OVERVIEW TO COVID-19 PANDEMIC

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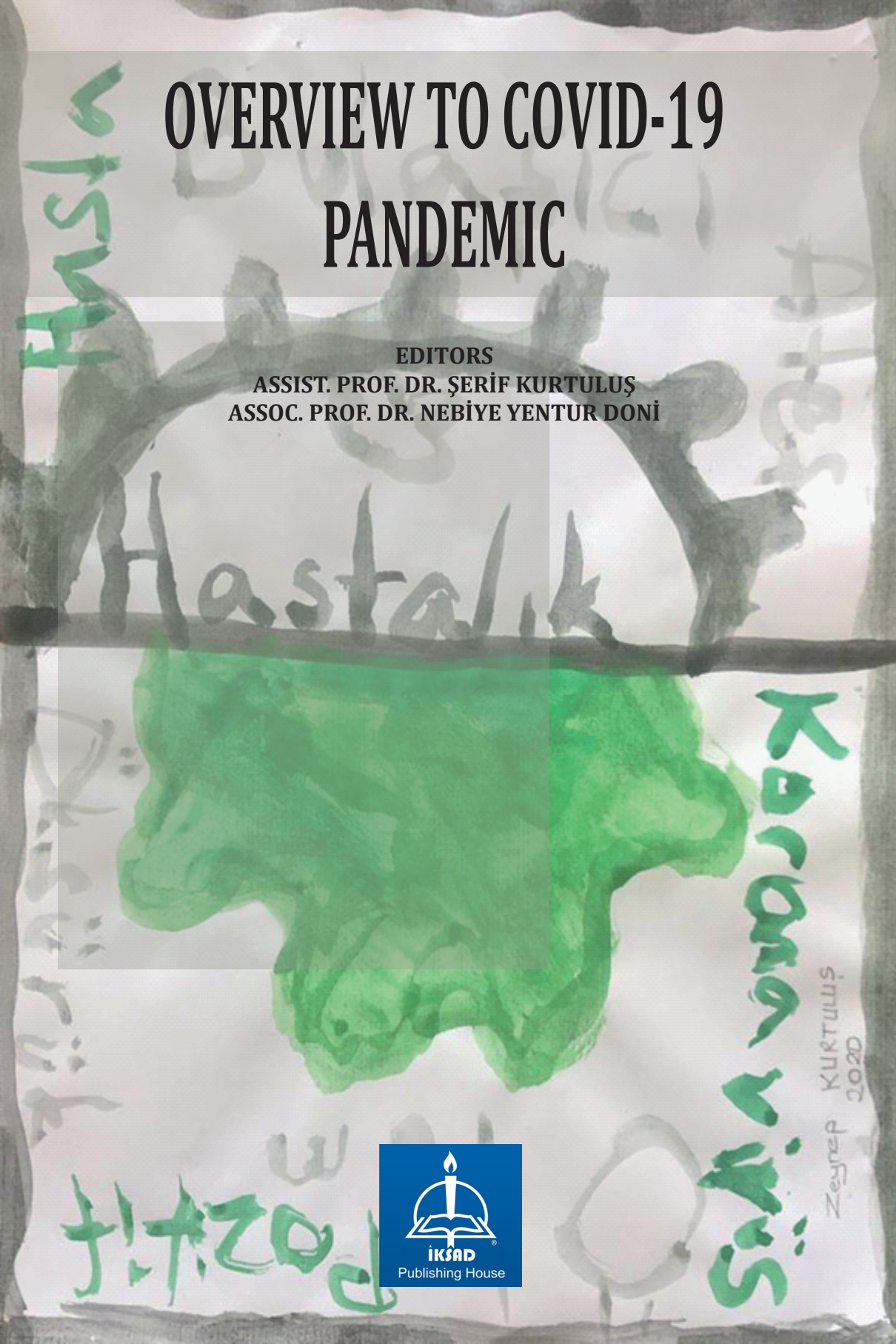

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CONTENTS

PREFACE

Covid-19 became threatening the world in a short time that its with spread and appearance in the fish market in Wuhan. With the delayed acceptance and declaration of the pandemic, humanity has entered into a total war with the epidemic. Since the Covid-19 outbreak is a dynamic process, many scientific information has lost its validity over time. It was replaced by new knowledge and experiences. Creating scientific memory in the pandemic is important for future generations. We have also tried to contribute by including the studies related to Covid-19 of health professionals.

Good reading…

Editors

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CHAPTER 1

TO COMPRESS OR NOT TO COMPRESS: CARDIOPULMONARY RESUSCITATION OF COVID-19 PATIENTS

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INTRODUCTION

Still spreading all over the world, COVID-19 has become a global disaster rather than disease. Despite promising development suchs as the impending first vaccines, the disease brings numerous issues to be addressed in the management of COVID-19 positive patients. Unlike the initial reports in the literature suggesting that the disease is predominantly seen in elderly people and with typical symptoms including fever, dry cough and dyspnea, as the outbreak spread it has been understand that even newborns can be infected by the virus and there are various other symptoms of the disease, which is now recognized to affect several organs and systems such as cardiac, neurovascular and gastrointestinal systems, making the management even challenging.

Cardiac arrest in suspected or confirmed diagnosis of COVID-19, namely SARS-CoV-2 is one of the most challenging conditions to manage mainly due to the risk of transmission through aerosolization of the patients during cardiopulmonary resuscitation (CPR). CPR in COVID-19 puts rescuers at risk of infection and needs to be performed differently from the routine application. Several guidelines have been published or the existing ones updated considering the disease. Rescuer personnel who perform CPR procedures are at the center of almost all guidelines. This chapter begins with an updating of the last status of COVID-19 worldwide and continues with a comprehensive discussion of CPR in the light of the literature.

1. COVID-19 UPDATING

The recent emergence of a China-origin novel coronavirus has caused a serious threat to public health worldwide (Wang et al. 2020). The high ability of infectivity and transmission of SARS-CoV-2 virus, also known as COVID-19 even among asymptomatic persons has resulted in rapid spread of the disease around the world, leading to global pandemic (Khatoon et al. 2020). SARS-CoV-2 (COVID-19) continues to wreak havoc on the world and to take millions of lives. As of December 13, 2020 WHO declared 70.461.926 confirmed cases and 1.599.704 deaths globally (WHO1 2020). Numerous vaccines are being developed in several countries in different regions of the world. These vaccines have reached various phases of the vaccine development process and a few of them completed these phases and are at the approval stage. The Federal Food and Drug Agency approved the first COVID-19 vaccine for emergency use in the United States of America (USA) (FDA 2020). And the first vaccination in the USA is expected to take place on December 13, 2020. In the United Kingdom, the first COVID-19 vaccine was made for the first time in a 90-year-old woman. (BBC 2020).

On the other hand preventive measures including social distancing, face mask and hand hygiene remain the most important precautions against the virus transmission. Partial or complete lockdown is effectively implemented in numerous countries; however, there is no marked decrease in spread of the disease and we have still a long way to go in order to eradicate or eliminate COVID-19 pandemic.

The burden brought by the disease is predominantly on the shoulders of emergency staff. Like many other outbreaks, COVID-19 is a crisis that should be primarily managed by emergency departments. In most countries, emergency departments (EDs) are in the frontline of the fight against the virus and patients with various undifferentiated symptoms are first met by EDs (Quah et al., 2020).

2. COVID-19 IN EMERGENCY MEDICINE

COVID-19 pandemic has challenged healthcare systems and especially EDs all around the world, as patients firstly present to EDs even if they have mild symptoms due to the fear of having a serious and fatal disease (Möckel et al. 2020) and has shown once again the globally critical role played by EDs. This role has been more important because of the increased intensity and added responsibilities. EDs are generally first contact of the patient infected by the virus. In addition to being already overcrowded, EDs have become overwhelmed with patients with concerns and fear of being infected due to this new and unexpected outbreak.

EDs should be prepared fast and effectively in order to response and meeting emergency medical need of patients presenting with suspicion of COVID-19 due to their symptoms such as fever, dry cough and difficulty in breathing and to cope with the disease without exceeding the capacity on the one hand, and to deliver emergency care to the other patients admitted to ED with various complaints and symptoms other than SARS-COV-2. However, preparedness of each ED has differed according to the factors such as size and level of the hospital,

number of cubicles and availability of resuscitation bays (Karaaslan et al. 2020). Furthermore, based on the symptoms and contact history of patients, differential diagnosis should also be established as soon as possible to correctly triage and manage these patients. During all these procedures, emergency staff should also protect themselves by personal protective measurements, making their service further difficult.

Cardiopulmonary events such as acute respiratory distress syndrome (ARDS), ventricular arrhythmias and myocardial damage that develop during the course of COVID-9 disease make some interventions such as cardiopulmonary resuscitation necessary especially in the severe cases.

3. CARDIOPULMONARY RESUSCITATION (CPR) OF COVID-19 PATIENTS

Majority of COVID-19 patients are either asymptomatic or have mild symptoms, although some patients require ventilatory support (Gupta et al 2020). It has been reported that 12-19% of COVID-19 patients require presentation to hospital, while 3-6% become critically ill (CDC, Wu & McGoogan 2020; Guan et al. 2020; Taha et al. 2020). COVID-19 disease causes a high risk of developing cardiovascular arrest. Cardiovascular arrest during the disease is caused by hypoxemia secondary to acute respiratory distress syndrome (ARDS), viral mediated myocardial injury, secondary ventricular arrhythmias or prolongation of QT because of the administration of hydroxychloroquine (Mercuro et al. 2020). Therefore, the rate of the

COVID-19 patients with cardiac arrest is likely to increase. Before COVID-19 outbreak, the survival rate of patients with cardiac arrest has been reported as 25% (Andersen et al. 2019). Whereas, in a study from the USA, none of the COVID-19 patients with cardiac arrest survived (Thapa et al. 2020), making cardiopulmonary resuscitation more critical in these patients. As is known, COVID-19 contamination occurs through air droplets from the mouth and/or nose. Some medical procedures produce air droplets from the patient. CPR is the medical procedure, which most frequently causes aerosolization, that is one of the important routes of the contamination of COVID-19 virus. According to the WHO, COVID-19 can transmit from people to people through respiratory droplets and contact (WHO2) .These air droplets especially produced by chest compression during resuscitation efforts can remain suspended in the air for a certain time and can be inhaled by the persons nearby (van Doremalen et al. 2020). Therefore, the objective of CPR in patients with suspected or confirmed COVID-19 is to ensure that patients suffering cardiac arrest receive the best care as much as possible, without putting rescuers who perform CPR at risk of contamination by air aerosolization. Because healthcare staff working at the frontline are at a high risk of transmission during procedures producing aerosolized virions such as CPR (Sher et al. 2020). On the other hand, COVID-19 negative persons with cardiac arrest should receive routine CPR. Nevertheless, the number of personnel in the room should be again minimized for social distancing purposes.

CPR procedure, which can be performed safely under normal conditions, has become a challenging procedure due to COVID-19 pandemic. The currently expanding COVID-19 outbreak has created important challenges in resuscitation efforts and necessitate modifications of established CPR practices and procedures. To overcome this challenge, in collaboration with several associations regarding emergency medicine, critical care, anesthesiology and pediatrics; American Heart Association (AHA) complied an interim guidance about CPR in COVID-19 patients including basic life support (BLS) and advanced cardiac life support (ACLS) algorithms for adult, pediatric and neonatal patients with COVID-19 (AHA). AHA guidance describes the strategies to follow during resuscitation of COVID-19 patients as follows (AHA):

1. All rescues should don PPE to protect themselves against contact with air particles according to the local emergency medicine service standards.
2. Personnel in the CPR bay should be minimized to only those who are required for the intervention.
3. Manuel chest compressions should be considered to be replaced by mechanical CPR devices in adult and adolescent patients who meet the weight and height criteria of the device manufacturer.
4. COVID-19 status of the patient should be clearly communicated to all rescues in the scene.
5. Before administration of any breath, a high-efficiency particulate air (HEPA) filter should be connected securely to any

manual or mechanical ventilation device on the pathway of the exhaled air.

6. After assessment of the rhythm, patients suffering cardiac arrest should be intubated with a cuffed tube at the first opportunity.
7. The likelihood of failed attempts of intubation should be minimized by:
   a. Approaching with the best chance of first-pass successful intubation.
   b. Stopping chest compressions to wait for intubation.
8. If available, a video laryngoscopy can reduce exposure of the intubator to air particles.
9. A bag mask with a HEPA filter and a tight seal or a nonrebreathing face mask covered by a surgical mask should be used before intubation.
10. Manual ventilation with a supraglottic airway or bag mask device should be considered in the case of delayed intubation.
11. When the circuit is closed, disconnections should be minimized to avoid aerosolization.
12. Considering the likelihood of the need for increased levels of care, goals of the care should be addressed with COVID-19 patients.
13. Considering patient risk factors for estimation of survival, emergency medicine systems (EMSs) and related healthcare systems should make policies to guide frontline healthcare providers.

14. Current data with regard to performing extracorporeal CPR in COVID-19 patients are not sufficient.

Advanced cardiac life support (ACLS) algorithm for suspected or confirmed cases of COVID-19 recommended by AHA is shown in Figure 1.

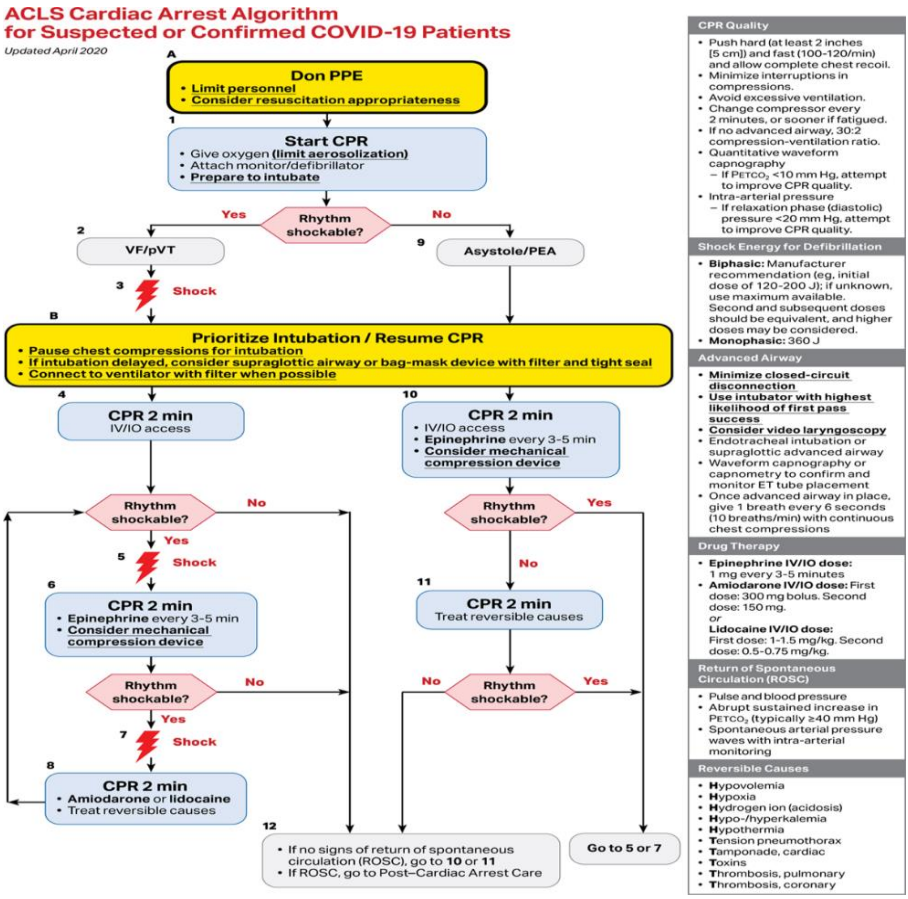

Figure 1. Advanced cardiac life support (ACLS) algorithm for suspected or confirmed cases of COVID-19 by AHA (Updated April 2020). CPR: cardiopulmonary resuscitation; ET: endotracheal; PEA: pulseless electrical activity; $PETCO_2$: end-tidal carbon dioxide; pVT: pulseless ventricular tachycardia; ROSC: return of spontaneous circulation; VF: ventricular fibrillation.

According to the guidance published by AHA; staff who will perform CPR should accurately put on the personal protective equipment (PPE), and especially the face mask should be put on carefully due to the risk of air droplets from the patient during CPR, the number of personnel should be minimized, and all rescuers should be informed about the patient's COVID-19 status (Edelson et al. 2020). The highest risk for medical staff performing CPR is air droplets produced by a COVID-19 patient during chest compression. Studies have reported that chest compression should be started as soon as possible, but only after the rescuer put on appropriate PPE, continuous chest compressions should be continued until advanced airway management becomes possible, and that mechanical chest compression should be used where it is available since this will reduce the number of personnel required for CPR (Couper et al. 2020). According to the recommendations by the European Resuscitation Council, chest compression should not be started before donning PPE, even this leads to a short delay. The minimum recommended PPE includes a filtering facepiece 3 (FFP 3) respiratory mask, if available, otherwise a N95 mask, eye and face protection, a long-sleeved gown and gloves (ERC). Delays are associated with morbidity and mortality; however, safety of rescuers is of paramount importance (Hwang et al. 2020).

Unfortunately, medical personnel performing resuscitation should be in close proximity with each other and with the patient when working due to the nature of the procedure. Whereas, safety of the personnel should be prioritized during risky medical interventions such as CPR

during the pandemic. Therefore, rescuers should carefully balance the immediate needs of a COVID-19 patient and their safety.

3.1 Out-of-Hospital CPR

People with suspected or confirmed diagnosis of COVID-19 may have cardiac arrest out of hospital. In about 70% of out-of-hospital cardiac arrest cases, the rescuers are family members, and therefore they are likely to have had exposure to COVID-19 in the infected children. On the other hand, CPR that will be performed with nearby bystanders has been shown to increase the likelihood of survival (Kragholm et al. 2017, Pollack et al. 2018). However, lay persons who perform CPR are at a higher risk of transmission, because they are less likely to access appropriate PPE for protecting themselves against aerosolization. In addition, cardiac arrest rescuers with comorbidities such as diabetes mellitus, hypertension or chronic obstructive pulmonary disease (COPD) are at further increased risk to be critically ill if infected by COVID-19 virus when performing CPR (Guan et al. 2020).

3.2 CPR in Pediatric Patients

Children seem to be mostly asymptomatic or have milder symptoms compared to adults. Of all patients with confirmed COVID-19, those < 10 years make up only 0.9% with approximately 18% of these pediatric patients being < 1 year (Wu & McGoogan 2020). Among pediatric patients with suspected or confirmed COVID-19, about 23% have been reported to have underlying medical conditions such as

cardiovascular disease, asthma and immunosuppression (CDC). On the other hand, a small portion of pediatric COVID-19 patients become critically ill requiring hospitalization or admission to intensive care units (Lu et al 2020; Dong et al 2020; Pathak et al. 2020). In a large pediatric COVID-19 series with 2143 cases from China (Cruz & Zeichner 2020), 2% of the patients had severe disease and 0.6% critical disease (Dong et al. 2020). Since children with COVID-19 are likely to develop acute cardiac decompensation, which is associated with multisystem inflammatory syndrome in children (MIS-C), life support medical procedures including CPR become more demanding in this setting (Belhadjer et al. 2020).

It is known that CPR with chest compressions only is not an effective method in pediatric age group (Resuscitation Council of UK 2020) This type of CPR is appropriate in some adults with cardiac arrest, but the etiology of cardiac arrest is progressive respiratory failure in most pediatric COVID-19 patients and thus, hands only strategy is not endorsed in this patient group (Topjian et al. 2020). CPR in pediatric patients with suspected or confirmed COVID-19 should preferably consist of chest compressions and ventilation with a bag mask plus a HEPA filter until a secure airway is established (Resuscitation Council of UK 2020). Although almost all guidance was updated and modified due to COVID-19 break; however, as the disease process is highly dynamic, guidance should be revised with certain intervals according to the accumulating new evidence. According to the latest updates of resuscitation in pediatric COVID-19 patients, rescue breath

must still be performed in, as cardiac arrest in this patient group is likely resulted from a respiratory problem (ERC). As in adult patients, PPE to be used during CPR should be determined at system level according to the presumed risk of transmission (WHO 3). In order to limit the risk of transmission and preserve the limited resources, only rescuers who will perform CPR on a child should be involved in CPR bay or room, and the door should not be open frequently. Particularly in children with suspected or confirmed COVID-19, rescuers may think that the benefit for a child is higher than their personal risk, but they should also consider their responsibilities towards themselves, their loved ones, relatives, colleagues and the wider community (Chan et al. 2020).

CONCLUSION

CPR procedure in suspected or confirmed COVID-19 patients presents a challenge due to the risk of transmission during the procedure. Since rescuers necessarily violate the social distancing rule, using correct PPE with caution becomes critically important. PPE should be put on before the resuscitation procedure begins even if this results in a short delay. In addition, rescuers who perform CPR should balance delivering the best care as much as possible to the patient with their own safety and protection against the transmission. In addition to the national policies and algorithms, each institution should develop its own CPR algorithms based on several factors such as the intensity of patient traffic, facilities, size and type of the hospital.

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CHAPTER 2

NEUROVASCULAR COMPLICATIONS IN COVID-19 DISEASE

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INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which named as COVID-19 (Lu R et al. 2020) and declared as pandemic (Castagnoli et al. 2020) by the World Health Organization, continues to spread and lead to a lots of deaths world wide without losing its effects nowadays, when this textbook is being written. According to the WHO data, the total number of cases is 62.662.181 and death toll is 1.460.223 worldwide as of December 2, 2020 (WHO 2020).

There is still no specific vaccination or medication introduced specific to pneumonia caused by COVID-19 virus. Vaccination studies have reached various phases in many countries, especially in the United States, China, Russia and Germany. Even two vaccines developed in the USA are waiting approval from the Federal Drug Administration (FDA 2020). However, unfortunately we have no clear information about long- and mid-term effects of vaccination. Some optimistic scientists declare that the point reached in vaccination studies is a triumph of science and humanity while others argue that they do not think the vaccine will be effective against the disease, because the process is very dynamic and the virus constantly mutates and acquires new features (Dawood 2020).

Looking at the relevant literature, almost all of the initial studies have come from China (Mao et al. 2020; Fung & Liu 2019; Li W et al. 2005; Zhou et al. 2020; Ji 2020, Wang C 2020). These first studies have stated that COVID-19 disease has a fatal course more commonly

in elderly people and it shows itself with dry cough, fever and dyspnea (Zhou et al. 2020; Mao et al. 2020). China-origin studies have reported that chest tomography is a safe diagnostic method and can be used for the diagnosis of COVID-19 in addition to polymerase chain reaction PCR test (Li M 2020).

However, as the pandemic rapidly spread around the world, different facts from the first known were revealed in studies in the literature from various countries, especially Italy and the USA. In this context, pediatric cases, different symptoms such as loss of taste and smell, headache, and involvement of different organ and body systems have been emphasized (Di Lorenzo & Di Trolio (2020); Zaim et al. 2020). Today, according to the data at our hands, especially the pulmonary system, numerous organ systems including gastrointestinal, cardiac and neurologic systems are influenced by COVID-19 virus. In addition, COVID-19 leads to many complications in the human body. Better understanding these complications will contribute to more effective treatment and management of the disease. Neurovascular system is one of the most vital systems of the human body. If the complications that may occur in this system are not controlled well, many other organ systems of the body will be affected. COVID-19 has been associated with hypercoagulation that leads to many cardiovascular and neurovascular complications (Bangalore et al. 2020). However, detailed assessment of neurologic system complications in COVID-19 is relatively challenging, because only some COVID-19 patients have neuroinvasion, CND tissue can not be sampled directly and it is difficult to distinguish direct neuroinvasion

and systemic cerebral viremia. This challenge limits determination of underlying pathophysiologic conditions. This chapter begins with the neurologic involvement of COVID-19 disease, and continues with neuroinvasion by SARS-CoV-2 with the incluison of the recommended possible mechanisms of invasion. Neurovascular complications caused by SARS-CoV-2 are given in light of the most updated studies in the relevant literature and post-infection neurological complications of SARS-CoV-2 are also included. Furthermore, the management of patients treated for COVID-19 with neurovascular complications is briefly discussed. This chapter of the textbook ends with future projections in neurologic research of COVID-19.

1. NEUROLOGIC INVOLVEMENT IN COVID 19

It is known that CoVs can invade the respiratory system as well as the central nervous system. Like the other CoVs, COVID-19 also mainly involves pulmonary system, causing pneumonia, although extrapulmonary involvement of several organs and organ systems including nervous system is increasingly reported in the literature (Mao et al. 2020). Emerging literature and clinical experience suggest that gastrointestinal, hepatobiliary, hematologic, dermatologic, ophthalmologic and neurologic systems can be affected by COVID-19 disease (Guan et al. 2020; Wu et al. 2020). Recent studies have reported that some SARS-CoV-2 patients have neurological symptoms such as vomiting, nausea and headache (Huang et al. 2020). COVID-19 can cause serious vascular damage and neurologic

involvement. The study administrated by Mao et al. on 214 patients who were suufered from SARS-CoV-2 reported that 88% of the patients with severe disease have neurological symptoms such as impaired consciousness and acute cerebrovascular diseases (Mao et al.2020). In that study, patients who developed neurologic complications tended to be older and have comorbidities, and presentation was due to a neurologic symptom in some of these patients. However, it has been suggested that the neurological symptoms seen in these patients, such as loss of taste and smell, may result from another viral infection or a serious systemic disease in the intensive care environment. Today, we have accumulated enough scientific evidence to show that SARS-CoV-2 may affect the nervous system and potentially neurotrophic. The number of studies showing that the central nervous system is affected is increasing (Heneka et al. 2020; Pereira 2020). Observational studies have reported confusion, headache, delirium, myalgia, ataxia, epilepsy and agitation suggesting possible neurologic involvement (Garg 2020; Wang D et al. 2020; Li Z et al. 2020). All these symptoms reported in patients who were suffered from SARS CoV-2 have attracted the attention of researchers to investigate a possible connection between SARS-CoV-2 and the neurovascular system. Data obtained from a novel meta-analysis study of neurologic involvement in nearly 4700 COVID-19 patients is given in Figure 1 (Wang S et al. 2020).

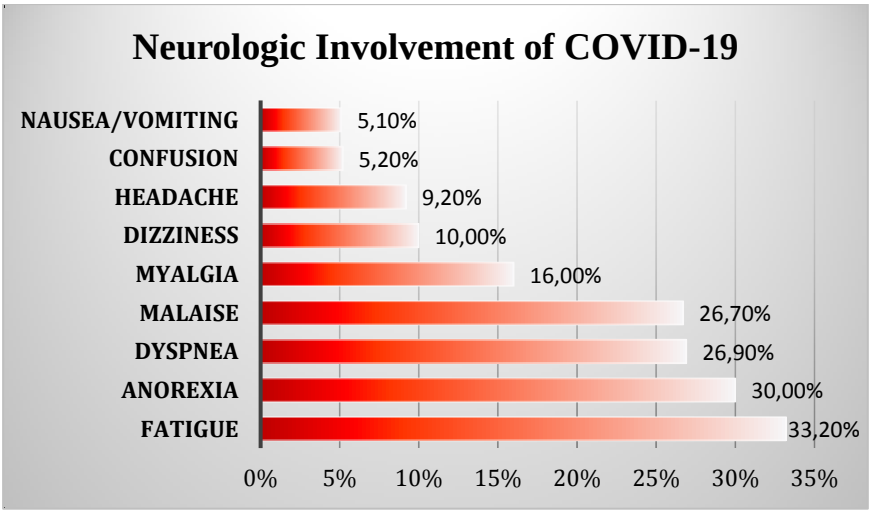

Figure 1. Rates of neurologic complications obtained from more than 4700 COVID-19 patients

1.1 Neuro-invasion of COVID-19

It was proposed in a review on the CNS that all viruses can invade the neurologic system depending on viral and host factors including mutations of a specific virus, and age and comorbidities in the host (Koyuncu et al. 2013). Better understanding of neuroinvasion by SARS-CoV-2 is of paramount importance to treat these patients. Neuro-invasion by COVID-19 has been proven in postmortem studies and autopsy series. In these studies, SARS-CoV-2 was identified in brain tissues taken from patients who have important symptoms related to the central nervous system (Gu et al. 2005). Again in autopsy series, viral mRNA (in brain tissue) (Solomon et al.2020) and viral protein residues (in endothelial cells in the olfactory bulb) were determined (Cantuti-Castelvetri et al.2020). Furthermore, Solomon et al. showed that there is neuron loss in patients who were suffer from

SARS-CoV-2 (Solomon et al.2020). At the result of a postmortem examination of a patient who deceased due to infection caused by SARS-CoV-2 by Mondolfi et al., the virus was happen to found in capillary and neural endothelial cells in the brain tissue. (Mondolfi et al.2020). The detection of the presence of the virus in the cerebrospinal fluid (CSF) by Moriguchi et al. indicates that the virus has neuroinvasion (Moriguchi et al.2020).

On the other hand, animal studies have shown that neurologic coronavirus invasion starts in the olfactory bulb and progresses towards the cerebral cortex (McCray et al. 2007). Former studies have indicated that SARS-CoV coronaviruses cause death in rats by entering through the nose and invading the brain starting from olfactory epithelial cells (Netland et al.2008). Figure 2 shows schematic entrance of SARS-CoV-2 to the brain.

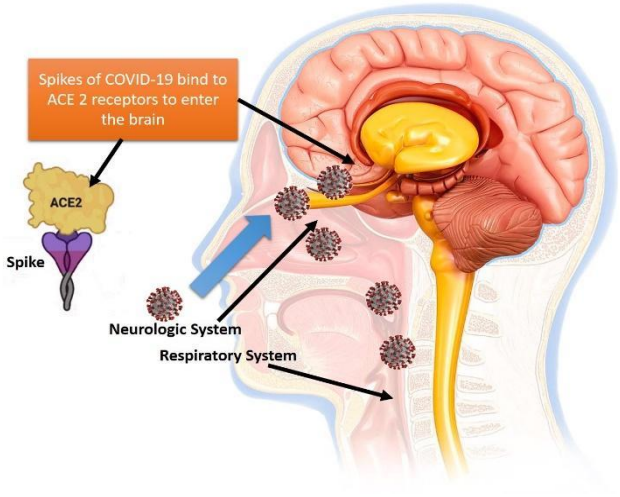

Figure 2. Entrance of SARS-CoV-2 virus to the brain through virus spikes binding to ACE receptors (©: Osman E Batcik. Can be used with permission).

Some studies suggest that the neuroinvasion of SARS-CoV-2 may cause the break down the respiratory center in the brain (Dey et al.2020). Neuroinvasive nature of the virus suggests possible impairment of blood-brain barrier (BBB). In turn, disrupted BBB causes an increase in neuroinvasion. Three main mechanisms have been proposed for neuroinvasion by SARS-CoV-2: endothelial dysfunction, coagulopathy and inflammation.

1.1.1 Endothelial Dysfunction

Endothelial dysfunction is one of the suggested etiologies of neuroinvasion. Because the main properties and structure of SARS-CoV-2 are parallel to other SARS-CoVs, endothelial dysfunction can also play a critical role in neuroinvasion by SARS-CoV-2 like other coronaviruses. ACE2 receptors have been proposed as the entry route of COVID-19 to the human brain. SARS-CoVs enter host cells mainly using angiotensin converting enzyme 2 (ACE2). Therefore, cells expressing ACE2 become targets for SARS-CoV-2. Since brain cells contain ACE2 receptors, it is suggested that SARS-CoV-2 would have neurotrophic potential. ACE2 receptors were reported to be expressed in human neurons, endothelial and arterial smooth muscle cells, glial cells making them targets for neuroinvasion (Xia and Lazartigues, 2008). Neuroinvasion, requires binding of the virus' spike to the ACE-2 receptor in order to affect the neurons. After binding to the ACE-2 receptor, the virus can cause impairment of the autoregulatory function. However, it is still not clear whether ACE-2 is the main gate of entrance of COVID-19 into the neuronal cells and contribution of

the neurotropic potential of COV-19 to mortality and morbidity has not yet been clearly defined (Baig et al. 2020).

1.1.2 Coagulopathy

Elevated D-dimer levels are suggestive of hypercoagulation. D-dimer, fibrin degradation products and fibrinogen are elevated in COVID-19 patients. High levels of D-dimer and fibrinogen values may contribute to the increased risk of developing thrombosis. Viral infection that causes sepsis and resultant disseminated intravascular coagulation (DIC) have been proposed as an indirect potential factor for COVID-19 related thrombosis (Tang et al. 2020). Neurologic complications resulted from hypercoagulability including ischemic stroke, cerebrovascular disease and hemorrhagic stroke are particularly of paramount importance. In addition, the most common neurological complications related to SARS-CoV-2 include venous thromboembolism, cerebral infarction, myocardial infarction and acute coronary syndrome. Sepsis induced coagulopathy (SIC), which is a form of disseminated intravascular coagulopathy (DIC), has been seen in the majority of patients who deceased due to infection caused by SARS-CoV-2 (Tang et al. 2020).

1.1.3 Inflammation

Systemic inflammation activates coagulation mechanisms through the generation of tissue factor-mediated thombins. Cytokines play a role in the pathogenicity of SARS-CoV-2 via a systemic inflammatory response, causing cytokine storms. This systemic inflammation may increase the risk of developing ischemic stroke as a result of cytokine

storm, especially in elderly COVID-19 patients. Cytokine storm is also named macrophage activation syndrome and is a response to systemic inflammation triggered by various infections including COV-19. In a cohort study carried out in 2019, higher levels of IL-6 have been found to be significantly associated with stroke (Jenny et al. 2019). As is known, IL-6 levels increase in COVID-19 patients. This suggests that stroke can occur in COVID-19 patients. However, more studies are needed to elucidate the link between SARS-CoV-2 and stroke outcomes. Figure 3 summarizes neuroinvasion of COVID-19 virus (Dey et al. 2020).

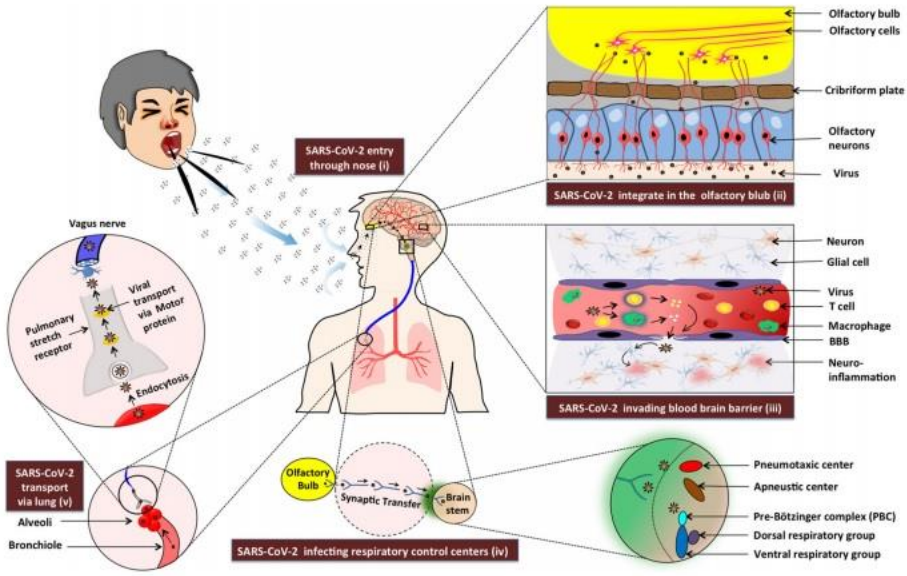

Figure 3. Neuroinvasion of SARS-CoV-2 virus. (i) virus enters through nasal cavity (ii) virus enters to olfactory bulb, reaching the brain (iii) invades blood-brain barrier

(iv) infects respiratory control centers (v) neuroinvasion via the lungs (Permission for using this figure was received from Dr Prem P. Tripathi, Indian Institute of Chemical Biology-Translational Research Unit of Excellence (IICB-TRUE), India. The figure was originally published in the article entitled "Neuroinvasion of SARS-CoV-2 may play a role in the breakdown of the respiratory center of the brain" by Dey et al. 2020).

1.2 Neurovascular Complications Caused by COVID-19

The reported neurovascular complications of SARS-CoV-2 are similar to those reported in other coronaviruses including severe acute respiratory syndrome (SARS) seen in 2003 and Middle East acute respiratory syndrome (MERS) in 2012. However, as these two endemics affected a much smaller number of people, comparison of neurovascular complications and features of these two diseases with COVID-19 may not be so realistic.

Since the COVID-19 process is highly dynamic, we still do not know much about the disease, its consequences and sequelae, especially in the mid and long-term. As new studies are published in the literature, our insight of the disease and its effects on various organ systems in the human body will increase over time. Nevertheless, what we currently know is that COVID-19 leads to numerous complications in the neurovascular system.

Vascular endothelial injury and downregulation of ACE2 receptors may cause numerous neurovascular complications of COVID-19. Various neurologic symptoms and neuropathies have been noticed in patients suffered from SARS-CoV-2 such as headache, altered mental status, loss of consciousness, ataxia, ischemic stroke, hallucinations,

psychotic symptoms, intracerebral hemorrhage, encephalopathy and encephalomyelitis (Pouga 2020, Montalvan et al. 2020). Furthermore, severe patients exhibit systemic symptoms such as coagulopathy , cytokine storm and hypoxia which cause encephalopathy, along with the direct effects of the virus. Radiological examinations of COVID-19 patients have revealed infarctions, posterior reversible encephalopathy syndrome and microhemorrhages (Mahammedi et al. 2020). Studies have noticed that COVID-19 is associated with inflammatory state, which predisposes to stroke (Mao et al. 2020; Oxley et al. 2020). Potential mechanisms of stroke induced by SARS-CoV-2 include vasculitis, endothelial injury, hypercoagulopathy, microvascular thrombosis, cytokine storm, cardiac alterations and systemic hypoxia (Spence et al. 2020). In a case study from Wuhan, stroke has been observed in 12 of 214 patients who suffered from SARS-CoV-2 (Mao et al. 2020). Stroke is reported in 5.7% of severe patients, leading to rapid clinical worsening (Oxley et al. 2020). It is more commonly seen in patients with comorbidities such as diabetes mellitus, hypertension or a history of cardiovascular events. Severe complications observed with the disease may be caused by direct neuroinvasion of the virus or immunologic response given by the body against the virus. In addition, hypoxemia triggered by the virus may lead to metabolic changes (Garg 2020). However, there are differences among the studies in the incidence of neurovascular complications and the reason for these differences remains unclear. This may be because COVID-19 is a recently described disease and was primarily reported with distinct symptoms such as fever, dry

cough and shortness of breath, while neurological symptoms such as dizziness, headache, loss of smell and taste were not initially emphasized. As our knowledge of the disease has increased, higher incidences of neurovascular complications caused by COVID-19 have been reported.

Central Nervous System Complications of SARS-CoV2

- Headache/Dizziness; is considered to be caused by hypoxia, leading to a decreased blood flow to the cerebral vasculature, cytokines and body response to several inflammatory mediators.
- Cerebrovascular events; Binding of SARS-CoV-2 spikes to ACE2 receptors on the epithelial cells leads to a massive inflammatory response resulting in severe damage to organs and stroke. The incidence of ischemic stroke has increased by 5% in patients admitted to the intensive care unit due to infection in China, and by 3.7% in Italy (Bridwell et al. 2020).
- Encephalopathy; is primarily treated with supportive therapies and usually shows partial or full recovery in patients who suffer from SARS-CoV-2.
- Meningitis/Encephalitis; Increased cytokines due to SARS-CoV-2 infection cause the immune system to deteriorate and increase the neurotrophic potential of the virus.
- Acute hemorrhagic necrotizing encephalopathy (ANE); ANE is a rare condition caused by cytokine storms as a result of impaired BBB by neuroinvasion of SARS-CoV-2. The pathophysiology of ANE has not been fully understood.

- Intracerebral hemorrhage; occurs as a result of the SARS-CoV-2 virus entering the central nervous system due to the disrupted blood brain barrier as a result of binding to ACE2 receptors in epithelial cells. Decreased ACE2 receptors negatively affect the regulation of central and peripheral nervous systems, causing intracerebral hemorrhage.

Peripheral Nervous System (PNS) Complications of SARS-CoV-2

- Chemosensory dysfunction; the most prevalent PNS symptoms seen in COVID-19 are loss of taste (ageusia) and smell (anosmia). Anosmia is developed due to inflammation of olfactory nerves. Ageusia is resulted from damaged taste receptors after binding off the virus spike to ACE2 receptors that are also expressed on the tongue.
- Guillain-Barre syndrome;
- Acute transverse myelitis; is caused by cytokine storms leading to overwhelming inflammatory response, which releases numerous chemokines, macrophages, interleukins and interferons.
- Skeletal muscle damage; in COVID-19 manifests with skeletal muscle injury and myalgy. According to a study by Han et al., 52% of adult patients (22-70 yo) exhibited myalgia and fatigue with most of them having comorbidities such as diabetes mellitus and hypertension (Han et al. 2020).

1.2.1 Complications İn Post-infection Period: COVID-19 Recovered Patients

Post-infection neurovascular complications of COVID-19 are also expected. Neurologic sequelae are resulted from activation of immune mechanisms. Functioning and the structure of the brain can damaged by many viral infections which lead to post-infectious diseases. SARS-CoV-2 also shows chronic neurovascular complications in recovered patients in the post-infection period such as microstructural changes and the impairment of brain integrity (Lu Y et al. 2020). In addition, diffusion tensor imaging (DTI) outcomes and cerebral volumetrics have shown major enlargement in volumes of hippocampi, bilateral olfactory cortices and right cingulate gyrus of COVID-19 recovered patients in the post-infection period (Lu Y et al. 2020). Some studies have claimed that SARS-CoV-2 causes complications in the central nervous system as well as the peripheral nervous system (Yan et al.2020). According to these reports, loss of smell and taste is an early indicator of anosmia and hypogeusia as important indicators of COVID-19. Coolen et al. reported that there was a correlation between loss of smell and olfactory bulb asymmetry in the COVID-19 patients they observed. Reports on post-infection neurologic complications of COVID-19 are growing. As data accumulates in the literature on these complications, management of patients who suffer from SARS-CoV-2 who develop complications after recovery will be more effective.

2. MANAGEMENT OF COVID-19 PATIENTS WITH NEUROVASCULAR COMPLICATIONS

Timely management of neurovascular complications caused by SARS-CoV-2 can increase survival rates and decrease long-term effects. All patients admitted to intensive care due to COVID-19 should be treated with prophylactic treatment against venous thrombosis. Anticoagulation should be given in therapeutic doses in patients with stroke and suspected cardioembolic mechanisms. Tang et al. reported that mortality was lower in COVID-19 patients with coagulopathy who received anticoagulants (Tang et al. 2020). Early administration of anticoagulants is also being discussed for preemptive management. Besides anticoagulation, thrombolytic treatment may also be considered in these patients.

The use of systemic corticosteroids or other antiinflammatory agents in selected cases of stroke from COVID-19 with suspected vasculitis is controversial. Clinicians should weigh the benefits against risks before initiating antiinflammatory therapy in these patients. One of the possible treatments for stroke caused by COVID-19 is ACE2 recombinant therapy. Intravenous (iv) immunoglobulins (IVID) and steroids can be given in patients with acute necrotizing encephalopathy (ANE) which is a rarely seen neurologic complication in COVID-19.

3. FUTURE PROJECTIONS

Currently, the existing literature about neurovascular complications of COVID-19 comes from clinical series without controls and population basis. Future research about the treatment of neurovascular complications caused by COVID-19 will focus on, prevention and treatment of thrombotic manifestations, virus neutralization and prevention of cytokine storm.

Longitudinal neurologic assessment of recovered COVID-19 patients will be substantial to understand effects of the virus in the brain and to control potential neurologic sequelae. On the other hand, social distancing and postponing all nonurgent clinical activities and limitations in access to hospitals have caused serious problems in the control of patients with chronic neurologic conditions. This will require increased long-term investments in the healthcare sector, better coordination between different organizations and funding of more research. Finally, detailed multicenter, multinational clinical, diagnostic and epidemiological studies are needed to be conducted by multidisciplinary teams in order to specify neurovascular manifestations of COVID-19.

CONCLUSION

Post-mortem studies, animal experiments, reports of cases and a growing number of studies show that COVID-19 causes neuroinvasion and causes neurovascular complications. The most common presentation symptoms related to the neurologic system

include headache, dizziness, anosmia, ageusia, encephalopathy, ischemic stroke, hemorrhagic stroke, meningitis, encephalitis and Guillain-Barre syndrome.

As the COVID-19 pandemic progresses, and the number of cases with extrapulmonary neurovascular complications increases, presentations and management of the disease will be better understood. Meanwhile, during this pandemic period, SARS-CoV-2 should be considered in patients presenting with or without specific neurological symptoms.

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CHAPTER 3

MATERNAL COVID-19 TRANSMISSION

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INTRODUCTION

SARS-CoV-2 outbreak is the first pandemic of this century. Pandemic has a devastating impact on the healthcare system as well as social, psychological and economic fields. The numbers of new cases and deaths reported everyday from various countries all over the world are frightening. SARS-CoV-2 infection is known to mainly be transmitted via air droplets, affect respiratory tracks, and especially the lungs, leading to pneumonia. Although several hypotheses have been proposed for the other transmission routes, none of them have been confirmed so far. One of these routes is maternal-fetal transmission which endangers the mother's life and also carries a great risk for the fetus and the infant after birth. There are great concerns about the possible consequences of this infection during pregnancy. Likewise, it is not exactly known whether the virus can pass from the mother to the fetus. According to recent data, the risk of developing coronavirus disease 2019 (COVID-19) is not greater in pregnant women than the general population (Dotters and Hughes 2020). However, since the number of new cases reported from all over the world is increasing, the possibility of COVID-19 transmission from the mother to the fetus is still considered controversial. This makes the approach to pregnant women challenging. In addition, the fact that almost all pregnant women with COVID-19 are asymptomatic requires clarification of the effects of COVID-19 on material and infant results, and especially the potential for intrauterine vertical transmission. Considering that many pregnant women around the world are likely to get COVID-19 during

the pandemic, it is of paramount importance to clarify maternal-fetal COVID-19 transmission.

This chapter starts with an update on the recent developments about COVID-19. Reasons that predispose to COVID-19 during pregnancy are discussed and maternal COVID-19 transmission is described in general. After explaining maternal COVID-19 transmission routes, the current literature is included briefly with studies that have reported or no maternal COVID-19 transmission. This topic is still quite debatable and the information included in this chapter aims to discuss the current knowledge and not to reach a definite judgement.

1. AN UPDATE ON COVID-19

COVID-19, which is one of the most devastating health disasters to date, is caused by severe respiratory syndrome coronavirus 2, still causing thousands of lives to die and hundreds of thousands of people infected (Han 2021). With its economic, sociological and psychological impacts, the disease continues to cause a great destruction globally, which is very difficult to reverse.

Screening programs are ongoing in various countries for the administration of 4-5 vaccines, whose Phase III studies were completed worldwide at the time of this chapter. However, data on the efficacy of these vaccines are very limited and medium term results are not available. According to the April 27, 2021 daily report published by the World Health Organization (WHO), 147,539,302 confirmed new cases and 3,116,444 deaths were reported and

961,231,417 doses vaccines were administered worldwide (WHO 2021).

The COVID-19 process has followed an extremely dynamic course since the disease was first seen in a seafood market in Wuhan, Hubei province, China, and mutated variants of the virus have emerged in many countries. From an academic point of view, it has been reported in publications at the beginning of the pandemic that the disease mainly affects elderly people and involves the respiratory system. However, in later times, studies have reported involvement of different systems such as neurological, gastrointestinal and cardiac systems, and younger patients. COVID-19 related literature has gained a dynamic structure and new information is added or the existing information is updated on a daily basis. According to the American Centers of Disease Control and Prevention (CDC), although the risk of severe illness is low, pregnant women are at increased risk of COVID-19 infection compared to non-pregnant women. CDC defines severe illness as a disease resulting in intensive care, mechanical ventilation or death. In addition, the risk of adverse pregnancy outcomes such as preterm delivery is increased in pregnant COVID-19 patients compared to non-pregnant patients. Data on the safety of COVID-19 vaccines in animal trials using various vaccines are currently limited. Studies involving pregnant women are constantly followed up by the WHO and CDC in terms of the effects of the disease, vaccination, and the side effects of vaccines on pregnancy outcomes and infants (CDC).

2. FACTORS PREDISPOSING TO COVID-19 DURING PREGNANCY

Pregnancy consists of complex physiological and immunological processes that make pregnant women more susceptible to infections, including viral pathogens (Zaigham and Andersson 2020). Anatomical and physiological changes in the respiratory system as well as immunologic and hormonal adaptations occurring during pregnancy make pregnant women susceptible to certain infections, including COVID-19 infection (Zhao et al. 2020). These changes include relaxation of rib ligaments, diaphragmatic elevation and decreased functional residual capacity of the lungs with the effect of progesterone. Various studies have reported that viral infections during pregnancy are associated with low birth weight and preterm delivery. Furthermore, fever seen in viral infections may increase certain birth defects (Yang et al 2020; Rasmussen ve ark. 2012; Silasi 2015). Since these changes are required to provide maternal-fetal balance, maternal immune response may play a critical role in the pathophysiology of coronavirus infections.

Maternal physiological adaptations to pregnancy are known to increase the risk of developing severe diseases such as influenza. Inıtial studies have suggested that the prognosis of COVID-19 infection may be severe in pregnant women (Savashi et al. 2020). It was reported in a recent study that pregnant women infected by SARS-CoV-2 have a higher risk of mortality than non-pregnant women. In addition, mortality index of neonates born from these

women was reported to be higher than the infants born from non-pregnant women (Villar et al. 2021).

Vertical transmission has not been documented with the other previous two coronaviruses SARS-CoV and Middle East Respiratory Syndrome (MERS). However, the studies with pregnant women reported to be infected are scarce and are not enough to draw a conclusion. Twelve pregnant women were reported for SARS-CoV and 11 for MERS (Wong et al. 2004; Alfaraj et al. 2019). Three of 12 pregnant women with SARS-CoV died during pregnancy, two experienced growth retardation in the second and third trimesters, and four had a miscarriage in the first trimester. No maternal transmission has been found in these women (Wong et al. 2004). Whereas, among the 11 pregnant women infected during MERS, premature delivery, intensive care required for newborns and clinical outcomes such as maternal and perinatal deaths were observed by 91%, but maternal infection transmission was not found (Alfaraj et al. 2019).

COVID-19 virus is known to bind to cells through angiotensin converting enzyme II (ACE II). ACE II is a membrane bound aminopeptidase enzyme, which plays a role in degradation of substances such as angiotensin I and II that are a basic protective mechanism in regulation of vascular and heart function, and is known as a COVID-19 receptor. ACE II is an enzyme found in many tissues including lungs, arteries, heart, kidneys, placenta and intestines. ACE II is widely distributed in specific cell types of the maternal-fetal interface. Cells that express ACE in the plasma include

syncytiotrophoblasts and cytotrophoblasts in villi, decidual stromal cells, endothelial and smooth muscle cells. The viral receptor ACE II, theoretically abundant in the human placenta, may increase the susceptibility of the placenta and possibly the fetus to COVID-19 (Ashary et al. 2020).

3. MATERNAL – FETAL COVID-19 TRANSMISSION

Viral pneumonia is an important cause of morbidity and mortality among pregnant women (Gorbalenya 2020). Maternal pneumonias are associated with adverse pregnancy outcomes. These changes include premature membrane rupture, preterm labor, intrauterine fetal demise, intraoperative growth retardation and neonatal death (Schwartz and Graham 2020). Prevention and control of the infection has become an important source of concern because of the high transmissibility of COVID-19 (Qiao 2020).

Pregnant women are more susceptible to respiratory pathogens and development of severe pneumonia compared to the general population. Cell mediated changes in immunity and pulmonary function that occur during pregnancy may increase susceptibility and severity of pneumonia. Pneumonia resulting from infectious etiology is the most common non-obstetric infectious condition in pregnant women (Jamieson et al. 2006). COVID-19 pneumonia is a complicated condition in pregnancy and management and treatment of these patients requires multidisciplinary team work including

gynecologists, nosocomial infection control specialists, internal medicine specialists, and psychologists (Luo and Yin 2020).

Currently, what is known about the effects of COVID-19 on pregnant women and infants is quite insufficient and there is still no recommendation specific to pregnant women for evaluation and management of COVID-19. CDC has prepared an interim guideline about breastfeeding for pregnant women with confirmed COVID-19 or those under investigation for the infection. It has been reported in the guideline that infants aged less than 12 months are at risk of severe illness due to COVID-19. However, the association of this risk with maternal transmission has not been emphasized (CDC 2021). Likewise, it is not known whether COVID-19 is transmitted through breastfeeding. Nevertheless, it is obvious that an infected mother can pass the virus to the infant via droplets during breastfeeding (Rasmussen et al. 2020). Transmission of the disease from the mother to the infant has been shown in some comprehensive virologic and pathologic studies (Vivanti et al. 2020). Transplacental transmission has been proposed to occur in three phases: 1) maternal viremia, 2) placental infection and 3) neonatal viremia. In addition, it is also possible that an undiagnosed / asymptomatic concurrent genital tract infection may pass the placenta and allow the virus to reach the amniotic cavity. Higher SARS-CoV-2 positivity has been demonstrated in placental and nasopharyngeal smears collected in infants born from women with severe or critical COVID-19 disease immediately after birth (Hosier et al. 2020; Penfield et al. 2020).

However, these findings are unstructured and newborn still do not show disease manifestations (Zaigham et al. 2020).

4. MATERNAL-FETAL COVID-19 TRANSMISSON ROUTES

Some viruses can pass between the mother and the fetus generationally. Placental transmission may occur with break of the placental barrier, at delivery and during breastfeeding. Many microorganisms may violate the maternal immune system barrier through placenta, leading to serious consequences. Viruses may show dynamic fluctuations in the immune setting of the placenta during pregnancy and contribute to fetal susceptibility (Mahyuddin et al. 2020). It has been proven that some viruses (HIV, toxoplasma gondii, rubella, cytomegalovirus and herpesviruses) are transferred from mother to child in this way. This is known as vertical transmission. COVID-19 is very rarely reported in newborns and there have been cases with a positive test within 24 hours after birth. A recent study reported that vertical transmission is most likely to occur when the mother becomes infected during the third trimester (Kotlyar et al. 2021).

In general, maternal-fetal COVID-19 transmission routes are:

1. Intrauterine vertical transmission
2. Transmission at birth
3. Transmission during breastfeeding

4.1. Intrauterine Vertical Transmission

Cytomegalovirus, rubella, Herpes Simplex, Zika and parvovirus are known to infect and/or pass through the placenta, subsequently affecting the unborn infant (Arora et al. 2018). When the known information is generally evaluated, there is no definitive evidence supporting vertical transmission of COVID-19 (Schwartz and Graham 2020). Studies reporting intrauterine COVID-19 transmission are limited, mostly in the form of case reports (Elkafrawi et al. 2020). However, vertical transmission can not be completely ruled out. Immunohistochemical placental studies on COVID-19 have shown cytoplasmic staining in the syncytiotrophoblastic cells, and ultrastructural examinations performed with transmission electron microscope have revealed viral particles compatible with SARS-CoV-2 (Vivanti et al. 2020).

However, the mechanism of intrauterine COVID-19 transmission could not be fully determined (Chen et al. 2020). This is explained with immune tolerance, which is a risk factor for viral and bacterial infection acquisition of pregnancy (Erlebacher 2013; Guerin et al. 2009). Even if the newborn is asymptomatic, there is a possibility of intrauterine vertical transmission of COVID-19 under these conditions: (1) if the mother is infected 14 days before to 2 days after the birth (2) if the virus was detected in neonatal respiratory smear (nasopharynx, oropharynx, or saliva) within the first 24 hours of life, and (3) if IgM test of the newborn is positive within the first 7 postnatal days (Byonanuwe et al. 2020).

4.2. Vertical Transmission at Birth

Delivery in the negative pressure isolation setting is recommended in the case of detected or suspected COVID-19 infection (Verma et al. 2020). Currently, data about COVID-19 in newborns are limited (Kimberlin and Stagno 2020). In addition, there is no evidence on optimal delivery timing, safety of vaginal delivery or whether cesarean section can prevent transmission (Karimi et al. 2020). Studies reporting the prevalence of maternal and neonatal complications have proposed that the risk of preterm delivery increases in pregnant women with COVID-19 (Di Mascio et al. 2020). In a study from China, the risk of preterm delivery and cesarean section was reported to increase in pregnant women with COVID-19 compared to those without COVID-19 (Yang et al. 2020). According to a report published by WHO, the number of pregnant women with COVID-19 is globally increasing and there is a concern about transmission from the mother to the infant in *in utero*, intra partum or early postnatal period (Allotey et al. 2020). Maternal infection should be diagnosed close to birth in order to diagnose transmission at birth (starting from 14 days before the birth until 2 days after the birth). Although a sample collected during cesarean section in which placenta and fetus can be delivered under sterile conditions is less prone to contamination than vaginal delivery, there is significant exposure to blood also in cesarean section. Therefore, the probability of detecting a virus in a sample taken during cesarean delivery is lower than vaginal delivery.

4.3. Transmission During Breastfeeding

Mother milk is the best source of nutrition for most infants and provides protection against many diseases. Although benefits of mother milk for the mother and the infant have been well-documented (Victora et al. 2016), there has been uncertainty about breastfeeding in the early stages of the pandemic. Evidence based recommendations are needed to eliminate this uncertainty. The probability of COVID-19 transmission via breastfeeding has raised concerns. According to the recommendations by WHO, mothers with confirmed or suspected diagnosis of COVID-19 should be encouraged to start or continue breastfeeding. The benefits of breastfeeding outweigh the potential risk of transmission (WHO 2020). In a study by Groβ et al., SARS-CoV-2 RNA was detected in breast milk. However, the authors stated that their findings should be carefully interpreted and further studies are needed on this issue (Groβ et al. 2020). COVID-19 transmission via breast milk has been reported as case reports. Nevertheless, none of these studies have included evidence of complete and/or active virus. On the other hand, contamination of breast milk by droplets from the mother during breastfeeding can not be ruled out. In conclusion, WHO, Unicef, CDC and Royal College of Obstetricians and Gynaecologists recommend mothers to continue breastfeed their infants (Leon et al. 2020).

5. SCIENTIFIC RESEARCH ON MATERNAL -FETAL COVID-19 TRANSMISSION

When the literature is examined, there is no consensus yet on the transmission of COVID-19 from the mother to the infant. Some studies have reported maternal-fetal COVID-19 transmission, while others stated no transmission. Some examples of these studies are discussed below.

5.1. Studies Reporting Maternal Transmission

There are studies reporting COVID-19 transmission from the mother to the fetus via the placenta, although some studies report no such transmission. In Wuhan province of China, the diagnosis of COVID-19 was confirmed with computed tomography and the results of RT-PCR test in six pregnant women. Samples were collected with throat swabs from mothers at birth and from neonatal blood. Virus specific antibodies were detected in the serum samples of the newborns. IgG concentrations were elevated in five newborns and transfer from the mothers to the fetuses occurred at the end of the second trimester (Zeng et al. 2020).

In studies conducted by Zeng et al. (2020) and Dong et al. (2020), SARS-CoV-2 specific IgG and IgM antibody levels were reported to increase in blood samples of three newborns born from COVID-19 infected mothers. Placental submembrane and coledon were reported to be positive in a 20-day miscarriage of a woman with COVID-19 (Baud et al. 2020).

In a study by Fenizia et al. (2020), the presence of SARS-CoV-2 genome was detected in umbilical cord blood and term placentas, vaginal mucosa and milk samples of 31 pregnant women. In this study, the rate of SARS-CoV-2 positivity was found as 6% (Fenizia et al. 2020). Likewise, there are studies reporting SARS-CoV-2 genome in term placentas (Vivanti et al. 2020; Algarroba et al. 2020; Hosier et al. 2020). When these studies are examined, it is seen that placental transmission of COVID-19 is possible and occurs in a small number of cases with maternal COVID-19 infection. The rates reported by these studies are similar to those reported with other pathogens that cause congenital infection. However, considering the low number of participants in studies on this subject and the limited data, especially based on the trimesters of pregnancy, a clear assessment can not be made in terms of placental transmission rates during pregnancy, fetal morbidity and potential risk of mortality. Moreover, it has been reported that all pregnant women who present for delivery and have a positive COVID-19 test were asymptomatic (Suptom et al. 2020).

5.2. Studies Reporting No Maternal Transmission

In a multicenter study by Marin Gabriel et al. (2020) with 242 pregnant women in Spain, vertical transmission was not found in newborns. Yan et al. (2020) found no vertical transmission in their series of 99 mothers with COVID-19 and none of the infants had positive tests. Liu et al. reported no placental transmission after birth in 19 mothers with COVID-19 and PCR tests of newborns were

negative. In the same study, PCR was negative also in amniotic fluid and breast milk samples (Liu et al. 2020).

In a published retrospective study, clinical characteristics of SARS-CoV-2 infection in pregnancy were reported to be similar to those in non-pregnant adults with SARS-CoV-2. In the same study, PCR test was negative in amniotic fluid, neonatal throat swab and breast milk samples of six pregnant women (Chen et al. 2020). In a case series from China, PECR test was negative in infants born from womens with confirmed diagnosis of COVID-19

CONCLUSION

Today, the COVID-19 infection is burning the whole world as a disaster, and devastating effects of the pandemic cause deep wounds in daily life of people in social, economic and psychological areas, and especially in health care systems. In many diseases, people with chronic diseases, elderly, children and pregnant women are considered as risky groups. The main reason for this is that the immune response given by the people in these groups to diseases and especially infections is reduced due to their conditions. In the patients in these groups, immunological developments are seen as a response during the course of the disease and a more intensive fight against diseases is experienced with antibodies produced by the body. Elderly people and those with chronic diseases are at risk for COVID-19 due to the mentioned reasons. The effects of the original and new variants of COVID-19 in infants and children have not been fully understood and

it is argued that children are more vulnerable against the new variants that have undergone mutation.

In pregnant women, the situation is a little more complicated. It is known that pregnant women adapt to the disease process as a result of the physiological, psychological and immunological changes they experience in many diseases. As a result of these changes, pregnant women are among the risky groups in numerous diseases. It has been previously known that maternal-fetal transmission occurs in many infections such as influenza. However, the issue of transmission of COVID-19 infection from mothers to infants has not been fully clarified. As discussed above, although there are some studies in the literature reporting maternal-fetal COVID-19 transmission, there are also studies reporting the absence of such a transmission. In these studies, negative test outcomes were obtained in infants of many mothers with COVID-19. However, given the limited number of these studies and study participants, it is not possible to draw a definitive conclusion about maternal fetal COVID-19 transmission.

COVID-19 infection has a very dynamic structure, and every day new transmission routes, new symptoms, complications, variants, etc. are added to what we know. Therefore, it is too early to reach a full conclusion about the maternal COVID-19 transition and there is still a long way to go. In conclusion, it is recommended to promptly test newborns born from pregnant women infected with COVID-19 infection and to evaluate the actual risks of maternal transmission in order to develop appropriate preventive and treatment strategies.

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CHAPTER 4

KNOWLEDGE, ATTITUDE AND BEHAVIOR OF TURKISH NURSES ABOUT COVID-19

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ABSTRACT

Aim: This study was conducted descriptively to determine knowledge, attitudes, and behaviors of nurses in Turkey about COVID-19 pandemic while fighting against the pandemic.

Method: The data of the study were collected by using descriptive characteristics form prepared by the researchers, questions determining attitudes and behaviors and information questions prepared based on the COVID-19 Guidelines prepared by T.R. Ministry of Health. The questionnaires were sent to the nurses working actively in Turkey between 13.04.2020 and 04.05.2020 through e-mail, Whatsapp and social media by using Google form and feedbacks were obtained from 1236 nurses. Necessary permissions were obtained from the ethics committee and the Ministry of Health for the study. For the statistical analysis, SPSS 21.0 package program was used and percentage, arithmetic mean and standard deviation were calculated.

Results: When the descriptive characteristics of 1236 nurses participating in the study were examined, it was found that 80.9% of nurses received training, 54.4% of those who received training got the in-service training from their institution, and 50.2% encountered a possible COVID-19 patient. To the information questions about structural characteristics of SARS CoV-2 and the conditions it causes, the nurses gave correct answers between 55.5% and 87.4%. The nurses gave correct answers of 47.5-93.1% to the information questions about the diagnosis and follow-up practices and they

responded correctly to the information questions about protection from COVID-19 disease at the rate of 58.5-96.1%. It was seen that the nurses exhibited abstaining attitudes toward COVID-19 disease and developed a high rate of prophylactic behaviors toward the disease.

Conclusion; It was determined that a great majority of the nurses received in-service training about COVID-19 and had correct information and behaviors toward coronavirus and its diagnosis-treatment, transmission and prevention methods. However, it was determined that the nurses were negatively affected by this process and they experienced fear, nervousness, anxiety, sleep problems and thus decreased job motivation toward COVID-19.

Keywords: COVID-19, Pandemic, Behavior, Attitude, Nursing

INTRODUCTION

Viruses are agents having only one of the DNA or RNA associated with proteins and causing infection (Hunt, 2016). Viruses which are transmitted in different ways and have many forms rapidly spread through respiratory tract diseases they cause. Therefore, it takes a long-term process to control and treat them (Ağca et al., 2019). Among viruses, coronaviruses are the virus family appearing at certain times and causing epidemics. Some types of these viruses, which are generally transmitted from animal to animal, can also transmit to human beings. Human coronaviruses can cause diseases from common cold to more serious illnesses such as Middle East Respiratory Syndrome (MERS) or Severe Acute Respiratory Syndrome (SARS) when they are transmitted (Yücel and Görmez, 2019; Şencan and Kuzi, 2020).

Coronaviruses first appeared in China in 2003. They caused SARS disease and spread across 37 countries in a short time like 4 months. This was reported as the first international health emergency of the 21st century (Yücel and Görmez, 2019). 9 years after this outbreak, the second coronavirus outbreak occurred in Saudi Arabia in 2012. This disease was defined as MERS. In both epidemics, almost 50% of individuals over 65 years of age who got the disease lost their lives (İnal, 2016). A new type of coronavirus (2019- nCoV), which has been announced as a pandemic by the WHO on March 11, 2020, and which has significantly affected the world, has been identified (WHO, 2020). The pandemic, which caused a major concern globally, was

detected by the China Country Office on December 31, 2019 with the reporting of unknown pneumonia cases in Wuhan city, China (WHO, 2020). The virus particularly causes severe acute respiratory infection. Therefore, it has been named as SARS-CoV-2 (COVID-19) by considering its resemblance to SARS disease. When droplet-borne COVID-19 disease first appears, its symptoms are fever, cough, and dyspnea. After observing the symptoms, death may occur as a result of severe respiratory failure due to lower respiratory tract infections such as bronchiolitis or pneumonia if the disease progresses (FIP Health Counseling, 2020). In addition to the severe cases resulting in death, there are quite a lot of cases that survive the disease without showing any symptoms in the outpatient clinic (Nanshan-Chen, 2020). The COVID-19 outbreak that affected the world was seen in approximately 150 million people and more than 3 million died. Although it first appeared in China, while China took the pandemic under control, our country ranks 6th after the United States, India and Brazil on the daily case list. (https://www.worldometers.info/ coronavirus/ Access: 26.04.2021). It causes a great concern for humans due to the fact that it has no proven definitive treatment, it spreads quickly via droplets, is fatal and has no proven vaccine (Sun et al., 2020; Ramaiah and Arumugaswami, 2020). For this reason, all countries have taken various measures against the virus. Spread of the virus has been tried to stop by taking strict measures such as restrictions on entrances and exits to countries such as China, Iran, Italy, Korea and the USA where the virus is seen, quarantine application for cases with high fever in passengers from these

countries, closing the workplaces, canceling crowd organization and entertainment, transition to distant education in schools, imposing a curfew, working at home or flexible hours, and obligation to wear a mask(https://thinktech.stm.com.tr/uploads/raporlar/pdf/642020135824738_stm_blog_covid_19_ile_mucadelede_ornek_ulkeler.pdf,Erişim:31.05.2020). In addition to the general measures many other measures such as establishing pandemic hospitals, quarantine application for individuals coming from abroad, the curfew for individuals under the age of 20 and over 65, reducing the capacity of public transportations to 50%, controlling the entrance and departure from the cities where the number of cases are high, quarantine application, and distributing masks for free, etc. have been taken in Turkey (TÜBA, 2020). In our country, Ministry of Health prepared coronavirus guides individually for healthcare professionals and public by setting up a science committee in Turkey and have constantly updated and made them available at its website. These guides have been a guide by clearly identifying what to do and treatment procedures for healthcare professionals in possible and certain cases (Bahadır, 2020; Er and Ünal, 2020). Stocks of personal protective equipment (gloves, liquid proof gowns and workwear, safety glasses, face shield, medical mask, alcohol-based hand disinfectant) have increased for healthcare personnel. All healthcare professionals were informed about standard, contact and droplet isolation measures for coronavirus cases in hospitals. Algorithms have been developed for the termination of isolation in COVID-19 patients, in patients who have no hospitalization indication but are followed-up at home and in

healthcare professionals with COVID-19 contact (T.R Ministry of Health, 2020).

As a result of the deaths of hundreds of thousands of people in epidemics, high cost vaccination and drug studies have revealed to the importance of health services. Additionally, this situation has caused health expenses to take place on the top among all expenditures in the world. Considering that coronaviruses are transmitted through droplets, health care workers who first encounter and treat patients with disease have more risk of pandemic than the general population. The fact that 20% of cases in SARS- CoV outbreak in 2003 were healthcare professionals proves this situation (Yücel and Görmez, 2019; Ludwig and Zarbock, 2020). Although there is no systematic and standard record about the number of nurses and healthcare professionals who got COVID-19 or died due to this disease around the world, according to the analysis of ICN it is stated that averagely 7% of all COVID-19 cases in the world are health care professionals. Hundreds of nurses have been reported to have died worldwide due to the COVID-19 outbreak. (https://www.icn.ch/news/more-600-nurses-die-COVID-19-worldwide, Erişim: 05.06.2020). Nurses, who have the largest population among healthcare professionals, are also at risk since they are responsible for one-to-one follow-up of the patients and get close contact with them. Therefore, having sufficient knowledge about COVID-19 disease and developing protective behaviors for nurses show that they will take a more active role in the pandemic. As a result of the COVID-19 state analysis result conducted by the

Turkish Nurses Association (THD), recommendations were made to improve knowledge and skills. The Turkish Nurses Association has suggested that the nurses who will work in pandemic services or COVID-19 intensive care units should receive a qualified and rapid orientation training program and then they should be gradually assigned in pandemic clinics and intensive care units, respectively under the guidance of experienced nurses (THD, 2020). It is also stated that while providing optimal treatment to the patients infected with COVID-19 in this process, personal protective measures and infection control measures should be applied carefully to prevent transmission to other patients and healthcare providers (Wax, Randy and Christian, 2020). In this context, it is very important for nurses to take preventive measures against transmission of coronavirus for primary protection, which is the first measure in epidemics, to know nursing interventions in possible-certain case situations not only for themselves but also for patients and other healthcare professionals. In addition, considering the educational role of nurses, their contribution in raising awareness in public can be effective in reducing the number of increasing cases.

MATERIAL METHOD

This descriptive study was conducted to determine the knowledge, attitudes, and behaviors of nurses in Turkey about COVID-19 pandemic while fighting against the pandemic.

Population and Sample of the Study

The population of the study was composed of nurses actively working in Turkey between 13.04.2020-04.05.2020. 1236 of the nurses completed the questionnaire completely. Since it is known that approximately 200.000 nurses are working in Turkey (Number of Healthcare Professionals, http://www.tuik.gov.tr/Start.do, Access: 25.05.2020), the collected 1236 data were determined to constitute adequate sample size with p=0.05 and sampling error of 0.03.

Data Collection

Data collecting; It consists of "Introductory Information Form" and "Information, Attitude and Behavior Form about COVID-19" created by researchers. Information questions prepared for COVID-19 in the questionnaire were prepared based on the “Current COVID-19 healthcare Professionals Guide” published by the Ministry of Health on March 25, 2020. Since the COVID-19 outbreak has continued during the study, the questionnaire questions could not be applied with face-to-face interview method. The data of the study were collected between 13.04.2020 and 04.05.2020 by using Google forms through e-mail, Whatsapp and social media (Instagram and Facebook). Nurses who agreed to participate in the study, filled out the online questionnaire completely, were actively working in any state, private, university hospitals or Family Health Centers in Turkey were included in the study. Necessary permissions were obtained by applying through the system set by the Ministry of Health for COVID-19 and from

Gaziantep University Clinical Trials Ethics Committee (Decision No: 2020/137) and T.R Ministry of Health in order to conduct the study.

Data Analysis

SPSS 21.0 package program was used in the data analysis. In order to determine descriptive characteristics of the nurses and their knowledge, attitudes and behaviors about COVID-19, percentage, arithmetic mean, and standard deviation were used.

RESULTS

When the descriptive characteristics of 1236 nurses participating in the study were examined, it was found that 81.4% were female, 64.5% had a bachelor's degree, 52.5% were married, and 55.1% had children. The mean age of the nurses was 30.4±7.6, and their working duration in the profession was 8.5±7.8 years. Of the nurses in the study, 69.5% were working in state hospitals, 24% were working in corona quarantine intensive care units established in pandemic hospitals, and 25.7% were working in other units (infection control unit, training unit, etc.). When their status of receiving information about COVID-19 was examined, it was found that 80.9% received training, 54.4% of those who received training received an in-service training from their institution, and 11.8% received training from the website of T.R. Ministry of Health. 85.7% of the nurses stated that they did not have chronic diseases and 50.2% stated that they encountered possible COVID-19 patients (Table 1).

Table 1. Descriptive Characteristics of the Nurses

Descriptive Characteristics		**n**	**%**
Gender	Female	1007	81.4
	Male	229	18.5
Education Level	High school	152	12.3
	Associate degree	140	11.3
	Undergraduate degree	798	64.5
	Graduate degree	146	11.8
Marital Status	Married	649	52.5
	Single	587	47.4
Children	Yes	554	44.8
	No	682	55.1
Health Organization	State Hospital	859	69.5
	University Hospital	180	14.5
	FHC	100	8.0
	Private Hospital	97	7.8
Unit	Emergency Department	200	16.1
	Surgery/Internal Medicine Service	200	16.1
	Corona Quarantine Service	153	12.3
	Corona Quarantine Intensive Care	297	24.0
	FMC Outpatient	68	5.5

	Clinic		
	Other	318	25.7
Presence of Chronic Disease	Yes	176	14.2
	No	1060	85.7
Status of Receiving Training about COVID-19	Yes	1000	80.9
	No	236	19.0
Sources of Information	In-service Training	673	54.4
	Out-service Training	14	1.1
	Television	87	7.0
	Social media	42	3.4
	Healthcare Professionals	36	2.9
	Ministry of Health website	147	11.8
	Internet	130	10.5
The status of encountering with a Possible COVID-19 Patient	Yes	621	50.2
	No	615	49.7
Age (X±SD)		30.4±7.6	
Duration of Working in Profession (X±SD)		8.5±7.8	

The nurses responded correctly with the rate of 55.5% and 87.4% to the information questions about the structural characteristics of new

type coronavirus which caused pandemic in the world and was named as SARS Cov-2 and the conditions it caused (Table 2).

Table 2. Nurses' Knowledge about SARS-CoV-2

Nurses' Information about SARS-CoV-2 n (%)			
	True	**False**	**I do not know**
It is a new coronavirus that has not been detected in human beings	765 (61.8)	407 (32.9)	64 (5.1)
It is a zoonotic virus that can cause various diseases from the common cold to severe acute respiratory syndrome.	1081 (87.4)	73 (5.9)	82 (6.6)
It is from the same virus family as the SARS and MERS epidemic seen in previous years.	1005 (81.3)	99 (8.0)	132 (10.6)
It is a subtype of influenza viruses with asymptomatic course without mortality risk.	113 (9.1)	999 (80.8)	124 (10)
It is a virus that first appeared in human beings.	241 (19.5)	895 (72.4)	100 (8.0)
It is not found in any other creatures other than human and bats.	239 (19.3)	695 (56.2)	302 (24.4)
It does not cause pneumonia	65 (5.2)	1086 (87.8)	85 (6.8)
There are many different	686	143	407 (32.9)

coronaviruses that have not yet been transmitted to humans	(55.5)	(11.5)	

When the nurses' knowledge about treatment and diagnosis of COVID-19 disease is examined, 65.1% of the nurses responded PCR (molecular test) for the definitive diagnosis method for the disease and the closest rate of 26.6% responded as lung tomography. To the practices made for the diagnosis and follow-up of the disease, the nurses responded correctly with the rates between 47.5%-93.1%. The rate of nurses who did not know if the obtained samples for diagnosis are kept at room temperature was striking (33.1%) compared to other data. The nurses answered correctly the typical symptoms of the disease at a very high rate (98.3%). The nurses responded correctly to the questions regarding the treatment of COVID-19 patients at the rate of 60.1%-98.1%. The rate of those (10.6%) who did not know the questions about whether symptomatic treatment in these patients can be applied or not was higher than those who responded incorrectly (5.5%) (Table 3).

Table 3. Nurses' Information on the Diagnosis and Treatment of COVID-19

Nurses' Knowledge about Diagnosis and Treatment of COVID-19			**n (%)**	
What is the final diagnosis method indicating the presence of COVID-19?	Chest x-ray 25 (2)	Lung Tomography 329 (26.6)	PCR 805 (65.1)	Blood Test 77 (6.2)
	True	**False**	**I do not know**	
Oropharyngeal or nasal swab is taken for diagnosis	1151 (93.1)	60 (4.8)	25 (2)	
Swab is taken from the rectal area for diagnosis	29 (2.3)	1129 (91.3)	78 (6.3)	
Samples taken for diagnosis are kept at room temperature	238 (19.2)	588 (47.5)	410 (33.1)	
Individuals from whom swabs were taken are reported to District Health Directorate	868 (70.2)	165 (13.3)	203 (16.4)	
The absence of COVID-19 in the first sample taken from the patient according to the possible case definition indicates that the patient is not COVID-19.	98 (7.9)	1088 (88.0)	50 (4)	
The most typical symptoms of the disease are fever, dry cough, and dyspnea	1215 (98.3)	21 (1.7)	-	
Patients can be treated in the first-line hospitals	368 (29.7)	744 (60.1)	124 (10)	
It has a proven definitive treatment	70 (5.6)	1118 (90.4)	48 (3.8)	
Antivirals and antibiotics can be used in treatment.	894 (72.3)	196 (15.8)	146 (11.8)	
Symptomatic treatment can be applied	1036 (83.8)	69 (5.5)	131 (10.6)	
Oxygen is applied in treatment	1173 (94.9)	42 (3.4)	21 (1.7)	
Despite treatment, the highest mortality rate is observed in 65 years and over.	1213 (98.1)	23 (1.8)	-	
There are proven vaccines available to prevent disease	15 (1.2)	1188 (96.1)	33 (2.6)	

When it was asked how COVID-19 disease is transmitted from person to person primarily-mainly, 58.5% of the nurses said droplets, 22.2% said contact and 19.1% said through respiration. The rate of nurses who knew that there is no well-proven vaccine developed to protect from the disease caused by the virus was 96.1%. When the responses given for the measures to be taken to prevent this disease were examined, the nurses responded correctly at the rates of 60.1%-92.6%. The nurses mostly stated that mask should be worn to prevent disease in crowded environments and when going out (92.6%). The rate of nurses, who stated that surgical masks, gloves, glasses and gowns should be worn when it is necessary to get close to the patients suspected to have COVID-19 less than 1 meter, was pretty high (87.1%). The rate of the nurses who stated that they should wear N95/N99 masks when doing intervention that will cause secretions or aerosolization of body outputs of the patient was also very high (96.3%) (Table 4).

Table 4. Nurses' Knowledge about the Protection from COVID-19 Disease

Nurses' knowledge for the protection from COVID-19 disease	**n (%)**		
	True	**False**	**I do not know**
Persons who had contact with infected individuals do not need to stay at home and away from public areas during the incubation.	100 (8)	1122 (91.9)	-
Personal protective materials should be kept in the patient's room and should be worn as soon as entering the room.	192 (15.5)	1004 (81.2)	40 (3.2)
The nurse who will be in close contact with the patient with COVID-19 suspicion less than one meter should be wearing a surgical mask, gloves, glasses and gown.	1077 (87.1)	159 (12. 8)	-
The mask should be removed before leaving the patient's room	156 (12.6)	1038 (83.9)	42 (3.4)
The blood pressure monitor, thermometer and stethoscope used for the diagnosed patients can be used for other patients after disinfestation.	743 (60.1)	437 (35.3)	56 (4.5)
Everyone should wear a mask when going outside/entering public places	1145 (92.6)	59 (4.7)	32 (2.5)
There are proven vaccines available to prevent disease	15 (1.2)	1188 (96.1)	33 (2.6)
What is the primary-main mode of transmission of the disease?	**Respiration** 237 (19.1)	**Droplet** 724 (58.5)	**Contact** 275 (22.2)
Which mask should be worn while conducting interventions that will cause secretions or aerosolization of body outcomes?	**N95/ N99 Mask** 1191 (96.3)	**Surgical Mask** 23 (1.8)	**I do not know** 22 (1.7)

The nurses exhibited various attitudes toward the disease in the COVID-19 pandemic. When the attitudes of Turkish nurses were

examined, 88.1% stated that they were negatively affected by the pandemic psychologically, 85.2% of the nurses who encountered with a patient with high fever stated that they got nervous and they were suspicious that the patients with flu can be COVID-19 patients (82.2%). The rate of the nurses (90%) who were afraid of coronavirus transmission from patients was quite high. While 45.9% of the nurses hesitated to communicate with a patient with COVID-19, 37.2% stated that they could communicate. 83% of the nurses stated that their motivation decreased due to increased cases and 76.9% of them stated that they had sleep problems. 89.8% of the nurses stated that they followed the updated number of cases in the world and in Turkey until late night from television or the Internet and 89% said that they prayed for the pandemic to end. In addition, it was seen that when Turkish people applauded healthcare professionals at 21:00 every day, this motivated 77% of the nurses. The rate of nurses who considered that giving care to the patient with COVID-19 causes anxiety was 78.5% and the rate of those who considered that personal protective equipment is sufficiently effective was 68.8%. More than half of the nurses (54.8%) stated that they wanted to have vaccine when it would be developed and 17.6% stated that prophylactic drugs should be used in order not to become infected. Nearly half of the nurses (42.1%) considered that the number of new cases would decrease with the increase in seasonal temperatures (Table 5).

Table 5. Nurses' Attitudes toward COVID-19 Disease

Nurses' Attitudes toward COVID-19 Disease	Yes	Undecided	No
I think I was negatively affected by the pandemic	1089 (88.1)	-	147 (11.8)
I get nervous when I encounter a patient with high fever	1054 (85.2)	34 (2.7)	148 (11.9)
I am afraid of getting infection of coronavirus from patients	1113 (90)	33 (2.6)	90 (7.2)
I hesitate to contact a patient with COVID-19	568 (45.9)	208 (16.8)	460 (37.2)
Providing care to the patient with COVID-19 causes me anxiety	971 (78.5)	82 (6.6)	183 (14.8)
I suspect that patients with the flu may have COVID-19	1016(82.2)	59 (4.7)	161(13)
My work motivation decreases due to the increase in cases	1027 (83)	-	209 (16.9)
Until late hours, I follow the latest number of cases from TV or Internet.	1111 (89.8)	-	125 (10.1)
I have sleep problems due to the pandemic	951 (76.9)	-	285 (23)
Applause of the people to the health personnel at 21:00 motivated me	952 (77)	-	284 (22.9)
I pray for the pandemic to end	1100 (89)	-	136 (11)
I want to get vaccinated when COVID-19 vaccine is developed	678 (54.8)	352 (28.4)	206 (16.6)

I think we should use prophylactic drugs (antibiotics, antiviral, malaria medicines, etc.,) to avoid getting infected.	218 (17.6)	190 (15.3)	828 (66.9)
I think that personal protective equipment, one of the protection measures, is sufficiently effective in protecting from the virus.	851 (68.8)	181 (14.6)	204 (16.5)
I think the number of new cases would decrease as the seasonal temperature increases	521 (42.1)	376 (30.2)	339 (27.4)

It was found that 9.6% of the nurses participating in the study stated that they did not always go to their home after leaving work due to the fear of infecting family members at home and stayed in the accommodation places such as dormitories and police house allocated by the Ministry of Health. In order to protect themselves from the virus, 48.5% of the nurses stated that they always took a shower right after they came home from work, 41.7% stated that they always washed their clothes separately and at high temperature and 61.8% stated that they cleaned the common areas in their houses with bleach. 37.7% of the nurses stated that they sometimes took immune-enhancing drugs to protect themselves from the virus and these were immune- enhancing drugs or supplements, Vitamins (B, C, D Vit.), Flu Drugs, Oxetalmivir, Hydroxychloroquine, Zinc, Selenium and Magnesium, respectively. In addition, the nurses also stated that they sometimes applied alternative medicine methods (52.7%). They also

mentioned that they sometimes consumed more fruits and vegetables than usual to protect themselves from the disease (64.3%). 23.3% of the nurses stated that they always washed the food and the stuff they purchased from the market with vinegar water. The rate of those who were always wearing personal protective equipment in case of encountering possible COVID-19 patients in their units was 32.6%, the rate of those who were always keeping mask, gloves and protective equipment at home was 50.4% and the rate of those who were always having cologne or disinfectant at home was 44.8%. Total rate of those who were always or sometimes stocking food at home along with the spread of the virus was 62.9%. 87% of the nurses stated that they always or sometimes avoid having close contact with their family and people around them such as kissing and hugging (Table 6).

Table 6. The Nurses' Preventive Behaviors of COVID-19

The Nurses' Preventive Behaviors of COVID-19	**n(%)**		
	Never	**Sometimes**	**Always**
I stay at accommodation places (dormitory, police house, hotel, etc.) that are arranged in order not to infect COVID-19 to my family members at home.	823 (66.5)	294 (23.7)	119 (9.6)
I take a shower as soon as I come home from the hospital	101 (8.1)	535 (43.2)	600 (48.5)
I take immune-enhancing medicines to protect myself from the virus	655 (52.9)	467 (37.7)	114 (9.2)

I always use personal protective equipment, considering the possibility of encountering a patient with COVID-19 in my unit.	133 (10.7)	700 (56.6)	403 (32.6)
I clean the common places in my house with bleach	107 (8.6)	765 (61.8)	364 (29.4)
I wash my clothes with normal detergent at 60-90 degrees separately from my family	135 (10.9)	585 (47.3)	516 (41.7)
I consume more vegetables and fruits than usual	160 (12.9)	795 (64.3)	281 (22.7)
I wash the food and stuff I purchase from the market with vinegar water	229 (18.5)	719 (58.1)	288 (23.3)
I use alternative medicine methods that I heard to protect myself from the virus	465 (37.6)	652 (52.7)	119 (9.6)
I keep protective equipment such as mask, gloves, etc. at home	192 (15.5)	623 (50.4)	421 (34.0)
I keep cologne or disinfectant in my house against COVID-19	134 (10.8)	548 (44.3)	554 (44.8)
I stock food in my home with the spread of the virus	458 (37.0)	700 (56.6)	78 (6.3)
I am not in close contact (such as kissing, hugging) with my family and people around me due to the pandemic	159 (12.8)	500 (40.4)	577 (46.6)

DISCUSSION

The world is fighting against COVID-19 pandemic which has infected more than 150 million people and has resulted in death of hundreds of thousands of people. Since the pandemic began to seen in Turkey, it has caused anxiety and fear in people. Since Turkey is a country that has closely monitored the pandemic seen in many countries of the world, it was foreseen that the virus would also be seen in Turkey. Therefore, various measures were started to be taken before the virus seen in Turkey and WHO announced the COVID-19 outbreak caused by the virus as a pandemic. These measures primarily included providing trainings about the virus and its possible situations. For this purpose, a "Scientific Committee" including distinguished academicians conducting researches in many important areas in Turkey was established by the Ministry of Health on January 10, 2020. Just 5 days after the first death occurred in Wuhan city on January 9, "2019-nCoV Infection Guide" prepared by the scientific committee was published on the website of the Ministry of Health on January 14 so that everyone get information. Then, many guides have been published about diagnosis, treatment and prevention and healthcare professionals and the public have been informed. Moreover, in-service trainings have been given in hospitals as soon as the guides were published and all healthcare professionals were trained before the reporting of virus in Turkey. In this study, the fact, that 80.9% of the nurses received training about COVID-19 and 54.4% of the trainings were in-service training, was remarkable.

Nurses, which have a special place in healthcare professionals, are an important human factor for health services. Correct training of this human factor is very important in controlling outbreaks, reducing deaths and enhancing the quality of care. Nurses who have reached sufficient information would work effectively during the outbreak periods without being infected and not transmitting the infection to others. In addition, this information will enable them to perform evidence-based practices (Buheji and Buhaid, 2020). The correct answers given by the nurses to the information questions about the structure of SARS CoV-2 virus and diagnosis and treatment of COVID-19 disease in the study indicated that their knowledge level was generally good (more than 50%). In their study, Nemati, Ebrahimi and Nemati F, (2020) stated that the knowledge levels of the nurses were higher than the average value and they stated that the most frequently used information sources were social media, Ministry of Health, and WHO, respectively. In this study, in-service training and the website of the Ministry of Health were among the primary information sources. In their study, Saqlain et al., (2020) stated that social media took place on the top for information source. In a similar study, it was also stated that the top sources they received information were the Internet and the Ministry of Health (Giao et al., 2020). This indicated that in most countries, nurses and the people got to correct information from the Ministries of Health.

In the study, almost all of the nurses (98.3%) knew the typical symptoms of the disease. Since the study was conducted in the period

when the number of cases was high in Turkey, the symptoms were learned by almost everyone with the public spot, social media and many poster works of Ministry of Health. Therefore, it is believed that the nurses who provide care for many COVID-19 patients every day also have knowledge. In addition, the most of the participants likely knew the symptoms since they were working in the clinics providing care to patients with COVID-19 (36.3%) and from other clinics (especially, training nurses, infection control nurses)(25.7%). In a similar study, the majority of nurses knew the clinical symptoms which are fever, cough and dyspnea (Maleki et al., 2020). Various tests are applied to diagnose patients with these symptoms. When the nurses were asked about the exact diagnosis method indicating the presence of COVID-19, 65.1% responded as PCR test and 26.6% responded as lung CT scan. When these rates were examined, it was seen that along with the nurses who knew the exact diagnosis method (PCR) determined in Turkey with high rate, there were also nurses stating that the lung ct scan is also correct since it supports the diagnosis. PCR test is performed in Turkey and consolidation on lung ct scan supports the diagnosis. If the patient has symptoms and known contact history, the treatment starts without waiting for the PCR result according to radiological findings and it is currently reported that PCR test is the definitive diagnosis method (T.R. Healt Minister, 2020). In their study, Ai, Yang, Hou et al., (2020) stated that there was a correlation between PCR test and lung ct scan. In addition, even if PCR was negative, findings were presented showing that the person would be a COVID-19 patient with high probability due to certain

attitudes as a result of tomography. In another study, it was emphasized that tomography findings were important in the diagnosis and treatment of the disease (Pan, Ye, Sun et al., 2020). Therefore, when the practices and studies in Turkey are examined, it is likely that the nurses believe that lung tomography will be used for diagnosis beside PCR.

Another important result in the study was that nurses stated droplets at the rate of 58.5%, contact at the rate of 22.2%, and respiratoion with the rate of 19.1% as the primary/main transmission way of COVID-19. In the study by Maleki et al., (2020), the nurses accepted “the virus is transmitted in situation requiring close contact” as true. WHO states that the disease is transmitted by droplets and the infection could be taken by droplets either orally or nasally from the contact site. Therefore, droplet and contact isolation measures should be taken.

When the information questions asked about the treatment of the diagnosed patients were checked, the rate of the nurses who stated that antibiotics and antivirals can also be administered in the treatment was 72.3%. In other studies, the nurses stated that antibiotics should not be used in the first place in the treatment of COVID-19. (Maleki et al, 2020; Saqlain et al., 2020). Although antibiotics are not used as the primary treatment in Turkey, antibiotics called “Azithromycin” are used for COVID-19 patients with hospitalization indication in the treatment algorithm of the Ministry of Health to treat pneumonia caused by COVID-19 (T.R. Healt Minister, 2020). This may have

caused nurses to accept the information of treatment with antibiotics correct.

Although vaccination studies continue to prevent disease in the world, there is no current vaccine with all phases completed and approved (Rothan and Byrareddy, 2020). A great majority of the nurses (96.1%) stated that there was no vaccine available for the treatment of COVID-19 disease. In the study by Saqlain et al., (2020), healthcare professionals stated that there was no proven vaccine (97.5%). Although the rate of the nurses who wanted to have the vaccine when it would be developed was more than half (54.8%), the rate of undecided nurses was determined as 28.4%. In the study by Giao et al., (2020), 92.4% of the nurses stated that they wanted to have the vaccine if it would be developed. When the comparison is made accordingly, although more than half of the nurses in Turkey wanted to have the vaccine, almost the remaining half stand aloof from the vaccine. It is thought that Its reasons include little faith to the vaccine or the hopelessness about the failure to find the vaccine.

It was found that 50.2% of the nurses participating in the study stated that they encountered with a patient with COVID-19 suspicion and 90% said that they were afraid of being infected. Therefore, the nurses stated that since they were afraid, they abstained from providing care and communicating with the patient with COVID-19 and they were worried while providing care. In addition, the nurses stated that they partially (40.4%) or always (46.6%) avoided close contact with their families, in order not to infect them. In the study conducted by Maleki

et al., (2020) in Iran, they stated that 26.2% of the nurses encountered with COVID-19 patients and 92.3% were worried and afraid of being infected and infecting their families. In other studies, it was reported that the nurses who encounter with patients COVID-19 suspicion and provide care to them, were afraid of being infected and infecting their families (Giao et al., 2020; Nayna Schwerdtle et al., 2020). International Council of Nurses (ICN) stated that 90 thousand healthcare professionals were infected and more than 260 nurses died in this process. Since nurses are one-to-one care providers and have close contact with the patients, they have fear with the increasing number of infected people (Mantovani, 2020; Mckay et al., 2020). Therefore, importance should be given to protect nurses at high risk by making risk assessment and the mortality rates should be reduced (Buheji and Buhaid, 2020). In the study conducted by Ran, Chen, Wang et al., (2020) in China, it was determined that there was a significant correlation between working in areas with high risk and long-working hours and getting infected by SARS CoV-2. It should not be forgotten that the common purpose of nurses is to save human lives and they are infected and die while providing care for patients (Jackson et all., 2020). Therefore, many healthcare professionals around the world preferred to stay in various places instead of going their home to protect themselves as well as their families (Baumgaertner and Karlamangla, 2020). In Turkey, many accommodation places have been allocated for the caregivers of the patients with COVID-19 in particular. 9.6% of the nurses participating in the study stated that they always stayed in the allocated places

while 23.7% stated that they sometimes stayed in those places. This fear has caused many psychological problems ranging from anxiety to depression. The National Federation of Nursing Professions of Italy (FNOPI) announced that a nurse who provided care for patients with COVID-19 in Italy, where the number of cases and death were quite high, committed suicide with the concern of infecting others since her COVID-19 test was positive. It is also stated that other working nurses feel also intense stress due to the fear of transmitting the disease to others (https://www.fnopi.it/2020/03/24/san-gerardo-infermiera-suicida/, Access: 25.05.2020). Most of the nurses participating in the present study exhibited behaviors such as taking a shower, cleaning common areas at home with bleach, washing their clothes separately and at high temperature in order not to infect their families. These behaviors showed how high the fear of nurses about infecting others.

Nurses fighting many stressors have shown great devotion to treat patients. With the declaration of 2020 as the "Year of Nurses and Midwives" by WHO, the emergence of COVID-19 pandemic and the nurses' devoted efforts in the pandemic showed once again how important nurses are in healthcare services all over the world. In all over the world, activities have been organized to give morale to healthcare professionals and it has been kept in mind that keeping their morale high will also be reflected on patients. For this purpose, all the people applauded healthcare professionals from their balconies in order to support them in Turkey. This behavior motivated most of

nurses (77%). In addition, the patients were discharged with applause all over the world, and each recovered patient became a source of motivation for nurses. The fact that 83% of the nurses stated that their work motivation decreased with the increase of the cases is also an indicator of this situation.

The American Nurses Association (ANA) (2020) states that the most effective protection during the pandemic is to use personal protective equipment. It was observed that the nurses participating in the study used the protective equipment at high rates considering the possibility of encountering with COVID-19 patients and kept gloves, mask and disinfectants in their homes. In addition, 68.8% of the nurses stated that personal protective equipment was sufficiently effective. 96.3% of the nurses knew that N95 mask should be worn when conducting intervention that will cause body aerosolization. Accordingly, most of nurses knew how to be protected from the virus.

The nurses stated that those who had contact should stay at home during the incubation period (91.9%). It was asked in other studies that the patients should stay at home during the isolation process and those who had contacts should be isolated during the incubation process (Saqlain et al., 2020; Giao et al., 2020). According to the "COVID-19 Guide" published by the Ministry of Health, it is known that although the incubation period is between 2-14 days, the duration may vary from person to person. For this reason, it is critical for patients suspected to have COVID-19 to isolate themselves by quarantine for 14 days (Ding, Lu, Fan et al., 2020).

When the mortality of COVID-19 disease is examined, WHO data indicates that the mortality rate is significantly higher in elderly individuals compared to the other age groups. Knowing that the disease is more fatal in the elderly will create awareness among nurses and they will better understand the importance of the care they provided (Barasteh et al., 2020). In the study, almost all of the nurses (98.1%) knew that the mortality rate was higher in older individuals. Therefore, their awareness was expected to increase in this direction.

The nurses participating in the study were asked to indicate if they were using prophylactic medication or supplements during the pandemic. In line with the responses given, it was determined that they took vitamins (B, C, D vit.), immune-enhancing medicines or supplements, flu drugs against influenza virus and drugs such as "Hydroxychloroquine and Oseltamivir" actively used in COVID-19 treatment in Turkey. As is known, vitamins A, D, and C strengthen the immune system (TÜBA, 2020). It is stated that especially high dosage of vitamin C is very beneficial because it has antioxidant properties and high immunity-enhancing feature and prevents cytokine storm in patients with Acute Respiratory Distress Syndrome (ARDS) (Boretti and Banik, 2020). High doses of vitamin C are also applied in Turkey to strengthen the immunity of COVID-19 patients and accelerate their recovery. (T.R. Healt Minister, 2020). Although the drug with hydroxychloroquine active substance used in the treatment of malaria is promising in patients, the studies are not yet sufficient. There are many discussions about the use of the drug in

patients (https://covid19.tubitak.gov.tr/covid19/guncel-haberler, Access: 10.06.2020). In some studies, no difference was found between the recovery rates of COVID-19 patients with and without medication (Chen, Liu D, Liu L, et al., 2020). Although the drug gives positive results in malaria treatment and rheumatic patients, which group of COVID-19 patients should receive and how long they should receive the medication should be determined. In addition, prescribing and taking this medicine by healthcare professionals for themselves and their families makes it difficult to access the medicine for patients, who are experiencing severe exacerbation periods and need this drug such as SLE and rheumatoid arthritis. Prophylactic use of this drug, which can cause ventricular arrhythmias and cardiac toxicity in patients, is controversial. It is recommended to use the drug primarily in sick people (Yazdany and Kim, 2020). Another drug used by nurses is "Oseltamivir" which is an FDA approved antiviral drug used in many diseases caused by influenza viruses. It is very important to start this drug early in patients (Çiftçi, Karbuz and Kendirli, 2016; Korten, 2006). This drug is used as an initial treatment for COVID-19 patients in Turkey (T.R. Healt Minister, 2020). In addition, there is a study showing that it was used for prophylaxis to prevent the spread of influenza virus and positive results were obtained (Welliver et al., 2001). Although the side effect of the drug is not much, there are studies showing that it causes gastrointestinal problems and serious neuropsychiatric symptoms (Çiftçi, Karbuz and Kendirli, 2016; Korten, 2006; Dalvi et al., 2011). It should not be forgotten that this drug is given to people for the purpose of treatment

rather than prophylaxis in the COVID-19 pandemic. In conclusion, it was believed that nurses used these drugs to keep their immune system strong and not to get infected.

CONCLUSION and RECOMMENDATIONS

It was found that a vast majority of the nurses received in-service training about COVID-19 and had correct information and behaviors for coronavirus and its diagnosis-treatment, transmission and prevention methods. In addition, nurses are heavily affected negatively by this process, they also experience fear, anxiety, concern, sleep problems and thus decreased work motivation toward COVID-19. In accordance with these results, it is recommended to support nurses who collide in the front lines in this challenging war in terms of continuing their training processes and psychologically.

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