordingly. On the other hand, based on the above-mentioned cytokine storm hypothesis, there is also different research in the scientific field, and although there is no scientific evidence yet, a study on the effect of Fingolimod on the treatment of COVID-19 is under way in Canada.

Ocrelizumab is a highly effective treatment for MS, but it can moderately increase the risk of viral infection. Disease-modifying therapies with immunosuppressive properties are assumed to increase the risk of severe COVID-19 in patients with MS. It is very encouraging to read the case report of a patient with primary progressive MS who was previously treated with ocrelizumab, an anti-CD20 monoclonal antibody, who had an uncomplicated COVID-19 infection (228). Although there is only one case report, the clinic of this patient who received immunosuppressive MS treatment with COVID-19 is very promising. This case supports the hypothesis that immunosuppression, or at least moderate immunosuppression associated with MS treatments, may protect against the development of severe COVID-19 infection. However, more data is needed on this issue. The evaluation of accumulated and published patient data in the coming days will allow for more objective interpretations.

Research on whether various immunosuppressive therapies can be a treatment option in ARDS associated with COVID-19 is ongoing. Some of these are fingolimod, tocilizumab, anakinra, and emapalumab.

Anti-CD20 treatments, including ocrelizumab and rituximab, are typically used regularly once every 6-months. It may be considered to give more intermittent applications, especially in patients with B cell depletion (as measured by CD19/CD20 lymphocyte counts) or low IgG levels during the next scheduled dose. Alemtuzumab, and, to a lesser extent, cladribine, lead to a transient and variable period of lymphopenia after each treatment process, so these drugs are in the higher risk group in terms of increasing the risk of COVID-19 infection. Patients receiving these treatments are advised to postpone their treatment for several months. The most important reason for these regulations is that patients should stay as far away from the hospital environment as possible.

Acute relapse treatment: MS relapses are often treated with short-term high-dose intravenous methylprednisolone. Chronic use of corticosteroids may increase the risk of infection and short-term use of high-dose corticosteroids may increase the risk of herpes. The use of pulse steroids is the gold standard treatment

of MS attacks. Neurologists should have a higher threshold for steroid treatment during the COVID-19 pandemic. An acute infection sometimes causes temporary worsening of symptoms in MS and other disorders (pseudo-relapse). Patients should be carefully screened for symptoms of active COVID-19 infection before receiving corticosteroid therapy. In case of relapse, steroid infusion can be limited to 3 days, but if longer-term treatment is required, the duration should be kept as short as possible.

Treatment of neuromyelitis optica (NMO) and spectrum diseases: Immunosuppressive drugs such as azathioprine and rituximab, which are often used in NMO and NMO spectrum diseases, should not be discontinued. In the case of rituximab treatment, infusion reversion may be performed for several months. Patients receiving azathioprine and other immunosuppressive treatments should be monitored for white cell and lymphocyte count.

Neurological Effects of New Methods Used to Treat Coronavirus Disease

There is no specific treatment for coronavirus disease that has been proven to be reliable and effective. The methods used in treatment can be grouped under three headings: viral RNA synthesis inhibitors (PIs and RNA-bound RNA polymerase inhibitors), treatments that prevent virus entry into cells, and immunomodulators and immunotherapies (194). Stroke can be seen in 3-5% of patients with COVID-19 diagnoses (195). Ritonavir is a potent inhibitor of CYP3A and therefore reduces the elimination of apixaban, edoxaban, and rivaroxaban. The risk of bleeding increases with increased blood levels of related drugs (Table 6) (196,197). Coronavirus can lead to epileptic seizures by 0.5% due to its neurotropic and neuro-invasive abilities. In combination with antiepileptics, antiretroviral agents PIs and non-nucleoside reverse transcriptase inhibitors, pharmacokinetic interaction may lead to disease progression and resistance to antiretroviral therapy (181,198). Ritonavir levels drop due to phenobarbital inducing the cytochrome P450 system. However, in combination with ritonavir and carbamazepine, carbamazepine toxicity can be observed. Ritonavir strongly inhibits CYP3A4 isoenzyme and plasma levels of carbamazepine rise. When combined with ritonavir/atazanavir and lamotrigine, the dose of lamotrigine should be increased by 50% as the serum level of lamotrigine is halved. However, in combination with phenytoin, the dose of lopinavir/ritonavir should be increased by 50%. When lopinavir and valproic acid are used together, lopinavir levels rise by 38% (Table 5) (181). Advanced age (over 50 years) is the most important comorbid risk factor for a severe course of COVID-19. Indinavir can lead to dyskinesia in patients with Parkinson's disease, when given together with levodopa and carbidopa. PIs can lead to extrapyramidal symptoms when used in combination with buspirone, risperidone, or quetiapine (199,200,201). In patients with COVID-19, headache symptoms were seen in around 13% (195). Ergotamine toxicity may develop if PIs, such as indinavir or ritonavir, are used together with ergot derivatives in patients with

Table 6. Interaction table of the drugs commonly used in neurologic diseases with the currently recommended COVID-19 drugs

	LPV/r	RDV	FAVI	HCLQ	RBV	TCZ	OSLMV
ANTIAGGREGANTS							
Acetylsalicylic acid	↔	↔	↔	↔	↔	↔	↔
Clopidogrel	↓	↔	↔	↔	↔	↓	↔
Prasugrel	↔	↔	↔	↔	↔	↓	↔
Ticagrelor	↑	↔	↔	↔	↔	↓	↔
THROMBOLYTIC							
Alteplase	↔	↔	↔	↔	↔	↔	↔
ANTICOAGULANTS							
Heparin	↔	↔	↔	↔	↔	↔	↔
Enoxaparin	↔	↔	↔	↔	↔	↔	↔
Apixaban	↑	↔	↔	↑	↔	↓	↔
Rivaroxaban	↑	↔	↔	↑	↔	↓	↔
Edoxaban	↑	↔	↔	↑	↔	↔	↔
Dabigatran	↔/↓	↔	↔	↑	↔	↔	↔
Warfarin	↓	↔	↔	↔	↓	↓	↑

LPV/r: Lopinavir/ritonavir, RDV: Remdesivir, FAVI: Favipiravir, HCLQ: Hidroksiklorokin, RBV: Ribavirin, TCZ: Tosilizumab, OSLMV: Oseltamivir, Numbers show increase or decrease due to drug-drug interaction in area under curve (AUC). **Black:** Co-administration of these drugs carries a high risk of drug-drug interaction and should not be administered together. **Grey:** Although there is a risk of drug-drug interaction in co-administration of these drugs, close monitoring is recommended for dose adjustment and possible adverse effects if there are indications. **Dark Grey:** There is a risk of poor/rare drug-drug interaction in co-administration of these drugs. No close monitoring is required. **White:** There is no risk of drug-drug interaction in co-administration of these drugs. The symbols in the table are: ↑ increased exposure to experimental treatment medication used together; ↓ reduction in exposure to concomitant therapy medication; ⇑ Increased exposure to COVID-19 experimental treatment drug; ⇓ Decrease in exposure to COVID-19 experimental treatment drug; ↔ There is no significant interaction between the neurological drug and the COVID-19 experimental therapy drug; ♥: It may cause prolongation in the QT/PR interval in the ECG, and ECG monitoring is required when used together

migraine. Due to the same mechanism, caution is required in the use of eletriptan and almotriptan together with PIs. Ritonavir can lead to headaches, taste disorders, and perioral paresthesia. Favipiravir can lead to psychiatric symptoms (202). In animal experiments, remdesivir was shown to be absorbed into brain tissue within 4 hours when given by intravenous infusion of 10 mg/kg. There is no information yet on the adverse effects that may develop with an overdose. Ribavirin reduces the effectiveness of warfarin, thus it may be necessary to increase the dose of warfarin by 40% (Table 6) (196,197). Hydroxychloroquine can lead to dose-dependent neuropsychiatric disorders (203). It can also lead to retinopathy or myopathy, depending on long-term use (194). Although neuropsychiatric disorders such as delirium and hallucinations have been reported in patients with influenza infection using oseltamivir, these neuropsychiatric adverse effects are thought to be more related to disease than medication because the drug has been found to pass the CNS at low concentrations (204). Tocilizumab is an IL-6 receptor antagonist with immunomodulatory effect. IL-6 released from macrophages in cytokine storm in acute necrotizing encephalopathy, which is rarely seen in patients with COVID-19, is effective (198). Following the use of tocilizumab, conditions such as demyelinating diseases, reversible vasoconstriction syndrome, and multifocal cerebral thrombotic microangiopathy may develop (205,206). IVIG may be a good choice for patients with COVID-19 with neurologic manifestations. IVIG treatment has been found effective in SARS and MERS outbreaks (203).

Stroke Management in New Coronavirus Disease

There are two important points in the approach to patients with stroke during the coronavirus pandemic. The first is that the patient should arrive at the hospital and be treated optimally; the second is that the health workers should be adequately protected from infection during this treatment. Stroke units are used for different purposes in many countries and stroke teams have to work in different areas due to the excess of patients with COVID-19. Moreover, as in our country, older people who are in the stroke risk group are advised not to go out on the streets, and patients do not present to health institutions because of fear of infection. Currently, data from areas heavily affected by COVID infections show that patients with a mild stroke or transient ischemic attack (TIA) have declined in hospital admissions (229). This decrease reduces the chances of good outcomes for patients with mild stroke who may benefit from acute treatment or patients who have TIAs who need preventive treatment. In this section, stroke treatment algorithms during the COVID-19 pandemic will be reviewed. In addition, the reported cases of stroke related to COVID-19 infection and possible prevention methods will be discussed.

Stroke Organization in the Pandemic Period

In our country, the majority of hospitals in the major cities were declared as "Pandemic Hospitals" and much space was devoted to the treatment of patients who were COVID-19-positive. Outpatient services were reduced in some areas and citizens aged over 65 were restricted from taking to the streets. Accordingly, many patients with chronic diseases and living alone had difficulties in getting treatment or presenting to emergency departments. In many countries, there have been calls for hospitals and emergency departments to be organized, and guidelines for recent pandemic conditions have been published, bearing in mind that stroke is an emergency and there is a chance of treatment at the acute stage (229,230,231). Stroke awareness is the first stage of the organization. It should be emphasized that patients with the signs of stroke should reach the hospital quickly without complying with the "stay home" call. However, it should be kept in mind that COVID-19 infection is mild or without symptoms in 80% of the population. Therefore, the principle should be seized that a patient with stroke who comes to the emergency department can also potentially become infected. Also, in case series published from China and the United States, stroke developed during COVID-19 infection, and major vascular disease in young patients has been reported (232). For this reason, it is recommended that the healthcare workers who perform the first examinations and triage during stroke management work with PPE, and in patients whose history is not clear, it is emphasized that the stroke team should work with similar protection. Patient with stroke should be examined while they are wearing a surgical mask unless there is a need for invasive respiratory support; oxygen should be given through a nasal cannula under the mask if necessary. The use of telemedicine in countries, where appropriate, is emphasized in the preliminary evaluation and inducement of patients.

In this section, the American Heart Association (231), Heart and Stroke Foundation of Canada (233), and the Canadian Protected Code Stroke (234) recommendations will be used.

Patients suspected of having a stroke should first be questioned for signs of infection when being taken to the ambulance or when entering the emergency department. Patients should be asked if they have fever, cough, headache, myalgia, loss of sense of smell, diarrhea or anyone with COVID diagnosis around them. However, because most patients are unable to respond due to aphasia or consciousness disorder, the history should be taken from a close relative, and if the patient does not have a relative, the person should be treated as possible infectious. In addition, because the diagnostic COVID-19 tests are not immediately concluded, the study of acute-phase reactants (CRP, ferritin, lactate dehydrogenase, D-dimer and decrease in lymphocyte count) common in people during infection will be a guide. The emergency team to conduct the first interrogation must wear PPE. At this stage, the proposals actually vary according to the country's facilities and experience.

Although the rate of intravenous thrombolytic (r-tPA) treatment is increasing in our country under normal conditions, thrombectomy cannot be performed in all centers. In daily practice, it is recommended to exclude intracerebral hemorrhage rapidly, to investigate major vascular pathology, and to administer r-tPA rapidly during this time, and to send the patient to the thrombectomy unit or center when infusion is ongoing. However, during the COVID-19 pandemic, the cleaning of the CT and angiography suite at the hospital, the distribution of the staff with intensive care and service beds reserved for infected patients at the hospital may hinder this algorithm. In fact, under ideal conditions, the organization in the Padova region in Italy seems to be interesting (235). Here, in the first triage, if infection is suspected or if COVID-19 is diagnosed, a different CT scan is evaluated, if the query is negative, the standard route is followed. After thrombolysis/thrombectomy, the patient is taken to the

stroke unit or COVID-19 ICU according to the infection condition (5). Although the mentioned regulation seems very attractive, unfortunately it may not be implemented everywhere because hospital logistics are quite different in our country, and it may not be possible to make a single proposal.

For this reason, it is important that patients with stroke, especially those with mild symptoms at the beginning, do not hesitate to present to health institutions. At this stage, patient orientation should be targeted by the 112 service depending on which hospital stroke team is active in the region and if there is enough room at the hospital. As in normal conditions; as many patients as possible should be given the chance of acute revascularization quickly by prioritizing the phrase "time is brain". To date, there are no data demonstrating a requirement for changes in standard thrombolysis and thrombectomy protocols. However, the protection of all medical personnel in the approach to the patient should be a priority. Glasses, visors, N95 masks, and protective clothing should be used for intubation, aspiration, and similar procedures that will produce droplets, which will be in this category for patients undergoing thrombectomy. The goal should be to protect the patient and the stroke team equally.

Coronavirus infection is known to have an increase in coagulation and a tendency to thrombosis. The treatment protocols used in Turkey include low-molecular-weight heparin and are intended to prevent such complications. It is also emphasized that anticoagulant treatments can be used in the early stages of strokes that develop during infection.

Medical practices are performed in extraordinary conditions during the pandemic period all over the world. Our main goal should be to use the most appropriate treatments to our conditions in our country. In addition, collecting information about COVID-19 and patients with stroke in a database and evaluating the data of our country will help us to develop the best treatment protocols for this disease, which will be with us for long time yet.

Endovascular Treatment in Acute Ischemic Stroke During the New Coronavirus Disease Pandemic

The organization for acute ischemic stroke (AIS) was affected by the pandemic. Although the frequency of ischemic stroke does not change, there may be inadequacies in acute recanalization treatments of patients with stroke due to disruptions in pre-hospital and in-hospital stroke organization. In a cohort study of six studies, the rate of cardiac and cerebrovascular disease in 1527 patients with SARS-CoV-2 infections was 16.4%. However, the incidence was 3-4 times higher in patients with COVID-19 who needed intensive care (60,61,179). For this reason, patients with AIS and COVID-19 infection may need neurologic intervention due to large vessel occlusion. In addition, treatment of neurogenic acute stroke, regardless of infection, is ongoing for all groups of patients.

Pre-hospital and emergency department organization in candidates for neurologic interventional treatment: Indications for neurologic treatment in patients with AIS should be accompanied by current guidelines. The pandemic should not lead to changes in acute stroke management. In out-of-town patient referrals, symptoms of cough, fever, and breathing difficulties should be questioned. During referral and patient admission in patients suspicious for or COVID-19-positive, patients should be wearing surgical masks and medical personnel should transfer patients with appropriate PPE. Patients with stroke who come directly to the emergency department should be asked about fever, cough, difficulty of breathing, history of hospitalization in a pandemic hospital, myalgia, diarrhea, and contact history. If there is a suspected COVID-19 disease in anamnesis, the emergency department team and stroke team should examine the patient with appropriate PPE and the patient should be wearing a surgical mask. Patients with suspected acute stroke who are candidates for recanalization therapy may be required to undergo CT and CT angiography examination at the first stage. Ideally, imaging suspicious patients for COVID-19 in centers with multiple CT units is done especially in reserved CTs for patients with COVID-19. However, because these conditions are not available in every hospital, it may be necessary to have the CT scanner cleaned after patients suspected of COVID-19 and wait an hour between patients (86,89,234). Low-dose thorax CT can be added to the stroke protocol for each patient undergoing interventional processing (236). If CT angiography is taken at a slightly lower level than the arcus, the lung can also be examined for COVID-19 findings in the thorax CT mode. If COVID-19 is suspected in the patient's anamnesis and/or if COVID-19-like lesions are present in the thorax CT, a PCR test can be performed and the patient can be prepared for neurologic interventional processing with COVID-19 suspicion. Anamnesis may not be sufficient because of aphasia, especially in patients with stroke. On the other hand, the importance of thorax CT will increase if the patient's relatives are not able to provide adequate anamnesis and the PCR test is not concluded very quickly. If COVID-19 is suspected in the anamnesis and examination in patients who have already had CT and CTA examinations from an external center, thorax CT examination may be required with PCR. Because time is particularly valuable in stroke, it would make sense to accept each patient as a potential COVID-19 case and move quickly and structure medical staff in this way. CT perfusion may be used in patients with an unknown stroke symptom, a wake-up stroke, and patients who have 6 hours after the symptom. ASPECTS score clinical mismatch criterion may be used in patients without CT perfusion to avoid contaminating cerebral MRI (237). These strategies may vary depending on the conditions of the center where the stroke center is located. Temporal parameters in neurologic interventional treatment are important, especially in major vascular occlusions in acute stroke. In this process, due to the COVID-19 pandemic, some problems may occur due to the organization. However, these defects can be reduced to a minimum with the steady implementation of certain algorithms during the diagnostic time (231,236,238,239).

Various hypotheses have been formed associated with COVID-19 and major vascular occlusion. Some of these are coagulopathy and vascular endothelial dysfunction. Some factors that are not currently revealed in research may also cause major vascular occlusion (232). DVT and patent foramen ovale coexistence in young people as a result of sedentary life at home, increased cigarette consumption, and stress may be other factors that cause major vascular occlusion (232).

Management of periprocedural endovascular procedures, including mechanical thrombectomy: In patients with major vascular occlusion, especially before the endovascular treatment, which type of anesthesia should be used or whether the operation can be performed with local anesthetic alone without conscious sedation should be decided. General anesthesia may be considered in patients who are unable to protect the respiratory tract, who have tachypnea, hypoxia, and severe agitation. In these patients, intubation should be performed with complete use of video laryngoscope, aerosol can and PPE by an anesthesia, neurology intensive care or emergency department team according to the COVID-19 protocol due to the risk of aerolization (231,236,238,239,240). Intubation should be performed in the emergency department (negative pressure room) as much as possible, and in the neuroangiography suite if not possible. Switching from the sedation protocol to the general anesthesia protocol greatly increases the risk of aerolization and is not recommended. Based on the patient's current situation, the strategy to be implemented should be determined earlier (231,236,238,239,240). The waiting rooms of the angiography units should contain a HEPA filter system as a precaution for future outbreaks in the period after the pandemic.

The number of people in the team that will perform the interventional neurologic procedures should be limited. It is recommended that a technician, a nurse, and an interventional neurologist to perform procedures. However, in some cases, a maximum of two interventional neurologists can participate in the process. The number of health personnel in the procedure and in the control room should be kept to minimum level. The whole team should have complete PPE. The angiography team should definitely be trained by the public health committee or a team that the hospital pandemic committees choose regarding the protection against COVID-19 infection. Only the most necessary equipment and cabinets should be in the angiography unit, unnecessary and less frequently used devices and equipment should be removed from the unit. To prevent contamination, frequently used equipment should be wrapped with plastic covers. If patients are to be taken to the procedure with conscious sedation, they must be treated while they wear a mask. In hospitals with multiple angiography units, one of the units can be used for patients suspected or diagnosed with COVID-19 in this process. It is recommended in publications that procedures should be performed in positive pressure angio rooms. Respiratory protective (e.g. giving gas anesthesia, avoiding remifentanyl and fentanyl) anesthesia and intubation strategies can be performed to the patient group that is known have COVID-19 and/or a wide lesion in thorax CT while respiratorily unstable. During the procedure, the anesthesia team or the neurological intensive care team should work under optimal conditions. In these patients, fluid balance should also be arranged with suspicion of pulmonary edema (231,236,238,239,240). In order not to extend the duration of the procedure, the patient should be treated with the most optimal technique for endovascular treatment. There is no difference in endovascular technique during the procedure. The COVID-19 pandemic has shown that interventional neurologists who perform acute stroke endovascular interventions must have a back-up in intensive centers. In this respect, the rule of having at least two interventional neurologists who work with the 24/7 principle in comprehensive stroke centers will make sense in the future.

If there is a need for CT after the procedure, cone beam CT (Dyna-CT, Expert-CT) can be performed for intracerebral hemorrhage retraction. In this way, the patient does not have to go to the radiologic CT unit again. It is appropriate to follow up in positive-pressure isolated ICUs because patients with high suspicion of COVID-19 infection cannot be hospitalized in the general stroke and ward-system ICUs. These patients can be followed up with a mentality that requires multiple medical disciplines in COVID-19-specific ICUs (231,238,239,240). The organization and principles of angiography in terms of endovascular intervention in acute stroke after the pandemic we experience today vary within certain rules and algorithms.

New Coronavirus Disease and Neurorehabilitation

Neurorehabilitation is a branch of neurology that covers the treatments used to achieve neurorestoration by healing the damage in the nervous system through structural or functional modifications, and takes its basis from the concept of neuroplasticity. Neurorehabilitation aims to fix circuits that survive in the nervous system. Often neurodegeneration and neuroregeneration progress simultaneously in these circuits. In addition to pharmacologic treatments after neurologic diagnoses, it is necessary to promptly start neurorehabilitation and ensure its continuity to change the process in favor of regeneration (241). Therefore, it is important that neurorehabilitation is not interrupted during the COVID-19 pandemic. It is necessary to keep patients in hospitals as little as possible and to maintain neurorehabilitation under home conditions because the priority in the general approach is to protect patients and their relatives from COVID-19. Even if the institution we serve is not a pandemic hospital, it is recommended to take this approach into consideration (242).

Our neurorehabilitation ambassadors at home are caregivers. Therefore, it should be explained by us how caregivers should approach their patients by following the general hygiene rules. If the caregiver with a suspected history of contact with a patient diagnosed as having COVID-19 does not have to closely attend their patient to give care, they must strictly follow the rules of not approaching more than 1 meter, not speaking for more than 15 minutes, and using masks and gloves (243). However, when this is not possible, it is imperative to provide a substitute caregiver.

In this section, sampling of neurorehabilitation activities that can be performed at home during the COVID-19 pandemic is presented by taking some common neurologic diseases such as MS, dementia, Parkinson's disease, and stroke as a model.

Multiple Sclerosis and Neurorehabilitation

Regular exercise in MS is important in dealing with depression and chronic fatigue, as well as spasticity. During the pandemic days at home, patients should be encouraged to perform cardio and stretching exercises three times a week for 30 minutes (or every day, 10 minutes) alternately. This process can also be an opportunity to encourage patients to learn effective exercises on walking, balance, and posture, such as pilates, from digital platforms. However, it should be reminded that patients should not exercise so much that

it increases their body temperature excessively; therefore, the total exercise time should not exceed 150 minutes per week (244,245).

Dementia and Neurorehabilitation

Generally, patients with dementia in the older age group are recommended to stay at home and continue their medication in accordance with the quarantine rules. In patients with advanced dementia, active or passive flexion-extension movements and frequent positioning, especially in bed, are important in reducing pain, and preventing contractures and pressure sores. To prevent aspiration pneumonia, the importance of nutrition in an upright position, just like in patients with stroke, should be reminded especially during this period (246). Mobile patients should be encouraged to take exercise by walking in areas such as corridors, and extending the exercise sessions over a period of time if necessary, without causing boredom. Directing the patients and their relatives to domestic activities, when the majority of the family members are at home, can provide a continuity of treatment that will turn into a habit in the future. It is important to ensure that the patient contributes to food and cleaning efforts without harm, and is directed to occupational activities such as knitting. It is also an important issue to ensure that worshipers continue their worship at home (247). Also, during the time at home, it is a great opportunity for patients with dementia to learn what cognitive exercises are for family members. Cognitive exercises begin with the "Reminder Exercise". In other words, the patient is asked to tell a topic that they like to talk about with pleasure or to sing a song they likes. In this way, the patient will become more open to communication for other exercises. Afterwards, place, time, and person orientation reminders should be made for "Reality Orientation Exercise". The other step, "Cognitive Memory Retention Exercises", focuses on the patient to feel functional. In this context, back and forth counts (days of the week, numbers) and word memorization exercises can be done together. Patients can do exercises to remember the faces of family members from the pictures at home and famous people from the internet. Activities such as painting, playing backgammon or doing jigsaws together should definitely be recommended (248). It should also be reminded that families with opportunities can access brain training programs for patients from their computers or mobile phones.

During this period, elderly people who stay in nursing homes, especially those with cognitive impairment, may become agitated due to their inability to take advantage of common areas of activity, hygiene rules they are not used to, and psycho-social isolation. Using music to reduce patients' stresses, well-lit rooms, and talking about different topics may offer short-term solutions. However, it is not possible to talk about the continuity of neurorehabilitation in institutions with insufficient space to provide contact isolation, lack of staff or hygienic precautions (249). In such places, after the necessary sanitation has been achieved by their management, it is necessary to reorganize the neurorehabilitation activities specific to COVID-19.

Parkinson's Disease and Neurorehabilitation

In patients with movement disorders, walking and balance exercises are of great importance in terms of improving the quality of life of patients and ensuring that they remain mobile for a long time. Strengthening and reducing rigidity exercises of back muscles and axial muscles are of great importance for Parkinson's disease (250). In-home exercises should be performed not only in this process, but lifelong parallel to drug treatment. Exercises should definitely be suggested to be performed with family members when learning the movements. Performing the exercises together will increase the sense of socialization that is lacking in our patients and decrease undesired consequences such as falling. In addition, walking exercises with music and rhythm, which are known to reduce freezing and falling, should definitely be recommended (251).

Stroke and Neurorehabilitation

If the situation is stable in patients with acute stroke (if hyperglycemia, hypertension and arrhythmia are under control), prompt discharge is an important issue. In the post-acute period, common rehabilitation areas should not be used, if possible, in in-hospital rehabilitation. Rehabilitation should be peformed in the patient's room, in isolation conditions, under the supervision of the primary caregiver and with the prohibition of visitation. Physiotherapists should ensure that they use the necessary PPE appropriately. Rehabilitation of patients whose body temperature is above 37.5 °C should be postponed after the necessary tests and treatments. Patients with no fever, but who are suspected of COVID-19 and have mild respiratory distress, should be given oxygen support and a surgical mask should be worn. FFP2 or FFP3 type masks should be used in patients without respiratory distress but suspected of COVID-19, following oxygen saturation. Neurorehabilitation of patients with acute stroke who are diagnosed as having COVID-19 should be terminated and their transport to the related isolated service should be ensured immediately. The general approach in patients without these risks is that experts should teach the caregivers the exercises to be done in the simplest way and to discharge the patient as soon as possible (242).

There are studies showing that home-based rehabilitation programs are especially useful in patients with stroke with low deficit (252). In light of this information, families' anxieties about their patients' late improvement in walking and speaking should be reduced. Families should be clarified about the benefits and harms of hospitalization and be encouraged to prepare the environment for the continuity of the process at home. In strict quarantine periods, the rehabilitation of some patients with subacute or chronic stroke may be delayed by certain clinics where they receive outpatient treatment. In this case, it is necessary to motivate patients and their caregivers to continue the exercises they have learned in the hospital within the home environment, and under the necessary hygiene measures.

In the COVID-19 pandemic, patients' lack of neurorehabilitation can cause delays, deficiencies, and even worsening of neurologic diseases. Thus, within this period, it is very important to teach patients and caregivers about the neurorehabilitation activities that can be performed in the home environment, and to produce new projects for the future.

Quality of Life and Stigma in the New Coronavirus Disease Period

The coronavirus pandemic also affects quality of life in various community groups, apart from the disease. First of all, with this outbreak, different practices in society came to the agenda. Many practices such as long-term stay at home, curfew limits for certain social segments (risky age group, chronic patients) in certain periods, social distancing, the necessity to wear masks in certain areas, and measurement of fever when entering some buildings, have affected the quality of life with different ways in different segments in society (253).

Individuals with chronic neurologic diseases, while trying to continue the treatment related to their diseases, on the other hand, experience anxiety as they think they are at great risk as a chronic patient, and also undergo stigma (stigmatization/labeling). The solution can be provided with appropriate information. Patients should be advised to decrease to a minimum their watching, reading or listening to news about COVID-19, which increases their anxiety levels, and to turn to reliable sources for information only. Patients should be advised not to pay attention to rumors or information from wrong sources, but rather to news and information from reliable sources (such as the Ministry of Health, specialized associations) while planning their daily lives, making practical plans, and taking steps to protect themselves and their loved ones, and they should do so in limited numbers and times during the day.

Associated with COVID-19, stigma rises as a more severe and more important social problem than we see in other neurologic diseases. There has been a similar situation in other diseases in history, for example, the so-called "Spanish flu", and this disease was named after a country, originating in England, Spain or China. There has always been a tendency to associate the onset of new infectious diseases with foreign countries and populations, and today, this trend has emerged in several countries for the disease caused by the SARS-CoV-2 virus (254). Irrational fear and stigmatization, and blaming foreigners are common by implying a causal relationship between a particular foreign population and the disease. Stigma associated with COVID-19 also manifests itself as an important problem. In the WHO's and international organizations' reports, there are increasing statements of stigmatization of people in regions affected by the pandemic. This means that people are labeled and discriminated against (255).

When this disease first appeared in our society, groups such as "those in other countries" and "those in other ethnicities", and when the disease came to the country, groups such as "those who went abroad-those who came from the Western countries or the Umrah" started to be identified and labeled in society. Then, news like "the elderly and those with chronic diseases get more sick", and after a while, "young people get more infected" caused some people and groups-people with chronic diseases, the elderly, refugees etc. -to be excluded and labeled. A significant part of these groups are also patients with neurologic disorders and the subject of stigmatization has started to seriously concern the Neurology.

There are actually three reasons why a stigma is associated with coronavirus infection: 1) It is a newly emerging, newly learned disease and still has many unknowns; 2) people are always afraid of the unknown, and 3) it is easy to associate this fear with "others" -e.g. immigrants, old people, those coming from Umrah. It can be understood that there is confusion, anxiety, and fear in society. Unfortunately, these factors also feed harmful stereotypes (256). Although the stigma appears to "contribute" to social isolation, as a result, the individuals' entire neuropsychological identity is affected, and stigma will have holistic negative effects due to its negative effects on the immune system. This could mean more serious health problems and difficulties in controlling the disease outbreak. Stigma directs people to hide the disease due to fear of discrimination, prevents the individual from receiving immediate healthcare, and prevents individuals from adopting healthy behaviors and habits.

In this case, it is recommended that the healthcare professional be very careful and sensitive about the following subjects;

1) While communicating with people-patient and patient's relatives-some words and expression styles may have a negative meaning for people and may increase their prejudging attitudes. Therefore, the words to choose are important. Expression style that will not increase fears and prejudices should be preferred,

2) Misconceptions about quarantine, tests and scans should be ruled out in a few words in patient interviews, false convictions that cause widespread fear should be prevented,

3) Usually it will be effective to use the term "human first" when explaining the subject to neurology patients,

4) This issue can be solved by giving the most accurate and up-to-date information to patients who tend to label the information they see from the media or the internet. Misconceptions with false, purposeful or distorted information should be prevented by constantly providing new developments and the most accurate information. Where there is true and pure information, there are no mistakes (257).

Another issue is "disabled stigma". While raising the awareness of patients, initiatives towards their needs are also important. For individuals with disabilities due to their neurologic conditions, it may be difficult to provide hygienic needs in optimum conditions in a pandemic environment. Disabled individuals with neurologic disease may have a higher risk of catching COVID-19 for the following reasons:

- Barriers to implementing basic hygiene precautions such as hand washing (for example difficulty in rubbing one's hands due to difficulty or weakness in physical access to sinks or water pumps),
- Difficulty to maintain social distancing due to their additional support or assistance needs or the care institutions they are in,
- The need to touch things to get information from the environment or for physical support, and various obstacles to accessing information in general.

If patients with special needs are quarantined, information about their diseases should be obtained from the patient's neurologist by the relevant medical staff. Patients with special conditions should be advised to stay away from crowded environments, it should be ensured that they do their shopping online or via telephone, and if they spend their days with the helper/caregiver, they should be kept at appropriate distances from them, while the hygiene barriers should be removed. In this way, when sufficient information is provided, it will be seen that the disability stigma caused by ignorance is largely overcome.

Apart from this, the ventilator, emergency tracheostomy, and intensive care situations, which are essential for use in certain neurologic diseases, may remain in the background by prioritizing patients with COVID-19. Even in some foreign documents, it is recommended to exclude 'chronic' neurologic diseases during pandemic process to give the whole attention to pandemic patients, of course, this is not a behavior appropriate for Turkish medical and sense of deontology (258,259). During the effort dedicated for COVID-19, neurology patients should not be deprived of treatment (260). Intensive care beds, or rather all hospital beds and resources, should continue to be allocated according to proper assessment methods. Patients with acute or chronic neurologic diseases should be able to exercise these rights whether or not they are infected with COVID-19, when needed.

Coping strategies are important in this period because constant indoor spaces, social isolation, and decreased physical activity bring additional psychological burdens. To protect the quality of life, it is important to find peace in loneliness (meditation, reading books, developing hobbies), not to completely stay back from bodily activities while keeping the mind peaceful, and to ensure required physical activity is done (261). It is necessary to continue to keep doing these activities and in contact (albeit in a virtual environment) with family/friends. On the other hand, patients should be reminded to avoid alcohol, tobacco, and unnecessary drug usage. It should be remembered that the most important step in overcoming stress is to know it and to protect oneself from it.

Another group of people whose quality of life should be carefully monitored is neurology health professionals, especially neurologists, and nurses. In addition to all health personnel, internal diseases, emergency medicine, chest diseases, infection, anesthesia-reanimation experts, public health specialists, family physicians, and research assistants working in the pandemic process, there are many neurologists and research assistants working in this war. In addition, there are neurology specialists and research assistants who are trying to continue their routine healthcare services completely despite limited opportunities during the COVID-19 pandemic, as well as many branch physicians have been doing. Neurologists feel emotional pressure and even psychological breakdown with the news about their colleagues, relatives, and patients who are infected and even lost their lives. It is important to take precautions for these situations, which affect quality of life. Support based on mutual interaction is prominent here. Individual measures should also be taken. When making difficult decisions, it is recommended that evaluation and prioritization decisions be made by more than one physician colleague, sharing the responsibility, and if possible, leaving it to the relevant specialist. It is important to take all kinds of hygienic safety precautions both for the physicians in the background and those who struggle in the front line to maintain normal functioning in some way. In addition, after seeing that some patient visits can be conducted by telephone and telemedicine, the option of working outside the hospital may also be considered. The fact that some neurologists (those in quarantine, busy with childcare, and those aged over 65 years) are doing the routine paperwork, following e-correspondences, and even responding to some simple telephone problems of patients who are constantly being monitored, will significantly contribute to the quality of life of our colleagues in the front line.

Apart from the specialty, the subject of study is also important. Physicians are subject to the duties of care for pandemic patients. In a pandemic, this duty of care is part of a fair and mutual practice, which shows solidarity while protecting the public from harm. To perform this duty of care, physicians may need to be flexible and work in places outside their normal practice or in clinical areas. This will be especially so for physicians who cancel their elective clinics, minor departments, and special procedures during the COVID-19 crisis. Physicians should be ready and supported to work outside their normal practice. This support should be in the form of material and training support and should continue, constantly (257,262). It should be reminded that the most important step in overcoming stress is to know it and to protect oneself from it. It should also be well known that this pandemic and its effects will continue for a while and that life needs to be planned accordingly; this is not a sprint, but a marathon. Another important issue regarding the quality of life is to start thinking about the aftermath of the outbreak and to plan the measures to be taken.

NEW CORONAVIRUS AND THE STRATEGIES

Telemedical Consultation and Telenourology in the Pandemic

Coronavirus pandemic and social isolation, as in all areas, are practiced in the field of health and entail minimizing physical contact between patients and physicians. This situation started to negatively affect chronic patients as well as physicians who want to follow their patients periodically. Therefore, neurology patients are the most affected group of diseases. Telemedicine is one of the methods that provide continuity of healthcare in such extraordinary situations. Telemedicine is a communication system related to the use of health services in clinical practice, treatment, and patient follow-up (263). With this technology-based method, it is ensured that the patient shares their current situation with the physician or healthcare professional via voice and/or video manner without going to the hospital. Not only examinations, but also radiology, consultations, and training can be conducted via telemedicine (264).

The aims of telemedicine include making quality health services available to everyone in more equal conditions and at less cost, facilitating situations where there are obstacles to reaching health workers such as epidemics and earthquakes (265). Especially in cases such as epidemics and pandemics, asymptomatic, suspicious, and symptomatic individuals requiring isolation living in the affected areas can be monitored via home-based telemedicine. Examples of this practice were used in Taiwan in the SARS outbreak in 2003, in China in the H1N1 outbreak in 2009, and in Africa in the 2014 ebola outbreak (228). The use of telemedicine in epidemic situations may facilitate epidemiologic research, disease control, and management of other non-epidemic chronic diseases. In addition, during pandemic times, healthcare professionals who use telemedicine applications to respond to the requested consultations for patients monitored in pandemic hospitals

or services will reduce the risk of infection to healthcare professionals. Thus, the loss in healthcare professional workforce will be avoided. In addition, many disposable and limited equipment that is essential during the inspection will be saved.

Telemedicine applications are based on the systems for storing and transmitting information, remote control, and monitoring of the stored information, and reactivation when necessary. The necessary technical infrastructure of this system is formed by any written text that contains prescribing with laboratory and imaging reports, fixed or animated imaging, video recordings of the examination, respiratory sounds, and voice data such as the patient's speech and voice tone (266). Although telemedicine may seem to transfer information between two people, the amount of mediated materials that it provides is plentiful. For example, telecommunication equipment, mobile units, software, hardware, and interfaces for mobile units, adaptation processes for special or existing instruments, and hospital services configured for this system are intermediate networks required for telemedicine operations. Most importantly, the legal infrastructure of the country should allow the system to function.

The secure storage and transmission of telemedicine data is called tele-security and its main purpose is to ensure the confidentiality, integrity, and availability of data. Deficiencies and errors in the software and operating system and situations such as not using the necessary security programs may create security gaps. Both users need to implement code/encryption/validation processes on their systems to avoid this (267).

The telemedicine system related to neurologic diseases is called teleneurology and a standardization is needed for this method to be used in national prevalence. For example, the American Academy of Neurology has documented on their web pages that they have made this standardization for their country. Accordingly, the programs and databases used for teleneurology should be licensed and authorized by state guarantee, and patients should be insured against improper practices. The pre-examination status of the patients (such as the first patient, patient at follow-up) should be determined. Interviews performed at the patients' own place are more successful. However, the telemedicine location should not be very important in extraordinary situations such as epidemics and earthquakes.

The issues to be considered in the examination with telemedicine method are as follows:

1) The patient and the patient's relative/caregiver should live in a bright and calm environment, their phone, tablet or computer must be their own, the patient's identity must be verified (e.g. Turkish Republic identity numbers, date of birth) and before the examination, they must have a consent form regarding their will to the examination.

2) Neurological examinations are mostly performed with a video call. With the video method, the general appearance of the patient, facial appearance, language examination, and tremor examination are performed. Vital findings are determined using household equipment.

3) To assess the patient's mental state, the short mental state examination test or the montreal cognitive assessment test is used and recorded. The patient's speech is recorded by voice, and their hearing is also evaluated.

4) Cranial nerves may require the help of the patient's relative. Visual field can be evaluated with a special display system connected to the screen, but it may be difficult to maintain attention in elderly patients. For pupil evaluation, an examination can be performed by moving the patient's eyes closer to the camera and enlarging the image. Extraocular muscles are evaluated by directing the patient to look up, down, right and left, with the help of their relative.

5) Motor and sensory examinations are performed using simple commands. For force, pronation, and digit quinti findings in the upper extremity; and standing up, walking on the heel, and walking on tiptoe examinations in the lower extremity are the easiest. For sensory examination, the patient's relative is asked to give symmetrical and comparative stimuli (such as touch, pain) to the described dermatoma regions.

6) Cerebellum examinations are performed with walking, balance, and the finger-nose maneuver.

7) Tonus and reflex examinations are quite difficult. Also, eye examinations, neuromuscular examinations, and vestibular examinations are difficult to perform (268,269,270,271).

In a retrospective case-control study, no significant difference was found between the teleconference method and face-to-face examinations in the evaluation of patients. Studies on telenourology have shown many neurologic diseases demonstrated successful examinations in which technologies were used, rather than traditional face-to-face interviews (272). A study has shown that migraine assessment is the easiest telemedicine method, also providing patient satisfaction (273). Performing the required cognitive tests for the diagnosis of the elderly and individuals with dementia using this technology reduces the cost of hospitalization and the time spent by patients' relatives in the hospital. With telemedicine, standard cognitive screening tests can be performed easily (274). The use of telemedicine enables non-drug treatments prescribed for cognitive and behavioral disorders for patients and caregivers, and applications such as physical therapy, occupational therapy, speech and language therapy used for sequelae in neurologic diseases (275). In studies that aimed to verify telemedicine use in neurologic diseases with current treatments, the positive effects of telemonitor applications that provide continuous support to caregivers, especially in cases of sudden emergence of assistance needs, were mentioned (276).

A study about patients with Parkinson's disease emphasized that practices increased patient quality of life and even made improvements (277). Like epilepsy, dementia is one of the areas of use of this method (278).

The fastest growing area of teleneurology is related to acute stroke treatment. Telestroke is mostly achieved with the use of video inspections and teleradiology. It is the most appropriate method for treatments that require advanced and rapid action (279).

While telemedicine practice requires different packages for each specialization, the following are particularly necessary for neurological telemedicine, or better phrased, teleneurology: video-camera-sound system, computer, server, scanner, microphone, monitorization interfaces, digital stethoscope, neurological examination software, ECG, EEG, video otoscope-video laryngoscope, blood pressure measuring device, body degree and blood gas measuring device, urine analyzer, glucometer, ultrasonography and teleophthalmoscope (280).

In cases of pandemic, such as with the coronavirus infection, computers or tablets used by healthcare professionals and patients should be cleaned in accordance with the previously well-defined infection control procedures.

There is no legal grounds for telemedicine systems in our country yet. However, the "Health Informatics Network" project has recently been initiated by the Ministry of Health, and its aim is to speed up the communication of health data between individuals and all institutions and organizations providing healthcare services, and to provide a more reliable feature. The initial related applications started as teleradiology only. The current health legislation makes doctor-patient meetings, treatment planning and prescription possible through face-to-face interviews. It is understood that telemedicine-teleneurology setup and application is not possible without making necessary changes in the current regulations (281).

Another important issue required for the establishment and spread of telemedicine and telecommunication applications is the repayment coverage of these applications by the Social Security Institution. Like all medical applications, it is important to get the value of this qualified health service provided through telemedicine applications. For this reason, procedures that can be performed within the teleneurology applications such as polyclinic examinations, follow-up examinations, outcome evaluations, consultations or ward visits should be classified, and score responses should be determined according to their importance and risk levels. In addition, it will be beneficial to hold the necessary negotiations to cover all or some of the financial compensation that may arise in malpractice cases arising from telemedicine or telecommunications practices under the scope of compulsory financial liability insurance for medical malpractice.

Today, during the COVID-19 pandemic, some health institutions have also started using telemedicine as a hotline. A university hospital in our country has reported that it has implemented an application under the name of "Telemedicine Outpatient Clinic System" in order to maintain health services for individuals with chronic diseases without serious disruptions. Apart from the pandemic, the use of teleneurology applications in our country in the near future will be a need to respond to patients with emergencies faster and use the limited physician workforce efficiently. In the newly built large city hospitals, in large university hospitals with hospitals on separate campuses or with scattered residential buildings, or in branch hospitals without neurology specialists, it will be necessary to use teleneurology practices for the reasons mentioned above, in cases of need for neurologic consultations in work, and particularly in shift conditions. Apparently, technology will be demanding to use processes in its favor.

The Turkish Neurology Society should establish an action plan in this process, and studies should be done in the presence of the Ministry of Health with a guide to be created by the study groups. Training of service providers, public awareness, technical infrastructure, consent forms, and data security should be established in the coming time.

Consequently, the use of telemedicine in the field of neurology should be determined as a primary target and implemented quickly, especially in the days when the COVID-19 pandemic is experienced.

Clinical Research in the Pandemic Period

In the coronavirus pandemic process, the drug and drug research industry is one of the most affected areas. Although in many countries of the world, vaccination and drug development studies against the coronavirus have become the primary health issue, a mandatory silence has prevailed in clinical studies investigating the quality and efficacy of potential drugs related to many areas of medicine. The most important reason for this silence is the shift of health priority in favor of the pandemic; nevertheless, it should not be forgotten that the policy that restricts the work and social lifeline routine to housing only and aims social distancing is dominant in cities and countries. The field of neurology is one of the most productive areas for clinical studies. In the world and in our country, it is necessary to briefly review the effect of COVID-19 pandemic on clinical studies in the field of neurologic diseases and how the studies should be conducted together with the process.

Clinical studies often start with more than one center and volunteer participants, then by adding new centers and participants the result is reached through the data obtained over the default time. During the process, the data related to the effects and adverse effects are recorded and accumulated for analysis, by visiting participants' homes or by inviting them to a center or health area. Clinical studies are a team game with its responsibles, employees, and participants, followed under a protocol (283).

Looking at the April 2020 data, there are announcements on the web pages of many pharmaceutical industries in the world about the current status of the ongoing clinical studies and what attitudes will be maintained (284,285,286). The Global Data Healthcare site, one of the major research centers, outlines the current neurologic studies and mentions that they will plan a new management for them (287). Looking at the views of the industry and the academy on the subject, it seems that there are difficulties in completing many studies, making the necessary visits for the research, and providing the medical materials required; many studies will be delayed or proceed with different alternative solutions. The difficulties detected and the methods proposed to overcome these difficulties can be listed as follows (288):

1) Starting a new study and including new centers and new participants in a conducted study requires a very detailed evaluation. Here, participants should be addressed in terms of additional risks and benefit/risk ratios, and new arrangements should be made in the protocol under the heading of risk assessment.

2) In ongoing studies, regular visits where the data of the participants are taken may not be made. Travel restrictions of states due to pandemics, difficulties in admitting participants to health centers or the need to isolate themselves at home lead to disruptions. Another reason for this is the different workloads of the personnel to deal with the pandemic.

3) The suggestions of the solution seekers include the postponement or complete cancellation of visits if they are made necessarily in the study centers; temporary closure of all or some study centers; obtaining the data of the working period

in accordance with the social distancing rules from the houses of the participants with the help of intermediate personnel such as home nursing; safety and protection of data; if it can be provided, using the telephone and telemedicine method for adverse effects, observation, medical conditions; and extending the working time. It should not be forgotten that the continuation or cessation of the works should be done on the basis of the health and safety of the participants, and all kinds of alteration in the study protocol should be presented for the participants.

4) It is more convenient to use the closest local centers for the laboratory and imaging methods used in the follow-up.

5) The reorganization of the studies can be initiated by the research center in dialogue with the sponsor. Ethics committees should be informed quickly in case the responsible researcher changes.

6) Continuity of the security data along with the study is very important. Care should be taken for collection of adverse-effect reports from the study while they are not prevented by reducing or postponing the participant visits.

Presuming that the coronavirus pandemic may have an impact on clinical trials conducted in our country and that measures will be required in this regard, an opinion has been reported by the Republic of Turkey Ministry of Health, Turkish Medicines and Medical Devices Agency (TITCK) on 20.03.2020 (289). Sponsors are advised to constantly evaluate risk and update their research organizations accordingly. It is recommended to conduct risk assessments by considering the priorities and urgency of COVID-19, to reduce the burden of research centers, and to ensure compliance with social isolation rules. The first thing to consider is the safety of the participants.

Among the opinions of the TITCK, it is stated that decisions are important such as temporary suspension of certain drug research, postponing the acceptance of new participants to the research or discontinuation of existing participants' treatment, and these precautions should not be avoided when necessary. It is noted that protocol changes in the process may not be required to be reported quickly to ethical committees and may be left to a later date.

The opinions of TITCK on study monitoring are as follows: monitoring activities may need to be postponed and/or rescheduled according to the research center's status. For example, remote monitoring may be done with the consent of the participant, or the evaluation of the participant can be made in another more convenient and secure center. An employee who provides homecare services can be used for participant visits at home. If none of these can be done, the participant can be removed from the study.

TITCK recommends that researchers' training and meetings be held online.

As a result, this extraordinary period we are going through gave us an opportunity to rethink our daily mediocrity, to create possibilities, and to enrich it with options. Our hope is to get through this process quickly and with minimum damage and starting from where we left our clinical studies as an instrument of our excitement for a farewell to neurological diseases such as neurodegenerative diseases, MS, stroke, epilepsy, migraine, and neuromuscular diseases.

Scientific Research and Publication in the Pandemic

As a result of the fact that clinics and laboratories have prioritized studies and research on COVID-19 during the pandemic process, many scientists began to experience difficulties in making research decisions on other issues, completing their ongoing projects, deciding to suspend or stop their projects, or international cooperation. On the other hand, many scientists turned to construct new studies compatible with the new conditions caused by the pandemic.

During this pandemic period, scientific publications have not stopped, but they undergo a transformation at least for a short period of time (290).

Organization of Scientific Research and Journals During the Pandemic Period

Due to the rapid transformation of coronavirus infection into a pandemic and high mortality rates, it is necessary to share experiences quickly, and information should be easily accessible to get the infection under control as soon as possible. Therefore, journals are implementing new regulations to guide scientific research and prioritize COVID-19-related publications.

PNAS has initiated a series of changes to ensure the rapid transmission of critical scientific findings related to the pandemic, together with more than 120 other scientific publishers, it has provided free access to coronavirus and COVID-19 research and information. With respect to COVID-19, Creative Commons (CC BY) permits commercial reuse of licensed articles, and has removed the CC BY fee of these articles (290). The Turkish Journal of Neurology is a media organ with an open access policy. It is licensed under the Creative Commons 4.0 International License. Access to and citing its articles is free of charge.

The transformation of coronavirus infections into a pandemic brought problems for healthcare organizations to face such as bed capacity, current workforce, access to tests, and procurement of protective equipment for personnel. We see publishers make invitations for research articles and case reports on these issues and organize special issues. Elsevier called for papers for a special issue of "Health Service; Journal of Science and innovations" on healthcare service presentation during the COVID-19 pandemic. Journal editors were also asked to share experiences on patient screening, ordering by emergency, telemedicine (277) for treatment, and the use of other information technologies (291). Initial statements were sharing of knowledge and experiences including the reorganization of healthcare according to the current situation, new methods in service delivery, and financial arrangements (291).

Proceedings of the National Academy of Sciences of the United States of America (PNAS) expanded and accelerated the opinions and news content in the front section regarding COVID-19 vaccine updates, coronavirus tests, and drug studies (290).

The WHO Strategic and Technical Advisory Group for Infection Risks pointed to gaps in COVID-19 studies in Lancet, March 2020. They reported that subjects such as well-defined infection and contagion periods, understanding the role of asymptomatic infection, comparative analysis of the efficacy and social validity

of different quarantine methods, clinical management, supporting standardized and evidence-based approaches for better results, randomized controlled studies for vaccines, developing animal models, and evaluating the validity of existing serological tests were open for research.

Looking at medical indexes, it is observed that more than 7000 articles have been published since December 2019 to date. According to the frequency order of these publications, they are in the following categories respectively; letters to the editor, reviews, case reports, guidelines, and a few metaanalyses and observational studies are also included in the indexes (PubMed).

It is noteworthy that international journals and publishers also make brief report calls to increase the knowledge sharing.

During the pandemic process, international medical directories have case reports and reviews accompanied by neurotrophic mechanisms of SARS-CoV-2 virus, neurolologic symptoms of the infection, smell and taste sensory impairment, cranial nerve paralysis, encephalopathy, epilepsy, vascular events, and GBS, as well as reports such as COVID-19 management or infection prevention in existing neurological disease (such as MS, NMO, MG) base (PubMed).

The neurology sub-specialty journals offer recommendations for a roadmap in monitoring the specific diseases in coronavirus pandemic (236,293,294).

Under the direction of Dr. Şerefnur Öztürk and Prof. Dr. M. Akif Topçuoğlu, the COVID-19 Commission was established with the participation of volunteer members from the Turkish Neurology Association. The Commission invites its members for collaboration in areas such as: 1- Raising the awareness of COVID-19 and its neurologic signs and symptoms in this still important process in our country; 2- Providing accurate and effective information to the field of science regarding the most frequently reported cerebrovascular disease conditions with COVID-19 and approach to the treatment; 3- Supporting and collaborating with the necessary organizations; 4- Supporting commission members who need help; 5- Creating databases and working templates to collect the most accurate data from our country; 6- Preparing informative documents and making arrangements for publication; 7- Preparing national and international research projects and participating in ongoing ones.

The planned "COVID-19 Database" will enable more reliable statistical analyses by gathering our national experience in the field of neurology in a pool instead of singular cases. It will also prevent data loss that may occur as a result of the fact that physicians whose workload is increased due to the pandemic do not have time to record their experiences.

The European Academy of Neurology (EAN) emphasizes the importance of observations of neurologists who monitor patients with COVID-19 in the ICU and inpatient services, such as the frequency and severity of neurologic symptoms, and the need for intensive care. In order to understand the biology of the disease, it emphasizes the necessity of neuropathologic examinations to assess the lower brain stem and medulla involvement in patients with suspected neuroinvasive SARS-CoV-2 infection (295,296).

Ethics Committee Approvals

Accelerating the publication process carries risks such as prematurely published research findings, creating unreal hopes in current conditions, deviating attention from steady reliable science, and increasing the dreadful number of deaths of the disease. Therefore, ethical approvals and referee evaluations should not be compromised (290).

The approval of ethics committees is required for the application of forward or backward research articles in the Turkish Journal of Neurology and international journals. For case reports, a consent form obtained from the patient or their relative is required. One hundred twenty-six ethics committees from university and education research hospitals are included in the TITCK's list of ethics committees (https://www.titck.gov.tr/dinamikmodul/84) However, the meeting periods (weekly-monthly) of the ethics committees are different from each other, and some ethics committees are not able to accept study applications because of the majority of their members are working in COVID-19 teams. In this case, researchers are required to contact ethics committees outside their own institutions.

COVID-19 Committee of Turkish Neurological Society is leading the formation of a national database. The application to the Ethics Committee for the research from this database was also made by the same commission.

Requirements for Rapid Share of the Scientific Information

In order to accelerate the control of the disease, journals issue additional special issues to enable rapid access of information. In addition, the articles are presented to the reader through "epub ahead of print" as soon as they are accepted (290,291).

In this period, referees must respond; editors and editorial staff have to be unusually flexible and creative in providing the new rapid workflow (290).

There are various practices to accelerate the publication process of texts that will contribute to the development of new treatments that will reduce the spread of the disease and save lives. It is thought that the use of the COVID-19 tag in the subject line in all internal correspondence of writers, editors, and referees will provide priority at every step of the process (290).

Although referees are asked to complete the review within 10 days, if the pandemic conditions prevent quick assessment, this period is slightly extended (290). Referees and editors should be reminded that the authors and referees may not be able to complete additional test requests before the publication, and these requests should not be requirements. Authors who are requested for post-review revision should be informed that they can reply to the referee comments within a period of 60 days, if the conditions require (290). Authors can be placed on the website of the association by asking for a title and a summary containing 100-150 words. In this way, attention can be drawn to new publications, such as EAN's breaking news or blogs in certain journals, so that those interested can be directed to the original text.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: Ş.Ö., M.A.T., K.U., Design: Ş.Ö., M.A.T., K.U., Data Collection or Processing: All authors, Analysis or Interpretation: All authors, Literature Search: All authors, Writing: All authors *etc.

*The parts of this article are brought together by M.A Topçuoğlu and K. Uluç; the unity is provided and the redaction is applied by removing the additions, repeating parts and literatures. The text is finalized by Ş. Öztürk.

SARS-CoV-2 and COVID-19: General Information, Terminology, The Process in the World and Our Country
(Füsun Ferda Erdoğan)
SARS-CoV-2 and Other Coronaviruses: What Should Neurologists Know?
(Ayşe Sağduyu Kocaman and Ali Ulvi Uca)
Prevention and Control of Transmission
(Semih Ayta ve Fettah Eren)
COVID-19: Symptoms, Findings and Potential Neurologic Effects of the Disease
(Firuze Delen and Gülşen Akman Demir)
COVID-19 and Pulmonary Involvement
(Ömer Karadaş and Esra Acıman Demirel)
COVID-19: Non-pulmonary Systemic Effects
(Türkan Acar and Özlem Kayım Yıldız)
Treatment of COVID-19: Specific Treatments
(E. Rabia Koç)
Treatment of COVID-19: Severe Patients and Intensive Care
(Ethem Murat Arsava and Tuğçe Angın Mengi)
Nutrition in The Pandemic and Nutrition in Patients with COVID-19
(Ayşe Deniz Elmalı and Erdem Yaka)
Neurologic Examinations in Patients with COVID-19
(Hakan Ekmekçi and Ufuk Ergün)
Electroencephalography in the Pandemic
(F. İrsel Tezer and Nerses Bebek)
Electromyography in the Pandemic
(Özden Şener)
COVID-19 and Neuroimaging
(Haluk Gümüş and Rana Karabudak)
COVID-19 and Headache
(Neşe Çelebisoy)
Disorders of Consciousness and Delirium in COVID-19
(Başar Bilgiç and Esen Saka Topçuoğlu)
The Management of Epilepsy in the COVID-19 Pandemic
(F. İrsel Tezer and Nerses Bebek)
The COVID-19 and Status Epilepticus
(Demet İlhan Algın, Hakan Ekmekçi and Oğuz Osman Erdinç)
COVID-19 and Neuromuscular Diseases
(Arman Çakar, Hacer Durmuş Tekçe and Yeşim Gülşen Parman)
COVID-19 and Neuroimmunologic Diseases
(Cavit Boz and Aylin Akçalı)
Neurological Effects of New Methods Used to Treat Coronavirus Disease
(Mehmet Uğur Çevik)
Stroke Management in New Coronavirus Disease
(Nazire Afşar)
Endovascular Treatment in Acute Ischemic Stroke During the New Coronavirus Disease Pandemic
(Atilla Özcan Özdemir)
New Coronavirus Disease and Neurorehabilitation
(Şevki Şahin)
Quality of Life and Stigma in the New Coronavirus Disease Period
(Rıfat Erdem Toğrol)
Telemedical Consultation and Telenourology in the Pandemic
(Demet Özbabalık Adapınar and Mehmet İlker Yön)
Clinical Research in the Pandemic Period
(Demet Özbabalık Adapınar, Aybala Neslihan Alagöz, Neşe Tuncer)
Scientific Research and Publication in the Pandemic
(Ayşe Bora Tokçaer)

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. T.C. Sağlık Bakanlığı. 14.4.2020. Available from: https://www.tjod.org/wp-content/uploads/2020/04/COVID-19_Rehberi-14.04.2020.pdf
2. Kilic AU, Kara F, Alp E, Doganay M. New threat: 2019 novel Coronavirus infection and infection control perspective in Turkey. North Clin Istanb. 2020;7:95-98.
3. Killerby ME, Biggs HM, Haynes A, et al. Human coronavirus circulation in the United States 2014-2017. J Clin Virol. 2018;101:52-56.
4. Akin L, Gözel MG. Understanding dynamics of pandemics. Turk J Med Sci. 2020;50(SI-1):515-519.
5. Killerby ME, Biggs HM, Midgley CM, Gerber SI, Watson JT. Middle East Respiratory Syndrome Coronavirus Transmission. Emerg Infect Dis 2020;26:191-198.
6. Swerdlow DL, Finelli L. Preparation for Possible Sustained Transmission of 2019 Novel Coronavirus: Lessons From Previous Epidemics. JAMA 2020;323:1129-1130.
7. Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls. Treasure Island (FL); 2020.
8. Şeker M, Özer A, Tosun Z, Korkut C, Doğrul M. TUBA-COVID-19 Pandemi Değerlendirme Raporu; 2020.
9. Qian X, Ren R, Wang Y, et al. Fighting against the common enemy of COVID-19: a practice of building a community with a shared future for mankind. Infect Dis Poverty 2020;9:34.
10. Wikipedia. Türkiye'de 2020 koronavirüs pandemisi. 2020. Available from: https:// tr.wikipedia.org/wiki/T%C3%BCrkiye%27de_COVID-19_pandemisi
11. T.C. Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. 2019-Ncov Hastalığı: Sağlık Çalışanları Rehberi. Yayın-Ocak-2020-Ulaşım 4.5.2020.
12. WorldoMeter. COVID-19 Coronavirus Pandemic. 2020.
13. Oksanen A, Kaakinen M, Latikka R, Savolainen I, Savela N, Koivula A. Regulation and Trust: 3-Month Follow-up Study on COVID-19 Mortality in 25 European Countries. JMIR Public Health Surveill. 2020;6:e19218.
14. Kamps B, Hoffmann C. COVID References Eng2020-3. Third edition 2020-3 uploaded on 23 April 2020.
15. UN-Department-of-Economic-and-Social-Affairs-Social-Inclusion. 2020. The Social Impact of COVID-19.
16. Acikgoz O, Gunay A. The early impact of the COVID-19 pandemic on the global and Turkish economy. Turk J Med Sci 2020;50:520-526.
17. Zhong NS, Zheng BJ, Li YM, et al. Epidemiology and cause of severe acute respiratory syndrome (SARS) in Guangdong, People's Republic of China, in February, 2003. Lancet 2003;362:1353-1358.

18. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med 2012;367:1814-1820.
19. Bogoch II, Watts A, Thomas-Bachli A, Huber C, Kraemer MUG, Khan K. Pneumonia of unknown aetiology in Vuhan, China: potential for international spread via commercial air travel. J Travel Med 2020;27.
20. World Health Organization (WHO). Novel Corona virüs-China Disease outbreak news: Update 12 January 2020.
21. Coronaviridae Study Group of the International Committee on Taxonomy of V. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536-544.
22. World Health Organization (WHO). Director-General's remarks at the media briefing on 2019 nCoV on 11 February 2020.
23. World Health Organization (WHO). General's opening remarks at the media briefing on COVID-19 - 11 March 2020.
24. Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Methods Mol Biol 2015;1282:1-23.
25. Masters PS. The molecular biology of coronaviruses. Adv Virüs Res 2006;66:193-292.
26. Li F. Structure, Function, and Evolution of Coronavirus Spike Proteins. Annu Rev Virol 2016;3:237-261.
27. Wertheim JO, Chu DK, Peiris JS, Kosakovsky Pond SL, Poon LL. A case for the ancient origin of coronaviruses. J Virol 2013;87:7039-7045.
28. Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. Virüses 2012;4:3044-3068.
29. Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 2019;17:181-192.
30. Woo PC, Yuen KY, Lau SK. Epidemiology of coronavirus-associated respiratory tract infections and the role of rapid diagnostic tests: a prospective study. Hong Kong Med J 2012;18 Suppl 2:22-24.
31. Rabi FA, Al Zoubi MS, Kasasbeh GA, Salameh DM, Al-Nasser AD. SARS-CoV-2 and Coronavirus Disease 2019: What We Know So Far. Pathogens 2020;9.
32. Forni D, Cagliani R, Clerici M, Sironi M. Molecular Evolution of Human Coronavirus Genomes. Trends Microbiol 2017;25:35-48.
33. Zhou P, Fan H, Lan T, et al. Fatal swine acute diarrhoea syndrome caused by an HKU2-related coronavirus of bat origin. Nature 2018;556:255-258.
34. Fan Y, Zhao K, Shi ZL, Zhou P. Bat Coronaviruses in China. Virüses 2019;11:210.
35. Rabaan AA, Al-Ahmed SH, Haque S, et al. SARS-CoV-2, SARS-CoV, and MERS-COV: A comparative overview. Infez Med 2020;28:174-184.
36. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med 2020;382:727-733.
37. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. Nat Med 2020;26:450-452.
38. Feyzioğlu B. SARS-CoV-2 Kökeni. J Biotechnol and Strategic Health Res 2020;Ozel sayi:1-9.
39. World-Health-Organization (WHO). Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. 2020.
40. Cook TM. Personal protective equipment during the coronavirus disease (COVID) 2019 pandemic - a narrative review. Anaesthesia 2020.
41. Wang H, Li X, Yan Z, Sun X, Han J, Zhang B. Potential neurological symptoms of COVID-19. Ther Adv Neurol Disord 2020;13:1-2.
42. Van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. N Engl J Med 2020;382:1564-1567.
43. World Health Organization (WHO). Rational use of personal protective equipment for coronavirus disease 2019 (COVID-19) 2020.
44. World Health Organization (WHO). Telemedicine in Member States: Opportunities and developments. Report on the second global survey on eHealth. Global Observatory for eHealth series-Volume 2, 2010.
45. Kim JM, Chung YS, Jo HJ, et al. Identification of Coronavirus Isolated from a Patient in Korea with COVID-19. Osong Public Health Res Perspect 2020;11:3-7.
46. Balazy A, Toivola M, Adhikari A, Sivasubramani SK, Reponen T, Grinshpun SA. Do N95 respirators provide 95% protection level against airborne viruses, and how adequate are surgical masks? Am J Infect Control 2006;34:51-57.
47. Qian Y, Willeke K, Grinshpun SA, Donnelly J, Coffey CC. Performance of N95 respirators: filtration efficiency for airborne microbial and inert particles. Am Ind Hyg Assoc J 1998;59:128-132.
48. Beckman S, Materna B, Goldmacher S, et al. Evaluation of respiratory protection programs and practices in California hospitals during the 2009-2010 H1N1 influenza pandemic. Am J Infect Control 2013;41:1024-1031.
49. T.C. Sağlık Bakanlığı. Covıd-19 Hastalığına Yönelik Sağlık Kuruluşu, Personel Ve Faaliyet Türüne Göre Kullanılması Önerilen Koruyucu Ekipmanlar.
50. PHAC-the-Public-Health-Agency-of-Canada. Community-based measures to mitigate the spread of coronavirus disease (COVID-19) in Canada. 2020.
51. Pascarella G, Strumia A, Piliego C, et al. COVID-19 diagnosis and management: a comprehensive review. J Intern Med 2020.
52. Lauer SA, Grantz KH, Bi Q, et al. The Incubation Period of Coronavirus Disease 2019 (COVID-19). From Publicly Reported Confirmed Cases: Estimation and Application. Ann Intern Med 2020.
53. Guan WJ, Ni ZY, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720.
54. Jin H HC, Chen S, Zhou Y, Wang Y, Mao L, et al. Consensus for prevention and management of coronavirus disease 2019 (COVID-19) for neurologists Stroke & Vascular Neurology 2020.
55. Rothe C, Schunk M, Sothmann P, et al. Transmission of 2019-nCoV Infection from an Asymptomatic Contact in Germany. N Engl J Med 2020;382:970- 971.
56. Lan L, Xu D, Ye G, et al. Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA 2020.
57. Li T, Lu H, Zhang W. Clinical observation and management of COVID-19 patients. Emerg Microbes Infect 2020;9:687-690.
58. To KF, Tong JH, Chan PK, et al. Tissue and cellular tropism of the coronavirus associated with severe acute respiratory syndrome: an in-situ hybridization study of fatal cases. J Pathol 2004;202:157-163.
59. Ozturk S. COVID-19 ve Nöroloji. Turk J Neurol 2020. DOI:10.4274/tnd.galenos.2020.73384
60. Mao L, Wang M, Chen S, et al. Neurological Manifestations of Hospitalized Patients with COVID-19 in Vuhan, China: a retrospective case series study. medRxiv 2020.
61. Wang D, Hu B, Hu C, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Vuhan, China. JAMA 2020;323:1061-1069.
62. Lau KK, Yu WC, Chu CM, Lau ST, Sheng B, Yuen KY. Possible central nervous system infection by SARS coronavirus. Emerg Infect Dis 2004;10:342-344.
63. Moriguchi T, Harii N, Goto J, et al. A first case of meningitis/encephalitis associated with SARS-Coronavirus-2. Int J Infect Dis 2020;94:55-58.
64. Baig AM. Neurological manifestations in COVID-19 caused by SARS-CoV-2. CNS Neurosci Ther 2020;26:499-501.
65. Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features. Radiology 2020;296:E119-E120.
66. Giacomelli A, Pezzati L, Conti F, et al. Self-reported olfactory and taste disorders in SARS-CoV-2 patients: a cross-sectional study. Clin Infect Dis 2020.
67. Alberti P, Beretta S, Piatti M, et al. Guillain-Barre syndrome related to COVID-19 infection. Neurol Neuroimmunol Neuroinflamm 2020;7:e741.
68. Camdessanche JP, Morel J, Pozzetto B, Paul S, Tholance Y, Botelho-Nevers E. COVID-19 may induce Guillain-Barré syndrome. Rev Neurol (Paris). 2020;176:516-518.
69. Virani A, Rabold E, Hanson T, et al. Guillain-Barre Syndrome associated with SARS-CoV-2 infection. IDCases 2020:e00771.
70. Zhao H, Shen D, Zhou H, Liu J, Chen S. Guillain-Barre syndrome associated with SARS-CoV-2 infection: causality or coincidence? Lancet Neurol 2020;19:383-384.
71. Gutierrez-Ortiz C, Mendez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19. Neurology 2020. DOI: 10.1212/WNL.0000000000009619

72. Zhao K HJ, Dai D, Feng Y, Liu L, Nie S. Acute Myelitis After SARS-CoV-2 Infection: A Case Report. medRxiv 2020;2020:20035105.
73. Wei H, Yin H, Huang M, Guo Z. The 2019 novel cornoavirüs pneumonia with onset of oculomotor nerve palsy: a case study. J Neurol 2020;267:1550-1553.
74. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020:1239-1242.
75. Xie J, Tong Z, Guan X, Du B, Qiu H, Slutsky AS. Critical care crisis and some recommendations during the COVID-19 epidemic in China. Intensive Care Med 2020;46:837-840.
76. Jiang F, Deng L, Zhang L, Cai Y, Cheung CW, Xia Z. Review of the Clinical Characteristics of Coronavirus Disease 2019 (COVID-19). J Gen Intern Med 2020;35:1545-1549.
77. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020;368:m1091.
78. Duffin J. Functional organization of respiratory neurones: a brief review of current questions and speculations. Exp Physiol 2004;89:517-529.
79. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020;92:552-555.
80. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. JAMA 2020;323:1488-1494.
81. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Vuhan, China. Lancet 2020;395:497-506.
82. Bernheim A, Mei X, Huang M, et al. Chest CT Findings in Coronavirus Disease-19 (COVID-19): Relationship to Duration of Infection. Radiology 2020:200463. DOI: 10.1148/radiol.2020200463
83. Kanne JP, Little BP, Chung JH, Elicker BM, Ketai LH. Essentials for Radiologists on COVID-19: An Update-Radiology Scientific Expert Panel. Radiology 2020;296:E113-E114.
84. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. J Autoimmun 2020;109:102433.
85. Feng Y, Ling Y, Bai T, et al. COVID-19 with Different Severities: A Multicenter Study of Clinical Features. Am J Respir Crit Care Med 2020;201:1380-1388.
86. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Vuhan, China: a descriptive study. Lancet Infect Dis 2020;20:425-434.
87. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.
88. Pan F, Ye T, Sun P, et al. Time Course of Lung Changes at Chest CT during Recovery from Coronavirus Disease 2019 (COVID-19). Radiology 2020;295:715-721.
89. Fan N, Fan W, Li Z, Shi M, Liang Y. Imaging characteristics of initial chest computed tomography and clinical manifestations of patients with COVID-19 pneumonia. Jpn J Radiol 2020;38:533-538.
90. Liu C, Wu C, Zheng X, et al. Clinical features and multidisciplinary treatment outcome of COVID-19 pneumonia: A report of three cases. J Formos Med Assoc 2020;S0929-6646(20)30144-3.
91. World Health Organization (WHO). Clinical management of severe acute respiratory infection when Novel coronavirus (2019-nCoV) infection is suspected: Interim Guidance. 2020.
92. Driggin E, Madhavan MV, Bikdeli B, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic. J Am Coll Cardiol 2020;75:2352-2371.
93. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Vuhan, China: a descriptive study. Lancet 2020;395:507-513.
94. Jin X, Lian JS, Hu JH, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020;69:1002-1009.
95. Lin L, Jiang X, Zhang Z, et al. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut 2020;69:997-1001.
96. Xiao F, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology 2020;158:1831-1833.
97. Ong J, Young BE, Ong S. COVID-19 in gastroenterology: a clinical perspective. Gut 2020;69:1144-1145.
98. International MG/COVID-19 Working Group, Jacob S, Muppidi S, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020;412:116803.
99. Gu J, Han B, Wang J. COVID-19: Gastrointestinal Manifestations and Potential Fecal-Oral Transmission. Gastroenterology 2020;158:1518-1519.
100. Holshue ML, DeBolt C, Lindquist S, et al. First Case of 2019 Novel Coronavirus in the United States. N Engl J Med 2020;382:929-936.
101. Xu XW, Wu XX, Jiang XG, et al. Clinical findings in a group of patients infected with the 2019 novel coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.
102. Feng G, Zheng KI, Yan QQ, et al. COVID-19 and Liver Dysfunction: Current Insights and Emergent Therapeutic Strategies. J Clin Transl Hepatol 2020;8:18-24.
103. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-422.
104. Qin C, Zhou L, Hu Z, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020;ciaa248. DOI:10.1093/cid/ciaa248
105. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:1-11.
106. Terpos E, Ntanasis-Stathopoulos I, Elalamy I, et al. Hematological findings and complications of COVID-19. Am J Hematol 2020;95:834-847.
107. Klok FA, Kruip MJHA, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. Thromb Res 2020;191:145-147.
108. Spiezia L, Boscolo A, Poletto F, et al. COVID-19-Related Severe Hypercoagulability in Patients Admitted to Intensive Care Unit for Acute Respiratory Failure. Thromb Haemost 2020;120:998-1000.
109. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: A meta-analysis. Clin Chim Acta 2020;506:145-148.
110. Keyaerts E, Li S, Vijgen L, et al. Antiviral activity of chloroquine against human coronavirus OC43 infection in newborn mice. Antimicrob Agents Chemother 2009;53:3416-3421.
111. Cortegiani A, Ingoglia G, Ippolito M, Giarratano A, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. J Crit Care 2020;57:279-283.
112. US Food and Drug Administration (FDA). 2020. Available from: https://www.fda.gov/media/136534/download
113. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Clin Infect Dis DOI:10.1093/cid/ciaa478
114. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents DOI:10.1016/j.ijantimicag.2020.105949
115. Cai Q, Yang M, Liu D, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study Engineering (Beijing) DOI:10.1016/j.eng.2020.03.007
116. Lescure FX, Bouadma L, Nguyen D, et al. Clinical and virological data of the first cases of COVID-19 in Europe: a case series. Lancet Infect Dis 2020;20:697-706.
117. Cao YC, Deng QX, Dai SX. Remdesivir for severe acute respiratory syndrome coronavirus 2 causing COVID-19: An evaluation of the evidence. Travel Med Infect Dis 2020;35:101647.
118. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020;382:1787-1799.
119. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. Life Sci 2020;248:117477.
120. T.C. Sağlık B akanlığı Sağlık Hizmetleri Genel Müdürlüğü. COVID-19 İmmün (Konvalesan) Plazma Tedarik Ve Klinik Kullanım Rehber. 2020.

Available from: https:// dosyamerkez.saglik.gov.tr/Eklenti/37320,covid-19-immun- plazma-tedarik-ve-klinik-kullanim-rehberi-r1-v1pdf.pdf?0&_tag1=F8E6A66A629175DA4A99810BDF399C485F1A9375

121. Kim E, Erdos G, Huang S, et al. Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. EBioMedicine 2020;55:102743.
122. Ozdemir C, Kucuksezer UC, Tamay ZU. Is BCG vaccination affecting the spread and severity of COVID-19?. Allergy 2020;75:1824-1827.
123. Miller A, Reandelar MJ, Fasciglione K, Roumenova V, Li Y, Otazu GH. Correlation between universal BCG vaccination policy and reduced morbidity and mortality for COVID-19: an epidemiological study. medRxiv 2020. doi: https://doi.org/10.1101/2020.03.24.20042937
124. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med 2020;8:506-517.
125. Murthy S, Gomersall CD, Fowler RA. Care for Critically Ill Patients With COVID-19. JAMA 2020. doi:10.1001/jama.2020.3633
126. Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). Intensive Care Med 2020;46:854-887.
127. Ai T, Yang Z, Hou H, et al. Correlation of Chest CT and RT-PCR Testing for Coronavirus Disease 2019 (COVID-19) in China: A Report of 1014 Cases. Radiology. 2020;296:E32-E40.
128. Dong X, Cao YY, Lu XX, et al. Eleven faces of coronavirus disease 2019. Allergy 2020;75:1699-1709.
129. Halacli B, Kaya A, Topeli A. Critically-ill COVID-19 patient. Turk J Med Sci 2020;50(Suppl 1)585-591.
130. Soldati G, Smargiassi A, Inchingolo R, et al. Is There a Role for Lung Ultrasound During the COVID-19 Pandemic?. J Ultrasound Med 2020;39:1459-1462.
131. Li L, Li R, Wu Z, et al. Therapeutic strategies for critically ill patients with COVID-19. Ann Intensive Care 2020;10:45.
132. Zhou D, Dai SM, Tong Q. COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. J Antimicrob Chemother 2020;75:1667-1670.
133. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. medRxiv 2020.
134. Borba MGS, Val FFA, Sampaio VS, et al. Effect of High vs Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized With Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection: A Randomized Clinical Trial. JAMA Netw Open 2020;3:e208857.
135. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discov Ther 2020;14:58-60.
136. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-1034.
137. Wang Y, Jiang W, He Q, et al. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther 2020;5:57.
138. Werdan K, Pilz G, Bujdoso O, et al. Score-based immunoglobulin G therapy of patients with sepsis: the SBITS study. Crit Care Med 2007;35:2693-2701.
139. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. Am J Emerg Med 2018;36:226-233.
140. Respiratory-Therapy-Group. Expert Consensus on Respiratory Therapy Related to New Coronavirus Infection in Severe and Critical Patients Chinese Journal of Tuberculosis and Respiratory Medicine 2020; 17: E020-E.
141. Wu CN, Xia LZ, Li KH, et al. High-flow nasal-oxygenation-assisted fibreoptic tracheal intubation in critically ill patients with COVID-19 pneumonia: a prospective randomised controlled trial. Br J Anaesth 2020;125:e166-e168.
142. Wahidi MM, Lamb C, Murgu S, et al. American Association for Bronchology and Interventional Pulmonology (AABIP) Statement on the Use of Bronchoscopy and Respiratory Specimen Collection in Patients with Suspected or Confirmed COVID-19 Infection. J Bronchology Interv Pulmonol 2020. doi:10.1097/LBR.0000000000000681
143. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020;46:1099-1102.
144. Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? Crit Care 2020;24:154.
145. Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello
D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med 2020;201:1299-1300.
146. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol 2020;17:259-260.
147. Muscogiuri G, Barrea L, Savastano S, Colao A. Nutritional recommendations for CoVID-19 quarantine. Eur J Clin Nutr 2020;74:850-851.
148. Joob B, Wiwanitkit V. COVID-19, School Closings, and Weight Gain. Obesity (Silver Spring) 2020;28:1006.
149. Dunn CG, Kenney E, Fleischhacker SE, Bleich SN. Feeding Low-Income Children during the Covid-19 Pandemic. N Engl J Med 2020;382:e40.
150. Barazzoni R, Bischoff SC, Breda J, et al. ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr 2020;39:1631-1638.
151. Reyes L, Arvelo W, Estevez A, et al. Population-based surveillance for 2009 pandemic influenza A (H1N1) virus in Guatemala, 2009. Influenza Other Respir Viruses 2020;4:129-140.
152. Calder PC. Feeding the immune system. Proc Nutr Soc 2013;72:299-309.
153. World Health Organization (WHO). 2020. Available from: http://www.emro.who.int/nutrition/nutrition-infocus/nutrition-advice-for-adults-during-the-covid-19-outbreak.html
154. Gomes F, Schuetz P, Bounoure L, et al. ESPEN guidelines on nutritional support for polymorbid internal medicine patients. Clin Nutr 2018;37:336-353.
155. Caccialanza R, Laviano A, Lobascio F, et al. Early nutritional supplementation in non-critically ill patients hospitalized for the 2019 novel coronavirus disease (COVID-19): Rationale and feasibility of a shared pragmatic protocol. Nutrition 2020;74:110835.
156. Reeves A, White H, Sosnowski K, Tran K, Jones M, Palmer M. Energy and protein intakes of hospitalised patients with acute respiratory failure receiving non-invasive ventilation. Clin Nutr 2014;33:1068-1073.
157. Leder SB, Siner JM, Bizzarro MJ, McGinley BM, Lefton-Greif MA. Oral Alimentation in Neonatal and Adult Populations Requiring High-Flow Oxygen via Nasal Cannula. Dysphagia 2016;31:154-159.
158. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. Clin Nutr 2019;38:48-79.
159. Bertran Recasens B, Martinez-Llorens JM, Rodriguez-Sevilla JJ, Rubio MA. Lack of dyspnea in patients with Covid-19: another neurological conundrum? Eur J Neurol 2020. DOI:10.1111/ene.14265
160. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. N Engl J Med 2020;382:2268-2270.
161. Natoli S, Oliveira V, Calabresi P, Maia LF, Pisani A. Does SARS-Cov-2 invade the brain? Translational lessons from animal models. Eur J Neurol 2020. DOI:10.1111/ene.14277
162. Toscano G, Palmerini F, Ravaglia S, et al. Guillain-Barre Syndrome Associated with SARS-CoV-2. N Engl J Med 2020;382:2574-2576.
163. Yin R, Feng W, Wang T, et al. Concomitant neurological symptoms observed in a patient diagnosed with coronavirus disease 2019. J Med Virol 2020. doi:10.1002/jmv.25888
164. National Health Commission tate Administration of Traditional Chinese Medicine. Diagnosis and treatment of COVID-19 (trial version 6). 2020. Available from: http://en.nhc.gov.cn/search.html?searchText=Diagnosis+and+treatment+of+COVID-19+%28trial+version+6%29
165. Shellhaas RA. Neurologists and COVID-19: A note on courage in a time of uncertainty. Neurology 2020;94:855-857.
166. American Clinical Neurophysiology Society. COVID-19 Resources. 2020. Available from: https://www.acns.org/practice/covid-19-resources
167. Haines S, Caccamo A, Chan F, Gupta P. Practical Considerations When Performing Neurodiagnostic Studies on Patients with COVID-19 and Other Highly Contagious Diseases. Available from: https://www.acns.

org/UserFiles/file/ASET_PracticalConsiderationsWhenPerforming NeurodiagnosticStudiesonPatientswithCOVID.pdf
168. Müller KI, Alstadhaug KB, Bekkelund SI. Telemedicine in the management of non-acute headaches: A prospective, open-labelled non-inferiority, randomised clinical trial. Cephalalgia 2017;37:855-863.
169. Westover MB, Gururangan K, Markert MS, et al. Diagnostic Value of Electroencephalography with Ten Electrodes in Critically Ill Patients. Neurocrit Care 2020. doi:10.1007/s12028-019-00911-4
170. American Association of Neuromuscular Electrodiagnostic Medicine (AANEM). 2020. Available from: https://www.aanem.org/getmedia/88faf677-8043-4ad3-ad0d-42c0cdd1dabe/Guidance-for-EMG-studies-during-COVIDpdf
171. Hacettepe Üniversitesi Tıp-Fakültesi Nöroloji AD EMG Birimi. Hacettepe Pandemi Döneminde EMG Laboratuvarında Çalışma Kılavuzu. 2020. Available from: https://www.noroloji.org.tr/TNDData/Uploads/files/hacettepe%20emg.pdf
172. Kocasoy Orhan E. İstanbul Üniversitesi İstanbul Tıp Fakültesi Nöroloji Anabilim Dalı Elektromiyografi Laboratuvarı'nda kullanılan "Pandemide EMG İncelemesi Sırasında Dikkat Edilmesi Gereken Adımlar". 2020. Available from: https://www.noroloji.org.tr/TNDData/Uploads/files/PANDEM%C4%B0DE%20EMG%20KURALLARI(1).docx
173. Liu Y, Ning Z, Chen Y, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. Nature 2020;582:557-560.
174. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA Neurol 2020;77:1-9.
175. Liu K, Pan M, Xiao Z, Xu X. Neurological manifestations of the coronavirus (SARS-CoV-2) pandemic 2019-2020. J Neurol Neurosurg Psychiatry 2020;91:669-670.
176. Zhou B, She J, Wang Y, Ma X. A Case of Coronavirus Disease 2019 With Concomitant Acute Cerebral Infarction and Deep Vein Thrombosis. Front Neurol 2020;11:296.
177. Rossi A. Imaging of acute disseminated encephalomyelitis. Neuroimaging Clin N Am 2008;18:149-161.
178. Wong AM, Simon EM, Zimmerman RA, Wang HS, Toh CH, Ng SH. Acute necrotizing encephalopathy of childhood: correlation of MR findings and clinical outcome. AJNR Am J Neuroradiol 2006;27:1919-1923.
179. Li Y, Wang M, Zhou Y, et al. Acute Cerebrovascular Disease Following COVID-19: A Single Center, Retrospective, Observational Study. SSRN Electronic Journal 2020.
180. Sharifi-Razavi A, Karimi N, Rouhani N. COVID-19 and intracerebral haemorrhage: causative or coincidental? New Microbes New Infect 2020;35:100669.
181. Birbeck GL, French JA, Perucca E, et al. Antiepileptic drug selection for people with HIV/AIDS: evidence-based guidelines from the ILAE and AAN. Epilepsia 2012;53:207-214.
182. Zhang T, Rodricks MB, Hirsh E. COVID-19-Associated Acute Disseminated Encephalomyelitis: A Case Report. medRxiv 2020.
183. Zhu J, Ji P, Pang J, et al. Clinical characteristics of 3062 COVID-19 patients: A meta-analysis. J Med Virol 2020. DOI:10.1002/jmv.25884
184. Borges do Nascimento IJ, Cacic N, Abdulazeem HM, et al. Novel Coronavirus Infection (COVID-19) in Humans: A Scoping Review and Meta-Analysis. J Clin Med 2020;9.
185. Collaborators GBDH. Global, regional, and national burden of migraine and tension-type headache, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:954-976.
186. Science alert. Updated: WHO Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms. Available from: https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms
187. FDA. FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19
188. Centers for Disease Control and Prevention (CDC). 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
189. Halker RB, Starling AJ, Vargas BB, Schwedt TJ. ACE and ARB Agents in the Prophylactic Therapy of Migraine—How Effective Are They? Curr Treat Options Neurol 2016;18:15.
190. Bozkurt B, Kovacs R, Harrington B. Joint HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. J Card Fail 2020;26:370.
191. Szperka CL, Ailani J, Barmherzig R, et al. Migraine Care in the Era of COVID-19: Clinical Pearls and Plea to Insurers. Headache 2020;60:833-842.
192. Wu Y, Xu X, Chen Z, et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 2020;S0889- 1591.
193. British Geriatrics Society European Delirium Association Old Age Psychiatry Faculty (Royal College of Psychiatrists). Coronavirus: Managing delirium in confirmed and suspected cases. BGS 2020 Available from: https://www.bgs.org.uk/resources/coronavirus-managing-delirium-in-confirmed-and-suspected-cases
194. Hoffmann C. Available from: https://amedeo.com/CovidReference02_fr.pdf
195. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: A systematic review. J Neurol Sci 2020;413:116832.
196. Aktoz M, Altay H, Aslanger E, et al. [Consensus Report from Turkish Society of Cardiology: COVID-19 and Cardiovascular Diseases. What cardiologists should know. (25th March 2020)]. Turk Kardiyol Dern Ars 2020;48(Suppl 1):1-48.
197. The-Liverpool-Drug-Interaction-Group. Detailed recommendations for interactions with experimental COVID-19 therapies. 2020. https://www.covid19-druginteractions.org/
198. Das G, Mukherjee N, Ghosh S. Neurological Insights of COVID-19 Pandemic. ACS Chem Neurosci 2020;11:1206-1209.
199. Clay PG, Adams MM. Pseudo-Parkinson disease secondary to ritonavir-buspirone interaction. Ann Pharmacother 2003;37:202-205.
200. Kelly DV, Béïque LC, Bowmer MI. Extrapyramidal symptoms with ritonavir/indinavir plus risperidone. Ann Pharmacother 2002;36:827-830.
201. Caparros-Lefebvre D, Lannuzel A, Tiberghien F, Strobel M. Protease inhibitors enhance levodopa effects in Parkinson's disease. Mov Disord 1999;14:535.
202. Şimşek YS, Ünal S. Antiviral treatment of COVID-19. Turk J Med Sci 2020;50(Suppl 1):611-619.
203. Tufan A, Avanoğlu Güler A, Matucci-Cerinic M. COVID-19, immune system response, hyperinflammation and repurposing antirheumatic drugs. Turk J Med Sci 2020;50(Suppl 1):620-632.
204. Hoffmann G, Funk C, Fowler S, et al. Nonclinical pharmacokinetics of oseltamivir and oseltamivir carboxylate in the central nervous system. Antimicrob Agents Chemother 2009;53:4753-4761.
205. Gonzalez Martinez A, Romero Palacián D, Dotor García Soto J, Sánchez P, Reig Roselló G, Zapata Wainberg G. Tocilizumab-Associated Reversible Cerebral Vasoconstriction: A Case Report. Headache 2019;59:259-263.
206. Jewell P, Ansorge O, Kuker W, Irani SR, Zamboni G. Tocilizumab-associated multifocal cerebral thrombotic microangiopathy. Neurol Clin Pract 2016;6:e24-e26.
207. Karimi N, Razavi AS, Rouhani S. Frequent Convulsive Seizures in an Adult Patient with COVID-19: A Case Report. Iran Red Crescent Med J 2020;22:e102828.
208. Han DH, Kim SY, Lee NM, et al. Seasonal distribution of febrile seizure and the relationship with respiratory and enteric viruses in Korean children based on nationwide registry data. Seizure 2019;73:9-13.
209. Holohan M. Nearly a week after COVID-19 diagnosis, 1-year-old is recovering, 'happy'. Today 2020. https://www.today.com/health/kids-coronavirus-1-year-old-recovering-after-covid-19-diagnosis-t177203
210. Lu L, Xiong W, Liu D, et al. New onset acute symptomatic seizure and risk factors in coronavirus disease 2019: A retrospective multicenter study. Epilepsia 2020;61:e49-e53.
211. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. Int J Infect Dis 2014;29:301-306.
212. Filatov A, Sharma P, Hindi F, Espinosa PS. Neurological Complications of Coronavirus Disease (COVID-19): Encephalopathy. Cureus 2020;12:e7352.

213. French JA, Brodie MJ, Caraballo R, et al. Keeping people with epilepsy safe during the Covid-19 pandemic. Neurology 2020;94(23):1032-1037.
214. T.C. Sağlık Bakanlığı Kamu Hastaneleri Genel Müdürlüğü Tedarik Planlama Stok ve Lojistik Yönetimi Dairesi Başkanlığı. COVID-19 Tedavisinde Kullanılan İlaçlar İlaç Etkileşimleri.
215. Patsalos PN, Berry DJ, Bourgeois BF, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49:1239-1276.
216. Sharma K, Tengsupakul S, Sanchez O, Phaltas R, Maertens P. Guillain-Barré syndrome with unilateral peripheral facial and bulbar palsy in a child: A case report. SAGE Open Med Case Rep 2019;7:2050313X19838750.
217. Kim JE, Heo JH, Kim HO, et al. Neurological Complications during Treatment of Middle East Respiratory Syndrome. J Clin Neurol 2017;13:227-233.
218. Padroni M, Mastrangelo V, Asioli GM, et al. Guillain-Barré syndrome following COVID-19: new infection, old complication? J Neurol 2020;267:1877-1879.
219. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21:335-337.
220. Guidon AC, Amato A. COVID-19 and neuromuscular disorders. Neurology 2020;94:959-969.
221. Rajabally YA, Goedee HS, Attarian S, Hartung HP. Management challenges for chronic dysimmune neuropathies during the COVID-19 pandemic. Muscle Nerve 2020;62:34-40.
222. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. N Engl J Med 2020;382:1969-1973.
223. Benveniste O, Longuet P, Duval X, Le Moing V, Leport C, Vildé JL. Two episodes of acute renal failure, rhabdomyolysis, and severe hepatitis in an AIDS patient successively treated with ritonavir and indinavir. Clin Infect Dis 1999;28:1180-1181.
224. Estes ML, Ewing-Wilson D, Chou SM, et al. Chloroquine neuromyotoxicity. Clinical and pathologic perspective. 1987;82:447-455.
225. Jallouli M, Saadoun D, Eymard B, et al. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. J Neurol 2012; 259:1290-1297.
226. Gummi RR, Kukulka NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbations of myasthenia gravis. Muscle Nerve 2019; 60:693-699.
227. Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020;76:233-235.
228. Novi G, Mikulska M, Briano F, et al. COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role? Mult Scler Relat Disord 2020;42:102120.
229. Markus HS, Brainin M. COVID-19 and stroke-A global World Stroke Organization perspective. Int J Stroke 2020;15:361-364.
230. Bersano A, Bornstein, N. Stroke Care at the Time of COVID-19 Outbreak. Eanpages 2020. Available from: https://www.eanpages.org/2020/04/17/stroke-care-at-the-time-of-covid-19-outbreak/
231. Lyden P. Temporary Emergency Guidance to US Stroke Centers During the COVID-19 Pandemic. Stroke 2020.
232. Oxley TJ, Mocco J, Majidi S, et al. Large-Vessel Stroke as a Presenting Feature of Covid-19 in the Young. N Engl J Med 2020;382:e60.
233. Smith EE, Mountain A, Hill MD, et al. Canadian Stroke Best Practice Guidance During the COVID-19 Pandemic. Can J Neurol Sci 2020;47:474-478.
234. Khosravani H, Rajendram P, Notario L, Chapman MG, Menon BK. Protected Code Stroke Hyperacute Stroke Management During the Coronavirus Disease 2019 (COVID-19) Pandemic. Stroke 2020;51:1891-1895.
235. Baracchini C, Pieroni A, Viaro F, et al. Acute stroke management pathway during Coronavirus-19 pandemic. Neurol Sci 2020;41:1003-1005.
236. Topçuoğlu M, Arsava EM, Özdemir AÖ. Acute Ischemıc Stroke Treatment in COVID-19 pandemıa: Expert Opinion. Türk Beyin Damar Hast Der 2020;26:91-94.
237. Desai SM, Tonetti DA, Molyneaux BJ, et al. Interaction between time, ASPECTS, and clinical mismatch. J Neurointerv Surg 2020. DOI:10.1136/neurintsurg-2020-015921
238. Aggour M, White P, Kulcsar Z, Fiehler J, Brouwer P. European Society of Minimally Invasive Neurological Therapy (ESMINT) recommendations for optimal interventional neurovascular management in the covid-19 era. J Neurointerv Surg 2020;12:542-544.
239. Fraser JF, Arthur AS, Chen M, et al. Society of NeuroInterventional Surgery recommendations for the care of emergent neurointerventional patients in the setting of covid-19. J Neurointerv Surg 2020;12:539-541.
240. Nguyen TN, Abdalkader M, Jovin TG, et al. Mechanical Thrombectomy in the Era of the COVID-19 Pandemic: Emergency Preparedness for Neuroscience Teams: A Guidance Statement From the Society of Vascular and Interventional Neurology. Stroke 2020;51:1896-1901.
241. Dimitrijevic MR. Outline of restorative neurology: definition, clinical practice, assessment, intervention. Clin Neurol Neurosurg 2012;114:428-431.
242. Bartolo M, Intiso D, Lentino C, et al. Urgent Measures for the Containment of the Coronavirus (Covid-19) Epidemic in the Neurorehabilitation/Rehabilitation Departments in the Phase of Maximum Expansion of the Epidemic. Front Neurol 2020;11:423.
243. World Health Organization (WHO). 2020. Available from: https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
244. Duff WRD, Andrushko JW, Renshaw DW, et al. Impact of Pilates Exercise in Multiple Sclerosis A Randomized Controlled Trial. Int J MS Care 2018;20:92-100.
245. Kalb R, Brown TR, Coote S, et al. Exercise and lifestyle physical activity recommendations for people with multiple sclerosis throughout the disease course. Mult Scler 2020:1352458520915629.
246. Coronado RA, Albers HE, Allen JL, et al. Pain-Reducing Effects of Physical Therapist-Delivered Interventions: A Systematic Review of Randomized Trials Among Older Adults With Dementia. J Geriatr Phys Ther 2020;43:159-169.
247. Marx KA, Scott JB, Piersol CV, Gitlin LN. Tailored Activities to Reduce Neuropsychiatric Behaviors in Persons With Dementia: Case Report. Am J Occup Ther 2019;73: 7302205160p1-7302205160p9.
248. Hsu TJ, Tsai HT, Hwang AC, Chen LY, Chen LK. Predictors of non-pharmacological intervention effect on cognitive function and behavioral and psychological symptoms of older people with dementia. Geriatr Gerontol Int 2017;(Suppl 1):28-35.
249. Trabucchi M, De Leo D. Nursing homes or besieged castles: COVID-19 in northern Italy. Lancet Psychiatry 2020;7:387-388.
250. Lee KH, Kim JM, Kim HS. Back Extensor Strengthening Exercise and Backpack Wearing Treatment for Camptocormia in Parkinson's Disease: A Retrospective Pilot Study. Ann Rehabil Med 2017;41:667-685.
251. Devlin K, Alshaikh JT, Pantelyat A. Music Therapy and Music-Based Interventions for Movement Disorders. Curr Neurol Neurosci Rep 2019;19:83.
252. Gelaw AY, Janakiraman B, Gebremeskel BF, Ravichandran H. Effectiveness of Home-based rehabilitation in improving physical function of persons with Stroke and other physical disability: A systematic review of randomized controlled trials. J Stroke Cerebrovasc Dis 2020;104800.
253. World Health Organization (WHO). Coronavirus disease 2019 (COVID-19) Situation Report - 35. 2020. Available from: https://www.who.int/doc s/default- ource/coronaviruse/situation-reports/20200224-sitrep-35- covid-19.pdf?sfvrsn=1ac4218d_2
254. CDC. Reducing Stigma 2020. Available from: https://www.cdc.gov/coronavirus/2019-ncov/daily-life-coping/reducing-stigma.html
255. Devakumar D, Shannon G, Bhopal SS, Abubakar I. Racism and discrimination in COVID-19 responses. Lancet 2020;395:1194.
256. Lum M. Covid-19: Stop the stigma and stereotyping of coronavirus sufferers. 2020. Available from: https://www.thestar.com.my/lifestyle/health/2020/03/17/fighting-against-the-stigma-of-covid-19
257. World Health Organization (WHO). Managing Ethical Issues in Infectious Disease Outbreaks. 2016. Available from: https://www.who.int/ethics/publications/infectious-disease-outbreaks/en/

258. NYS Workgroup on Ventilator Allocation in an Influenza Pandemic. Allocation of ventilators in an influenza pandemic: Planning document. New York State Task Force on Life and the Law. 2007. Available from: https://www.cidrap.umn.edu/sites/default/files/public/php/196/196_guidance.pdf
259. New York State Task Force on Life and the Law. Ventilator allocation guidelines. 2015. Available from: https://www.health.ny.gov/regulations/task_force/reports_publications/docs/ventilator_guidelines.pdf
260. World Health Organization (WHO). 2020. Available from: https://www.who.int/publications-detail/disability-considerations-during-the-covid-19-outbreak
261. General-Medical-Council. Utils pour les personnes de 70 ans et plus et leurs proches (Tools for people aged 70 and over and caregivers). 2020. Available from: https://cmha.ca/blogs/tools-for-people-aged-70-and-over- and-caregivers
262. General Medical Council. Joint statement: Supporting doctors in the event of a Covid-19 epidemic in the UK. 2020. Available from: gmc-uk.org/news/news-archive/supporting-doctors-in-the-event-of-a-covid19-epidemic-in-the-uk
263. Craig J, Patterson V. Introduction to the practice of telemedicine. J Telemed Telecare 2005;11:3-9.
264. Ranschaert ER, Binkhuysen FH. Erratum to: European Teleradiology now and in the future: results of an online survey. 2013;4:399.
265. Ekeland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: A systematic review of reviews. Int J Med Inform 2010;79:736-771.
266. Vo A, Shore J, Waugh M, et al. Meaningful use: a national framework for integrated telemedicine. Telemed J E Health 2015;21:355-363.
267. Kamphof I. A Modest Art: Securing Privacy in Technologically Mediated Homecare. Found Sci 2017;22:411-419.
268. American Academy of Neurology (AAN). TELENEUROLOGY AND COVID-19. 2020. Available from: https://www.aan.com/tools-and-resources/ practicing-neurologists-administrators/telemedicine-and-remote-care/
269. Awadallah M, Janssen F, Körber B, Breuer L, Scibor M, Handschu R. Telemedicine in General Neurology: Interrater Reliability of Clinical Neurological Examination Via Audio-Visual Telemedicine. Eur Neurol 2018;80:289-294.
270. Timpano F, Bonanno L, Bramanti A, et al. Tele-Health and neurology: what is possible? Neurol Sci 2013;34:2263-2270.
271. Ciemins EL, Holloway B, Coon PJ, McClosky-Armstrong T, Min SJ. Telemedicine and the mini-mental state examination: assessment from a distance. Telemed J E Health 2009;15:476-478.
272. Hatcher-Martin JM, Adams JL, Anderson ER, et al. Telemedicine in neurology: Telemedicine Work Group of the American Academy of Neurology update. Neurology 2020;94:30-38.
273. Stubberud A, Linde M. Digital Technology and Mobile Health in Behavioral Migraine Therapy: a Narrative Review. Curr Pain Headache Rep 2018;22:66.
274. Moyle W. The promise of technology in the future of dementia care. Nat Rev Neurol 2019;15:353-359.
275. Grosch MC, Weiner MF, Hynan LS, Shore J, Cullum CM. Video teleconference-based neurocognitive screening in geropsychiatry. Psychiatry Res 2015;225:734-735.
276. Mantani A, Kato T, Furukawa TA, et al. Smartphone Cognitive Behavioral Therapy as an Adjunct to Pharmacotherapy for Refractory Depression: Randomized Controlled Trial. J Med Internet Res 2017;19:e373.
277. Ben-Pazi H, Browne P, Chan P, et al. The Promise of Telemedicine for Movement Disorders: an Interdisciplinary Approach. Curr Neurol Neurosci 2018;18:26.
278. Rasmusson KA, Hartshorn JC. A comparison of epilepsy patients in a traditional ambulatory clinic and a telemedicine clinic. Epilepsia 2005;46:767-770.
279. Solenski NJ. Telestroke. Neuroimaging Clin N Am 2018;28: 551-563.
280. Bagot KL, Cadilhac DA, Bladin CF. Recommendation for an internationally agreed minimum data set for teleneurology. Nat Rev Neurol 2018;14:687.
281. T.C. Sağlık Bakanlığı. Teletıp Sistemi. 2020. Available from: https://teletip.saglik.gov.tr/
282. Ege Üniversitesi Haber Ajansı. 2020. Available from: https://egeajans.ege.edu.tr/?p=13708
283. TITCK-Türkiye İlaç ve Tıbbi Cihaz Kurumu. 2020. Available from: https://www.titck.gov.tr/faaliyetalanlari/ilac/klinik-arastirmalar
284. Alzforum. Coronavirus Takes Its Toll on Alzheimer's Clinical Studies. 2020. Available from: https://www.alzforum.org/news/community-news/coronavirus-takes-its-toll-alzheimers-clinical-studies
285. FDA. Clinical Trial Conduct During the COVID-19 Pandemic. Available from: https://www.fda.gov/drugs/coronavirus-covid-19-drugs/clinical-trial-conduct-during-covid-19-pandemic
286. Ledford H. Coronavirus shuts down trials of drugs for multiple other diseases. Nature 2020; 580:15-16
287. Clinical Trials Arena. Covid-19: Healthcare daily update - two thirds of cases may be undiagnosed - pandemic impacting on clinical trials in neurology. 2020. Available from: https://www.clinicaltrialsarena.com/special-focus/covid-19/covid-19-healthcare-daily-update-two-thirds-of-cases-may-be-undiagnosed-pandemic-impacting-on-clinical-trials-in-neurology/
288. Ema. Guidance on the Management of Clinical Trials During the COVID-19 (coronavirus) Pandemic. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf
289. TITCK-Türkiye-İlaç-ve-Tıbbi-Cihaz-Kurumu. COVID-19 Pandemisi Nedeniyle Klinik Araştırmalarda Alınacak Tedbirler 2020. Available from:https://titck.gov.tr/storage/Archive/2020/announcement COVID19KATedbirlerSSS_1cf892e0- 737f-42a5-b6ba-06949429be3e.pdf
290. Berenbaum MR. PNAS and the pandemic. PNAS 2020;117:9650-9651.
291. Elsevier. Special Issue on COVID-19. Available from: https://www.journals.elsevier.com/finance-research-letters/call-for-papers/special-issue-on-covid-19
292. Bedford J, Enria D, Giesecke J, et al. COVID-19: towards controlling of a pandemic. Lancet 2020; 395: 1015-1018.
293. Bhidayasiri R, Virameteekul S, Kim JM, Pal PK, Chung SJ. COVID-19: An Early Review of Its Global Impact and Considerations for Parkinson's Disease Patient Care. J Mov Disord 2020;13:105-114.
294. Dafer RM, Osteraas ND, Biller J. Acute Stroke Care in the Coronavirus Disease 2019 Pandemic. J Stroke Cerebrovasc Dis 2020;29:104881.
295. Sellner J, Taba P, Öztürk S, Helbok R. The need for neurologists in the care of COVID-19 patients. Eur J Neurol 2020. DOI:10.1111/ene.14257
296. Helbok R, Öztürk S. COVID-19 Statement of the EAN Scientific Panel Neurocritical care April 16, 2020. https://www.eanpages.org/2020/04/16/covid-19-statement-of-the-ean-scientific-panel-neurocritical-care/