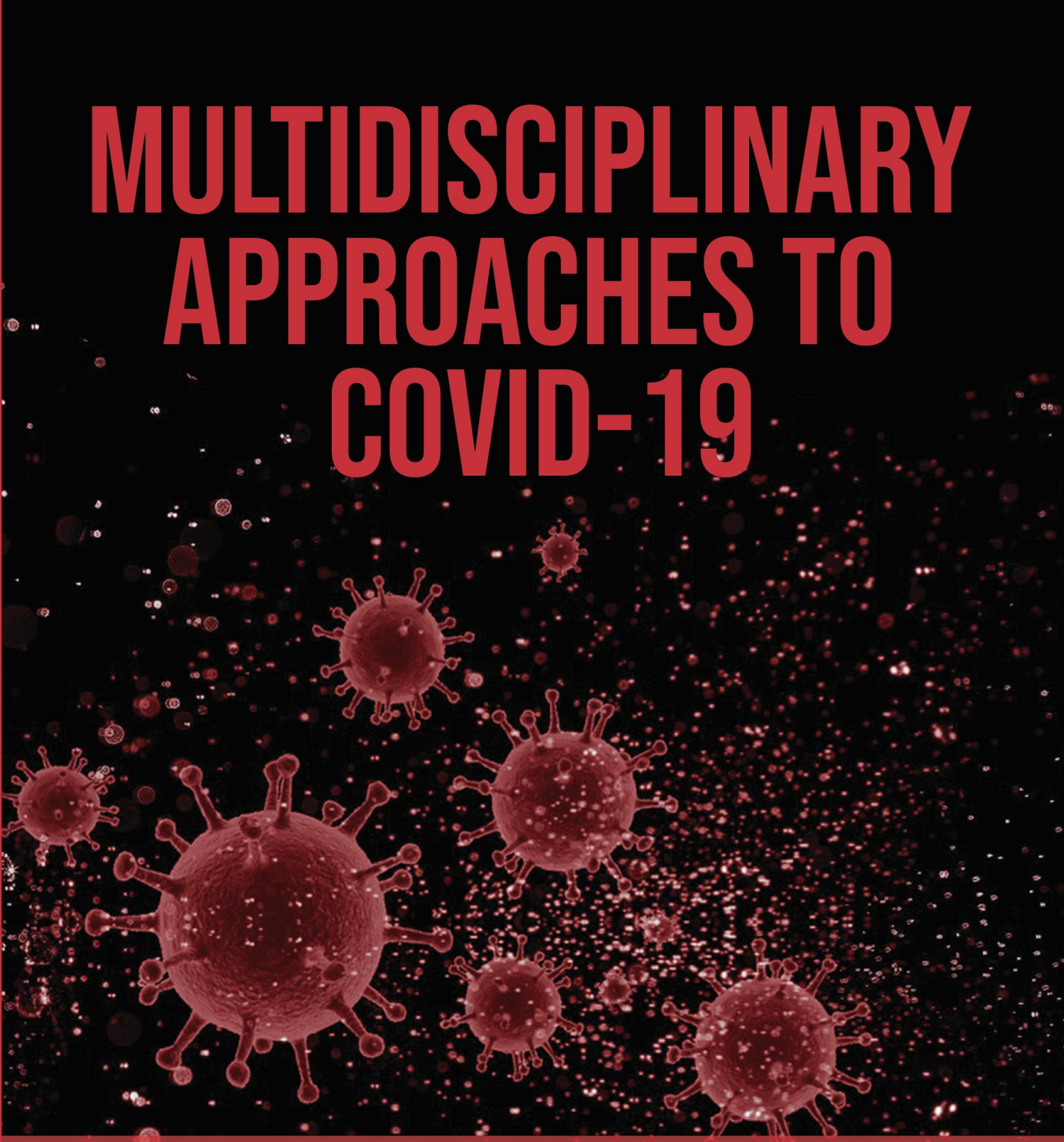
MULTIDISCIPLINARY APPROACHES TO COVID-19



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Multidisciplinary Approaches To Covid-19

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PREFACE

Dear reader,

In late 2019, the world witnessed a pandemic coronavirus disease that it was not used to. The rapid spread of the disease affected both society and the health system. The rapid action of scientists has created an opportunity to combat the epidemic more effectively. In addition, hundreds of scientists and clinicians have updated many aspects of this new infectious pandemic through research.

a) characteristics, ecology and evolution of coronaviruses;
b) epidemiology, genetics and pathogenesis of the disease;
c) diagnosis, prognosis and clinical manifestations of the disease in pediatrics, geriatrics, pregnant women and newborns;
d) co-occurrence of the disease with other infections, cardiovascular diseases, hypertension and cancer;
e) multimodal and interdisciplinary approaches to solving the problem with bioinformatics methods; It has been constantly updated with new studies in the field.

In this book, we discuss the Covid-19 infection with its different dimensions with the studies and researches of valuable researchers from different disciplines and share their experiences with the readers. While the infection still continues in our country, I would like to thank all of our professors who contributed to the rapid creation of this very valuable source of information.

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CONTENTS

PREFACE **I**

Chapter i: Effect Of Covid-19 On Ace 2, Tmprss 2 and Raas Mechanism 1

1. Introduction 1
   - 1.1. Relationship between SARS-(CoV)-2 and 2019-(nCoV) 3
   - 1.2. Association of the RAAS system with SARS-(CoV)-2 3
   - 1.3. Association of SARS-(CoV)-2 with ACE-2 4
   - 1.4. Association of ACE inhibition – ACE2 Increase and COVID-19 Progression 6
2. Discussion and Conclusion 6
3. References 8

Chapter ii: Covid-19 and Pneumonia 13

1. Introduction 13
2. COVID-19 14
   - 2.1. Etiology (Cause of Disease) 14
   - 2.2. Epidemiology 14
   - 2.3. Clinical Features 15
3. What Is Pneumonia? 15
4. COVID-19 Pneumonia 15
   - 4.1. COVID-19 Pneumonia Symptoms 15
   - 4.2. What Does COVID-19 do to the Lungs? 16
   - 4.3. How Is It Treated? 18

References 19

CHAPTER III: CHEST CT FINDINGS OF COVID-19 21
1. Introduction 21
2. Imaging Findings 21
2.1. Usual Computed Tomography Findings 22
2.1.1. Ground Glass Opacity 22
2.1.2 Consolidation 23
2.1.3. Crazy Paving Pattern 24
2.1.4. Air Bronchogram and Airway Changes 24
2.1.5. Pulmonary Vascular Enlargement 25
2.1.6. Reticular Pattern and Linear Opacification 25
2.1.7. Pulmonary Thromboembolism 26
2.1.8. Nodules and Halo/Reversed Halo Sign 26
2.2. Unusual Computed Tomography Findings 27
3. Conclusion 27
References 27

CHAPTER IV: THE EFFECT OF COVID-19 ON THE ANATOMY OF THE CARDIOVASCULAR SYSTEM 31
1. Introduction 31
2. CORONARY ANATOMY 32
2.1. Acute Coronary Syndromes 34
2.2. Pathophysiology of coronary artery disease 34
2.2.1. Atherosclerosis 34
3. COVID-19 INFECTION 35
3.1. Epidemiology 35
3.2. Pathophysiology 36
3.3. Clinical Course 38
3.4. Laboratory Findings 40
3.5. Radiological Findings 41
3.6. Diagnosis 41
3.7. Treatment 43
3.8. Immunization 43
4. Cardiovascular system and Covid-19 43
4.1. Myocardial injury and myocarditis 44
4.2. Acute Coronary Syndrome 44
4.3. Heart failure 44
4.4. Arrhythmia and sudden cardiac arrest 45

4.5. Coagulation Disorders and Thrombosis 45
4.6. Covid-19 and Hypertension 45
4.7. Covid-19 and ischemic heart disease 45
4.8. Venous Thromboembolism 46
5. ACE-2 and Cardiovascular symptoms 46
6. Treatment 46
REFERENCES 47

Chapter v: Effects of Covid -19 Infection on Central and Peripheral Nervous System Anatomy 53
1. Introduction 53
2. Neural Invasion of SARS-CoV2 and Possible Routes of Transmission 55
2.1. Neuronal Pathway 55
2.2. Hematogenous Pathway 55
2.3. Target Cell 56
3. Covid 19 and Nervous System Symptoms 56
3.1. Central Nervous System Symptoms 56
3.2. Peripheral Nervous System Symptoms 57
3.3. Neuromuscular Symptoms 57
4. Result 58
References 58

Chapter vi: The Anatomical Approach To Sars-Cov-2 and Stroke 63
1. The relationship between SARS-CoV-2 and central nervous system 63
2. Stroke 64
2.1. The Anatomical approach to stroke 65
3. The relationship between stroke and SARS-CoV-2 66
3.1. The relationship between stroke and circulation in patients with SARS-CoV-2 66
3.2. The relationship of biomarkers with stroke in SARS-CoV-2 67
3.3. The relationship of cytokine storm with stroke in SARS-CoV-2 68
3.4. The relationship between stress with stroke in SARS-CoV-2 68
4. Discussion 68
5. Conclusion 70
6. References 71

Chapter vii: Effects of The Covid-19 Pandemic on Orthopedics and Traumatology 77
1. General Information About Covid - 19 77

2. Covid-19 Pandemic in Turkey 78
3. New Pre-Normalization Approaches 78
4. New Normalization Period Approaches 78
5. Management of Patients in Orthopedics and Traumatology during the Covid-19 Pandemic Process 78
5.1. Emergent cases 80
5.2. Urgent cases 80
5.3. Elective cases 80
6. Conclusion and Discussion 82
References 83

Chapter viii: Diabetes and Covid-19 85
1. Introduction 85
2. Possible potential mechanisms in diabetes mellitus and COVID-19 87
3. COVID-19 and New-Onset Diabetes 90
4. Diabetes Management During the COVID-19 Pandemic Process 91
4.1. Evaluation of People with Diabetes and COVID-19 Infection 92
4.2. Glycemic Controls 92
4.3. Blood Sugar Controls 92
4.4. Antidiabetic Agents 93
4.4.1. Dipeptidyl peptidase -4 (DPP4) inhibitors 93
4.4.2. Glucagon-like peptide 1 (GLP-1) Receptor Agonists 93
4.4.3. Sodium-glucose cotransporter 2 (SGLT2) inhibitor 93
4.4.4. Thiazolidinediones (TZD) 93
4.4.5. Insulin 94
5. Conclusion 94

Chapter ix: Covid-19 and Human Fertility 95
Introduction 95
COVID-19 and Human Fertility 96
COVID-19 and Male Fertility 97
COVID-19 and Sex Hormone Abnormalities 98
COVID-19 and Testicular Dysfunction 99
COVID-19 and Spermatogenesis 101
SARS-CoV-2 in Semen Samples 101
COVID-19 and Erectile Dysfunction 102
COVID-19 and Female Fertility 102
SARS-CoV-2 on Endometrium and Menstrual Cycle 103
The Effects of SARS-CoV-2 on Ovarian Reserve and Hormones 104

COVID-19 and Follicular Fluid, Oocytes and Embryos 104
SARS-Cov-2 Infection in Pregnancy and Intrauterine Transmission 105
Conclusion 106
References 107

Chapter x: Covid-19 Presentation in Children 115
References 122

Chapter xi: Neurological Findings of Covid-19 In Children and Effects on Children With Neuromuscular Disease 127
1. Introduction 127
2. COVID- 19 128
3. COVID- 19 in Children 129
4. Neurological Findings in Children 131
5. COVID-19 in Children with Neurological Disease 132
6. Conclusion 134
References 134

Chapter xii: A Current Approach to Covid-19 Infection and Mis-C Syndrome in Children 139
1. Introdactıon 139
2. Mıcrobıologıcal Propertties and Pathogenesıs 141
3. Dıagnosıs and Clınıc 141
4. Treatment 143
   4.a. Antiviral treatments 143
   4.b. Other treatments 144
   4.c. Respiratory Failure and Oxygen Therapy 145
5. Protectıon and Precautıon 146
References 147

Chapter xiii: Microanatomic Effects of Covid-19 on the Retina Layer 151
1. Introduction 151
   1.1. Occurrence of COVID-19 (SARS-CoV-2) 151
   1.2. Characteristics of Coronaviruses 151
   1.3. Serotypes of Coronaviruses 152
   1.4. Pathophysiology of COVID-19 152
      1.4.1. Binding of the SARS-CoV-2 Virus 152
      1.4.2. Humoral Immunity 153
      1.4.3. The Pathogenesis of COVID-19 153
   1.5. Clinical Manifestations of COVID-19 154

1.6. Diagnosis and Laboratory Tests in COVID-19 155
1.6.1. RT-PCR Test 155
1.7. Coronavirus Treatment Approach 155
1.7.1. Treatments for Coagulation in COVID-19 155
1.8. Endothelial Dysfunction and Hemostasis 156
2. Eyeball 157
2.1. Fibrous tunic 157
2.2. Vascular tunic 157
2.3. Nervous tunic (Retina) 157
2.3.1. Retinal embryology 157
2.3.2. Retinal Anatomy 157
2.3.3. Retinal Histology 158
2.3.4. Macula Lutea 160
2.3.5. Optic Disc (Optical Nerve Head) (ONH) 160
2.3.6. Retinal Veins 161
3. COVID-19 and Retina 162
References 164

CHAPTER XIV: THE EFFECT OF COVID-19 ON THE REGIO OLFACTORY ANATOMY AND ANOSMIA 173
1. Introduction 173
2. Olfactory anatomy 174
2.1 The olfactory brain rhinencephalon 175
3. Olfactory physiology 175
3.1 Olfactory transmission 176
3.1.1 Olfactory perception 177
4. Physiopathology of olfactory loss in COVID-19 178
5. Anosmia 179
6. Conclusion 182
References 182

CHAPTER XV: COVID-19 AND PULMONARY PATHOPHYSIOLOGY 187
INTRODUCTION 187
Transmission and Clinical Manifestations of COVID-19 187
ACE-2 Receptor and Viral Entry 188
Pathophysiology of COVID-19 190
Pathophysiology of COVID-19 Lung Injury 191
COVID-19-Associated Pneumonia 192

Hypoxemia in COVID-19 193
COVID-19 and ARDS 194
COVID-19 and Cytokine Storm 195
CONCLUSION 197
REFERENCES 198

Chapter xvi: Cancer and Covid-19 Pandemic 209
1. Introduction 209
2. Patients with Cancer during the COVID-19 210
3. Conclusion 212
References 213

Chapter xvii: Covid-19 and Pulmonary Rehabilitation 217
1. Introduction 217
2. Covid-19 217
2.1. Epidemiology 218
2.2. Contamination and Protection from Contagion 218
2.3. Clinical features 218
2.4. Imaging Findings 219
2.5. Laboratory Findings 219
2.6. Pulmonary manifestation 220
2.7. Extrapulmonary Manifestation 220
2.8. Diagnosis and Treatment 221
3. Pulmonary Rehabilitation 221
3.1. PR in Covid-19 223
3.1.1. PR for mild cases of Covid-19 223
3.1.2. PR for case with pneumonia of Covid-19 224
3.1.3. PR for severe cases of Covid-19 226
3.2. PR the Post-Covid 19 228
4. Conclusion 228
REFERENCES 229

Chapter xviii: Telerehabilitatinon: Interface Between Physiotherapist and Patient 235
1. INTRODUCTION 235
2. HİSTORY 236
3. TELEREHABILITATION APPLICATIONS 236
3.1. Why Do We Need Telerehabilitation Application? 237

3.2. Usage Fields Of Telerehabilitation Applications 239
3.2.1. Follow-up 239
3.2.2. İntervention 240
3.2.3. Supervision 240
3.2.4. Training and consultancy: 241
3.3. The Benefits of Telerehabilitation 241
3.4. Lacks of Telerehabilitation 242
4. CONCLUSIONS 243
REFERENCE 244

Chapter xix: Covid-19 and Palliative Care 247
1. Introduction 247
2. Palliative Care 248
3. Palliative Care During The COVID-19 Pandemic 248
4. CONCLUSION 250
References 251

Chapter xx: Evaluation of the Effectiveness of Tests, Contact Tracing, and Isolation Measures in Covid-19 Cases in Turkey in Comparison With Italy and South Korea 253
1. Introductıon 253
2. Materıals And Methods 254
2.1. Statistical Analysis 255
3. Results 255
4. Dıscussıon 258
References 262

CHAPTER I

EFFECT OF COVID-19 ON ACE 2, TMPRSS 2 AND RAAS MECHANISM

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1. Introduction

In December 2019, an outbreak of pneumonia of unknown etiology occurred in the Chinese province of Wuhan and quickly spread throughout the country. A new β-coronavirus named SARS-(CoV)-2, which is defined by the Chinese Center for Disease Control and Prevention as a type of Coronavirus that causes severe acute respiratory failure syndrome, has been reported. It was the third coronavirus epidemic of zoonotic origin, which is transmitted from person to person and threatens global health in the current century. (1, 2)

The Chinese state resorted to extraordinary measures and they managed to contain the epidemic. As of March 2020, the pandemic had reported nearly 100,000 cases and 4,000 deaths in China, and 40,000 cases and 1400 deaths in other countries around the World. (2) WHO has defined COVID-19 as a pandemic and announced that all countries should be concerned about the global spread and severity of the epidemic. (3) A new species belonging to the family Coronaviridae has been identified as the cause of respiratory and gastrointestinal tract infections in Coronavirus. (4) Scientists have described SARS-(CoV)-2 as an enveloped beta-coronavirus with a single-stranded RNA genome. Several phylogenetic analyzes of the origin of the virus suggested that the bat is the most likely animal source. According to the genome sequencing, SARS-(CoV)-2 was found to be approximately 85% similar to human SARS-(CoV), 90% to bat SARS variant, and approximately 50% to SARS-(CoV). The SARS-(CoV) virus, which started in China in 2003 and spread to 26 countries, has been

associated with thrombotic complications and hematological manifestations, similar to COVID-19. (5, 6)

A different strain of coronavirus was reported in Saudi Arabia in 2012 and named "SARS-(CoV), invisible respiratory virus". Similar to COVID-19 and SARS-(CoV), MERS-(CoV) have also been associated with hematological findings. However, it was seen more limited than SARS-(CoV)-2 and SARS. SARS-(CoV) and MERS-(CoV) have been reported to be transmitted from bats to camels and from them to humans. Therefore, scientists have come to the conclusion that there is another intermediate host between the bat and the human. (1, 2)

Researchers thought pangolins were likely hosts because their genomes were highly similar to SARS-(CoV)-2, GD/P1L and GDP2S, which have approximately 86% to 93% similarity with SARS-(CoV)-2, which phylogenetically represent its two sublines. (7) Similarly, the similarities of SARS-(CoV)-2 between different animal species suggest that it is recombinant of bat coronavirus and human coronavirus. (8)

According to WHO known a biomarker as any structure, substance or process that can be measured in the human body and which affects or predicts the incidence or outcome of disease. (9) Angiotensin converting enzyme as known ACE converts Angiotensin-I (Ang-1) to Angiotensin-II (Ang-2) in the Renin – Angiotensin - Aldosterone System (RAAS). Its serum level is mostly used in the detection of Sarcoidosis disease. Cells on the outer margins of small tumors-like granulomas under the skin found throughout the body, formed by immune system cells, inflammatory cells, and fibrous tissue, secrete high amounts of ACE. In addition, granulomas can be seen in certain infections such as leprosy, active histoplasmosis, and tuberculosis. (10) SARS-(CoV)-2 virus uses the similar receptor as SARS-(CoV), Angiotensin converting enzyme-II as known ACE-2, and spreads mainly through the respiratory system. (11) The RAAS is mostly related to blood pressure regulation, but it also has some effects on the lungs, heart, and vascular organs. The first axis in the RAAS system is (ACE) /(Ang-2)/(AT1R), while the second axis is (ACE-2)/(Ang (1-7))/(Mas) axis. The (ACE)/(Ang-2)/(AT1R) axis causes profibrotic, proinflammatory effects in the respiratory system, myocardial fibrosis, vascular dysfunction, increased insulin resistance and nephropathy and insulin secretion defects. (ACE-2)/(Ang (1-7))/(Mas) axis has antifibrotic and antiinflammatory effects on the respiratory system; in the cardiovascular system, it has antioxidative, antiinflammatory and protective effects on vascular functions, moreover protects the myocardium against fibrosis.(12) Today, biomarkers such as WBC count, CRP, procalcitonin and d-dimer are more accepted in the diagnosis,

treatment, follow-up and prognosis prediction of pneumonias. ACE inhibitors used as antihypertensives can reduce serum ACE levels via the ACE/Ang-2/AT1R axis.(13, 14) Experimental study results show that RAAS blockade by statins as well as ACE inhibitors, Antagonists of Ang-II-Type-I receptors and mineralocorticoid antagonists increase ACE-II levels in humans. (15) Increased ACE-2 enzyme level may increase the binding of SARS-(CoV)-2 virus to the airway in the lungs, resulting in progression of COVID-19 disease.

1.1. Relationship between SARS-(CoV)-2 and 2019-(nCoV)

The coronavirus surface glycoprotein binds to receptors on host cells. SARS-(CoV)-2 spike protein (S/protein) is reported to bind with ACE-2 as a receptor to invade host cells. (6) The amino acid sequence of the S/protein in SARS-(CoV)-2 is 76.5% similar to that of the SARS virus and has similar structural and electrostatic properties as an interaction interface. Residues at positions 442aa, 472aa, 479aa, 487aa and 491aa in the SARS-(CoV)-2 S-protein have been shown to be in the ACE-2 and receptor complex (37). The furin-like cleavage site is cleaved by the proprotein convertase furin, enhancing viral fusion through host cell membranes. (16) A study in 2020 reported a furin-like cleavage site in the S-protein of SARS-(CoV)-2, which is absent in other coronaviruses. (17) In addition, another study reported a furin recognition site replacing a single arginine with the S1/S2 protease cleavage site in SARS-(CoV)-2. The binding affinity between SARS-(CoV)-2, S-protein and ACE-2 is stronger than SARS. This may explain the ability of SARS-(CoV)-2 to transmit from person to person more rapidly than other coronaviruses. (18, 2)

1.2. Association of the RAAS system with SARS-(CoV)-2

The RAAS system is a group of peptides that regulate key points in human physiology. This system has a serious effect on the maintenance of plasma sodium/potassium concentration, extracellular fluid volume and arterial blood pressure. (19) It has been observed that SARS between 2002-2004, MERS in 2012 and SARS-(CoV)-2 viruses that started in China in 2019 are transmitted and affected by using RAAS and ACE-2 as physiological receptors. It is known that two important components that make up the RAAS system are renin and angiotensin. (19, 20, 21) The renin/angiotensinogenase enzyme is secreted by the kidney granular cells. These enzymes circulate in the blood in response to a low sodium diet and vasodilation. While prorenin, which is the precursor protein of renin protein, contains 406 amino acids, it has 340 amino acids in its active form. If a mutation occurs in the REN gene, which encodes the renin protein,

it affects the function of this protein. In the formation of such a mutation, diseases such as anemia, chronic kidney failure, multiple inflammatory and hyperuricemia may ocur. (21) Alpha 2 globulin, one of the plasma proteins, is defined as a center with a strong vasoconstrictive effect resulting from the effect of angiotensin renin enzyme on angiotensinogen. The kidney-secreting enzyme renin, a versatile effector peptide hormone, converts angiotensinogen to angiotensin I (Ang-I). As a result, ACE and angiotensin II (Ang-II) are formed especially in the pulmonary circulation. (21) Ang-II has four types of receptors: AT1, AT2, AT3 and AT4. Although the effects of AT3 and AT4 have not been explained yet, they show their effects on AT1 and AT2. Angiotensin II stimulates aldosterone secretion by acting directly on the zona glomerulosa of the adrenal cortex. Ang-II increases sodium reabsorption from the renal tubules at normal blood pressure and inhibits it at high blood pressure. (21)

1.3. Association of SARS-(CoV)-2 with ACE-2

ACE-2 is an important regulatory enzyme that reduces Ang-2 to Ang (1-7), reducing its effects on sodium retention, vasoconstriction and fibrosis. Ang-II is the primary substrate of ACE-2, but this enzyme converts Ang-1 to Ang (1-9) and participates in the hydrolysis of other peptides (Figure 1 and 2). (19) In a study conducted in humans, it has been shown that the SARS-(CoV)-2 receptor ACE-2 is commonly found in lung alveolar epithelial cells, heart and kidney in tissue samples taken from some organs. (19, 22)

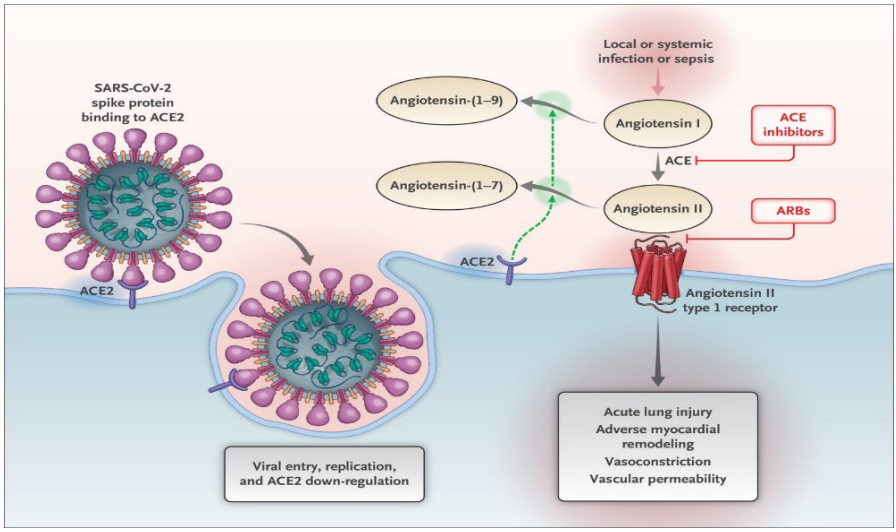

Figure 1: Entry of SARS-CoV-2 into the cell by endocytosis via ACE2. (19)

The physiological effects of angiotensin II occur in skeletal muscle, heart, kidney, pancreas, adipocytes and adrenal tissues through both angiotensin type I receptor (AT1R) and angiotensin type II receptor (AT2R). Effects of AT1R mediated angiotensin II; a) vasoconstriction of vascular smooth muscle cells in the arterioles, b) sodium retention in the kidney proximal tubules, and c) aldosterone release from the adrenal zonaglomerulosa. The effects of AT2R mediated Angiotensin II are mostly opposed to AT1R mediated effects. Effects of Angiotensin II; It produces a) vasodilation of arterioles, b) anti-inflammatory effects on vascular smooth muscle cells, and c) anti-proliferative effects on myocardium. (22, 23)

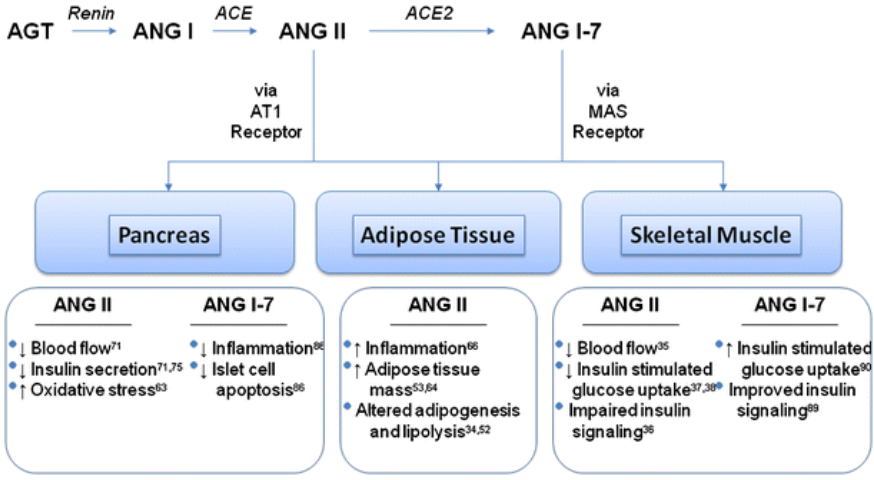

Figure 2: Effects of Angiotensin II and Angiotensin 1-7 on pancreatic adipose tissue and skeletal muscle. (22)

The discovery of Angiotensin II synthesis, the new Angiotensin II metabolite and its receptors, reveals that it is possible to develop new therapeutic strategies in the treatment of renal and cardiovascular diseases. For example, the ADE2/Ang (1-7)/Mas and Angiotensin type 2 (AT2) receptor axis have opposite effects to those produced by AT1 receptor activation. ACE-2 is a mono carboxy peptidase that converts Ang-II to Ang-(1-7). By destroying Ang-II, it can prevent this mediator from causing toxic effects through the AT1 receptor. In addition, Ang-(1-7) produced by ACE-2 can antagonize the harmful effects of the AT1 receptor by inducing the Mas receptor, showing vasodilator, natriuretic, antiproliferative, antihypertrophic, and antifibrotic effects. It has been suggested that this enzyme may play a key role in the pathophysiology of hypertension, cardiovascular and

renal diseases due to the fact that ACE-2 plays an essential role in the conversion of Ang-II, which has vasoconstrictive, hypertrophic and proliferative effects, to Ang (1-7). Clinical studies in serum or urine have provided evidence that ACE-2 level can be used as a new biomarker in the diagnosis and prognosis of cardiorenal diseases. (23, 24, 25, 26)

1.4. Association of ACE inhibition – ACE2 Increase and COVID-19 Progression

The RAAS system generates Ang-2 from Ang-1 via ACE, and Ang-2 helps to establish vascular tone by retaining water and salt via the AT1R receptor, while triggering the chemotactic and profilerative processes of immune cells. (27) As the relationship between ACE-2 and RAAS, which entered the literature in the 2000s, was understood, it took its place in the literature as ACE-2 over time. ACE-2 has been localized as an enzyme bound to the membrane of cells in the heart, lungs, kidneys, arterial vessels, and intestines. (28, 29) ACE-2 reduces blood pressure by converting Ang-2 to Ang (1-7) in RAAS, inhibiting the vascular tone-enhancing effect of Ang-2 through Mas produced afterwards (Figure 2.7). (30) In addition, ACE-2 RNA has been proven to be found in the cerebral cortex, striatum, brain stem, and hypothalamus in the brain. (31)

The S1 protein of SARS-(CoV)-2 attaches to the enzymatic domain of ACE-2, and the resulting complex enters the cell with ACE2 receptors. (32) ACE-2 levels increase with the inhibition of ACE, which catalyzes the formation of Ang-2 from Ang-1. It is thought that this situation may contribute to the progression of the disease. In studies on rodents, it was thought that ACE inhibitors and ARBs used to treat high blood pressure both increase the amount of ACE-2 and therefore may increase the severity of coronavirus infections. In another study, ACE-2 levels were reduced in an experiment on mice, but it was observed that the damage in the lungs increased with the decrease in Ang (1-7) levels in the continuation of the pathway. In clinical practice, in a meta-analysis published in July 2012, data were obtained that using ACE inhibitors reduced the risk of pneumonia by approximately 35% compared to the control group. (33)

2. Discussion and Conclusion

RAAS; It contains the active hormones Ang (1-7), Ang (1-7), enzymes that mediate tissue protective effects (ACE-2) and receptors (AT2 and Mas). Ang (1-7)

is produced from Ang-II by the carboxypeptidase ACE-2 and interacts with its receptor Mas. Many of the classical actions of this heptapeptide, Ang-II, appear to be antihypertensive, antihypertrophic, antifibrotic, and against improving metabolic status. In addition, the AT2 receptor is activated by Ang-II and has been reported to interfere with receptor-dependent processes with anti-fibrotic, anti-proliferative, anti-inflammatory, anti-apoptotic and neurodegenerative cytokines and growth factors. (34)

Some researchers think that drugs that interfere with the RAAS, including ACE inhibitors and ARBs, may increase susceptibility in infections caused by coronavirus. The origin of this hypothesis is based on the results that coronaviruses interact with ACE-2 on entry into the cell and that altered expression of ACE-2 is affected by the use of ACE inhibitors and ARBs observed in animal model studies. Influenza (H7N9, H5N1 and H1N1) has been shown to use the ACE2 receptor to mediate a pathology similar to lung injury that occurs in coronavirus infections. Understanding the similar mechanism of action between coronaviruses and influenza may help address the issue of how ACE inhibitors and ARBs may affect the manifestations of viral respiratory infections. (35)

In animal studies, it has been stated that ACE-2, which is overexpressed in the heart, lungs and other tissues, is used as a receptor for intracellular entry of coronavirus infections. ARBs and ACE inhibitors are considered drugs of first choice as they both increase ACE-2 expression in heart failure, myocardial infarction, hypertension, and chronic kidney disease. Given these data, he developed the hypothesis that the use of ACE inhibitors could alter susceptibility to infection in humans with SARS-(CoV)-2. However, there is no consensus on whether the risk and severity of SARS-(CoV)-2 infection will increase with the use of such agents. (36)

Clinical data so far are mostly limited to small, uncontrolled studies with a small sample size of demographic and clinical characteristics of patients with coronavirus disease (SARS-(CoV)-2) at the time of infection in 2019. Considering the lack of sample and information in these studies, RAAS blockers may affect the sensitivity and severity of SARS-(CoV)-2, which is a very urgent and effective issue, it was thought that problems may arise. Recent reports have shown that widespread use of these drugs results in a marked increase in the risk of secondary complications and mortality with the withdrawal of RAAS blockers under infection conditions. (18, 2, 36)

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CHAPTER II

COVID-19 AND PNEUMONIA

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1. Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (1,2).

Illness or sickness is the name given to a specific abnormal condition in the body or mind that causes discomfort, distress, and dysfunction. It is used in a broad sense to encompass injury, disability, syndromes, symptoms, and abnormal variants of normal structure and function (3-6).

Some diseases are contagious and can be transmitted through various mechanisms. For example, influenza can be transmitted by small droplets from coughs, while bites of insects or other vectors, or contaminated water or food can also carry disease (3-6). Like other diseases, cancer and heart disease are not contagious since they are not caused by an infection, even if microorganisms play a role in their development (3-6).

Infection means that an infectious agent enters the body and multiplies within the body. However, symptoms of the disease may not be seen at this time. It is considered to be an infectious disease if symptoms of the disease occur together with the formation of infection. Signs and symptoms of infectious diseases can be very different (7-9).

However, one infectious disease, that has affected the whole world since 2019 and was declared a pandemic, has emerged in the world. This contagious

disease is COVID-19. The novel coronavirus (SARS-COV-2) emerged in December 2019 in the city of Wuhan, Hubei province, China. Cases began to be seen in other cities in China and all over the world with the spread of the disease. After cases started to be seen all over the world, it was declared a pandemic by the WHO. Although many preventive controls and medical treatment methods were implemented, the rate of increase of the pandemic in China was stopped to a certain extent. Afterwards, the pandemic decreased in many Chinese cities, but the number of cases increased dramatically in other countries around the world (10).

2. COVID-19

2.1. Etiology (Cause of Disease)

The new coronavirus (SARS-CoV-2) is a virus belonging to the coronavirus b coronavirus genus, with a diameter of 60-140 nanometers (nm), round or oval shape and enveloped structure. When SARS-Cov-2 is examined in terms of genetic characteristics, it was different from SARS-CoV-1 and MERS-Cov (80% similar to SARS-CoV-1). SARS-CoV-2 was reported to be sensitive to ultraviolet light and temperature (30 minutes at 56 °C). In addition, it is inactivated by ether, 75% ethanol, disinfectants containing chlorine, and oil-dissolving solvents such as chloroform. However, chlorhexidine was shown to be ineffective (10).

2.2. Epidemiology

For COVID-19;

1) Source of infection: symptomatic (with symptoms) or asymptomatic infected patients are sources of this infection. Asymptomatic patients are thought to be the main source of the spread of infection.
2) Transmission route: SARS-CoV-2 was reported to spread through respiratory droplets and close contact. It was reported that aerosol (airborne) transmission can occur when people are exposed to high concentrations of virus-containing aerosols in relatively enclosed areas for a long time. Note: aerosol is defined as suspended solid or liquid particles. Its dimensions can range from 0.003 micrometer to 100 micrometer in diameter.
3) Susceptible population: All people are generally predisposed to COVID-19. It is not yet clear why some people do not show any symptoms, and why some people show symptoms and experience the disease severely (10).

2.3. Clinical Features

According to current epidemiological data, the incubation period is between 1-14 days, but most patients show symptoms within 3-7 days. Fever, dry cough and malaise are the main symptoms. Other symptoms include nasal congestion, runny nose, sore throat, myalgia, and diarrhea. The prognosis may be relatively worse in elderly patients and patients with comorbidities. The course of COVID-19 pneumonia in pregnant female patients is similar to that of patients in the same age group. The severity of symptoms in children was observed to be relatively mild compared to other patients.

Mild cases have mild fever and mild malaise, while there are no visible signs of pneumonia. Severe cases present with dyspnea and/or hypoxemia within 1 week of onset. Notably, some severe cases have mild fever throughout the illness, and some reported no fever at all (10).

3. What Is Pneumonia?

Pneumonia is a lung infection that causes inflammation of the small air sacs in the lungs. Antipyretic cough medicines and pain relievers are recommended for treatment. However, in severe cases, treatment is offered in a hospital setting to receive respiratory assistance with a machine called a ventilator. Pneumonia can develop as a complication of viral infections such as COVID-19 or the flu, or even the common cold (11,12).

4. COVID-19 Pneumonia

In the case of COVID-19 pneumonia, damage to the lungs is due to the coronavirus that causes COVID-19. Moreover, COVID-19 pneumonia usually occurs in both lungs, not in one lung or the other. Like other respiratory infections that cause pneumonia, COVID-19 can cause short-term lung damage (13-17).

4.1. COVID-19 Pneumonia Symptoms

The first signs of disease are usually dry cough and fever. After about 5-7 days, lung functions deteriorate and shortness of breath occurs. However, shortness of breath may occur earlier in people with additional diseases and weak immunity. In young people without comorbidities, the duration of dyspnea may be prolonged. Secondary to the inflammation in the lung, oxygenation is disrupted by the deterioration of gas exchange and hypoxemia occurs (13-17).

4.2. What Does COVID-19 do to the Lungs?

Diffuse alveolar and endothelial damage was observed in pulmonary small arteries associated with thrombus (13). In post-mortem autopsy cases, diffuse alveolar damage, capillary congestion with microthrombus, venous thromboembolism, pulmonary embolism, bronchopneumonia, tracheitis, and a small amount of submucosal inflammation were found in bronchitis/bronchioles (11,14). Lung histopathologies in COVID-19 cases were compared with lung histopathologies in H1N1 Influenza A and SARS. The findings of organized fibrosis were more common in COVID-19 cases than the other two diseases, and diffuse alveolar damage was found to be similar in all three diseases. Pulmonary thrombus and microthrombus lesions are more common in COVID-19 and SARS cases (11,14-16). COVID-19 causes infiltration in the lung by infecting the airways and alveoli of the lung. As a result of pneumonia, the patient develops hypoxia. Viral proliferation, lung inflammation, pulmonary vasoconstriction, intravascular thrombocytosis, and cytokine secretion increase in the hypoxic environment. While this environment deepens hypoxia, it also causes an increase in lung infiltration. As a result, a vicious cycle occurs (16). It is suggested that lesions of the lung parenchyma (ground glass) are a result of hypoxia and consequent necrosis, and not a direct effect of the inflammatory process caused by the virus. SARS-CoV-2 encodes the production of structural proteins (for the structure of the virus) and other non-structural proteins during the viral replication stage after entering the host cell. One of these nonstructural proteins invades hemoglobin, removes the iron atom, and binds to the site of interest, preventing the transport of oxygen.

This may explain the rapidly developing hypoxia. It is also suggested that the change in the structure of red blood cells causes vascular damage and diffuse intravascular coagulation. As a result, it is thought that viral load is responsible for determining the severity of the disease in people without comorbidities, since theoretically risky hemoglobin is present (12,15).

Attempts were made to explain the mechanism for formation of hypoxemia in COVID-19 infection with various hypotheses. One of these hypotheses is that atypical hypoxemia may be associated with opening of the patent foramen ovale (PPFO). Oxygen support therapy used to correct hypoxia will increase the possibility of intrathoracic shunt. The use of mechanical ventilation in a patient like this will not close the shunt nor can it correct hypoxia. Barotrauma due to increased pulmonary vascular resistance and high inflation pressures causes excessive stretching of the alveoli and wet lung development as a result

of more fluid leakage. While type 2 alveolar cells are not yet largely damaged by the virus, the presence of lung fluid and protein infiltrating the alveolar spaces affects surfactant biophysics. It may contribute to the development of atelectasis by increasing the respiratory load (16-21). Another hypothesis states that hypoxemia seen in patients is classified as dyspneic and non-dyspneic (silent) hypoxemia and it can be explained by neurological mechanisms. Hypoxemia in COVID-19 patients with extensive lung injury may be associated with three different types: a) hypoxic and hypocapnic respiratory failure; It is mainly due to increased pulmonary shunt fraction and ventilation-perfusion mismatch (V/Q defects) in the injured lung. b) Hypoxic and hypercapnic respiratory failure; Although hypercapnia contributes to shortness of breath in normal individuals, some COVID-19 patients do not complain of shortness of breath despite developing severe hypoxemia. c) Hypoventilation is characterized by hypoxemia in the presence of normal arteriovenous oxygen gradient, which is extremely rare among these patients (20). The decrease in the perception of dyspnea in COVID-19 can be explained by two mechanisms. It may be caused by the direct invasion of SARS-CoV-2 into ACE2, which is expressed in brain cells in the limbic system (especially in the insular region), or by the indirect toxic effect of cytokine storm in the corticolimbic network, which has the main role in expressing the perception of dyspnea (22,23). The central nervous system is involved in SARS-CoV-2 through two mechanisms; a) direct hematogenous route or neurogenic route, and b) indirect mechanism; drugs, hypoxia, systemic inflammation, coagulation imbalance, cardiovascular damage, critical illness and comorbidities. In hematogenous involvement, SARS-CoV-2 binds to ACE2 receptors and crosses the vascular endothelium. It infects glial cells and vascular endothelium as the permeability of the blood-brain barrier increases. Cell damage and necrosis occur. It crosses the blood and brain barrier via diapedesis. It infects glial cells and neuronal cells. The neuronal mechanism was suggested as the second mechanism. In this mechanism, SARS-CoV-2 can pass from the peripheral nerves to the brain stem via retrograde transsynaptic spread or involve the olfactory bulb and frontal lobe via the cribriform plate. Hypoxemia occurring in this period is called silent hypoxemia (23).

Infection of the carotid bodies was also considered in the formation of silent hypoxemia. The decrease in oxygen in the arterial blood is sensed by the carotid bodies. The stimulus from here stimulates the brain stem, causing hyperventilation and tachycardia. In humans, bilateral removal of the carotid bodies leaves individuals unaware of hypoxemia, and the hypoxic ventilatory

response is completely abolished (24). Happy or silent hypoxemia is not only seen in COVID-19, it can also occur in patients with atelectasis, intrapulmonary shunts (i.e. arterio-venous malformations), and right-to-left intracardiac shunts. Happy hypoxemia is the absence of dyspnea symptoms despite low oxygen concentration. Recognition of "happy hypoxia" as a feature of COVID-19 pneumonia guides physicians in terms of treatment (25,26).

SARS-CoV-2 infection induces rapid lung inflammation and alveolar-capillary destruction. As a result of pneumolysis, progressive hypoxemia develops, followed by hypercapnia and pulmonary shunt. Hypoxia deepens, hypocapnia is seen as a result of hyperventilation. As the disease progresses, ventilatory failure develops and hypercapnia occurs. With respiratory acidosis, decreased hemoglobin count, and respiratory stress, the person remains out of breath. If the patient recovers, it is expected that fibrosis and sequelae will develop in the future (26).

For early diagnosis and treatment of asymptomatic hypoxia in these patients with a "mild clinical presentation", it is important to regularly monitor oxygen saturation with pulse oximetry, complemented by blood gas analysis. Even if they are asymptomatic, "symptom of dyspnea" should be systematically questioned (18,27). As seen in studies, when shortness of breath develops, it may be too late. Oxygen level decreases due to virus-related alveolar collapse, but CO2 exchange continues. For this reason, the process progresses without awareness of the developing hypoxemia. The easiest detection of the change in oxygen saturation can be made with a pulse oximeter (19).

4.3. How Is It Treated?

There is currently no specific treatment approved for COVID-19. However, various drugs are being investigated as potential treatments. Treatment of COVID-19 pneumonia focuses on supportive care. This includes relieving your symptoms and making sure you're getting enough oxygen. People with COVID-19 pneumonia often receive oxygen therapy. Severe cases may require the use of a ventilator. Sometimes people with viral pneumonia can also develop a secondary bacterial infection. If this occurs, antibiotics are used to treat the bacterial infection (28).

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CHAPTER III

CHEST CT FINDINGS OF COVID-19

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1. Introduction

Coronavirus disease 2019 (COVID-19), which was declared as a pandemic by World Health Organization in March 2020, is a disease caused by the severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2). The standard diagnostic method of COVID-19 is reverse transcription-polymerase chain reaction (RT-PCR) made from oropharyngeal and nasopharyngeal swab. However, the sensitivity of this test is low, particularly in the early period of the disease. (1) Computed Tomography (CT) can be used as a complementary to RT-PCR test in necessary cases in the diagnosis of COVID- 19 pneumonia. (1,2) In patients with negative RT-PCR test but clinical suspicion, CT is important in early diagnosis. (2,3) In a large study of 1014 patients, CT sensitivity was reported as 97% in the diagnosis of COVID-19. (1) Considering its contribution to diagnosis, the importance of knowing the most common and typical findings in thoracic CT increases. In this study, especially frequently detected CT findings of COVID-19 pneumonia are explained with images.

2. Imaging Findings

It has been found that SARS-CoV-2 virus enters the cell through angiotensin converting enzyme 2 (ACE-2) receptors and it causes first interstitial damage and then parenchymal damage in the lungs. (4) In the diagnosis, the sensitivity of direct chest X-ray is low and normal X-ray cannot exclude the disease. For these reasons, thoracic CT is at the forefront in diagnosis. If there is no complication

with contrast-enhanced CT indication such as pulmonary embolism, it is taken without contrast, as high resolution and thin sections. Table 1 shows the usual and unusual CT findings of COVID-19 pneumonia.

Table 1: CT Imaging Findings of COVID-19 Pneumonia

Usual Imaging Findings	**Unusual Imaging Findings**
Ground Glass Opacity (GGO)	Lymphadenopathy
Consolidation	Pleural Effusion
Crazy Paving Pattern	Cavity
Air bronchogram	Pericardial Effusion
Airway Changes	Lobar/Segmental Consolidation
Pulmonary Vascular Enlargement (PVE)	Tree-in-bud Pattern Nodules
Reticular pattern and linear opacification	
Nodules and Halo/Reversed Halo Sign	

2.1. Usual Computed Tomography Findings

2.1.1. Ground Glass Opacity

Ground glass opacity (GGO) is the most common CT finding of COVID-19 pneumonia. They are mild parenchymal density increases seen in the lung without vascular structures being erased. It is caused by partial alveolar filling, increase in capillary blood flow, partial alveolar collapse, interstitial lung disease or a combination of these. (5) It is detected in approximately 98% of patients and it is generally seen in the early phase of the disease, in patients with mild pneumonia or in asymptomatic cases. (6) GGO is typically bilateral, multilobar, peripheral and posteriorly located (Figure 1). However, it can also be unilateral. Although involvement is dominant in the middle and lower lobes and posterior, the upper lobes are also involved in the later stages of the disease and patients with severe pneumonia. (7) GGO can be the only finding, or it can be seen with findings such as consolidation, crazy paving pattern and interlobular septal thickening. (8)

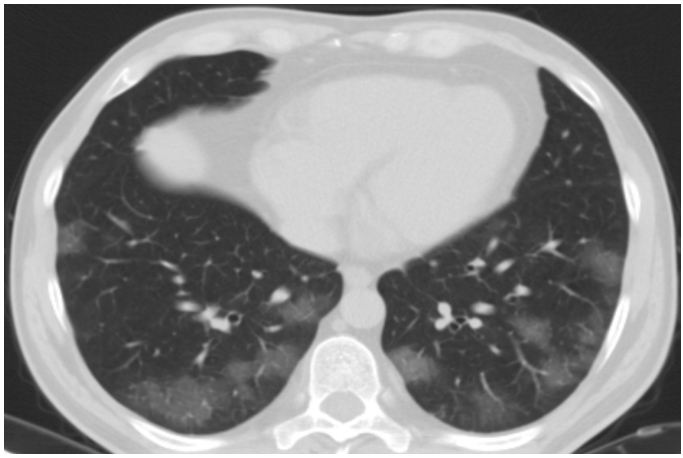

Figure 1: Noncontrast chest CT shows GGOs dominantly at peripheral and posterior areas of bilateral lower lobes.

2.1.2 Consolidation

Consolidation is the increase in density in lung parenchyma caused by the replacement of air in the alveoli with fluid, blood, pus or cells. Its difference from GGO is the disappearance of vascular borders. (5) Multifocal, segmental, patchy and peripherally located consolidations are usually seen in COVID-19 pneumonia (Figure 2). It can be seen less frequently in peribronchovascular area. It is often accompanied by GGO. (9) Consolidation is a finding of progressive disease and it is seen especially in advanced age, critical and severe cases. (8,10) Consolidations usually occur 10-12 days after the onset of symptoms. (11)

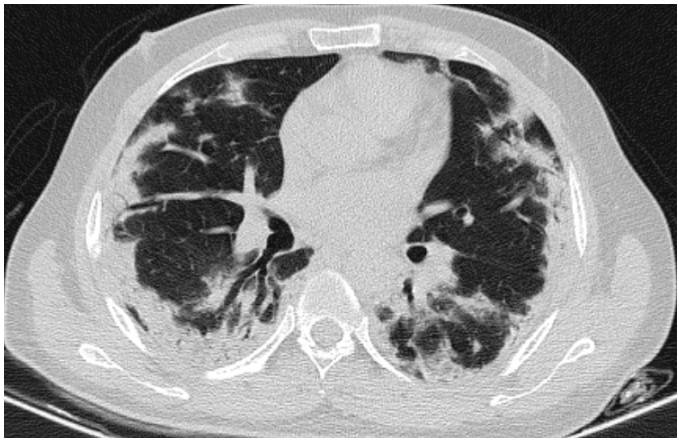

Figure 2: Multifocal, segmental, patchy, irregularly consolidations with an air bronchogram, generally located in the lower lobe and peripheral.

2.1.3. Crazy Paving Pattern

It is formed by the superimposed of thickened intralobular and interlobular septa on GGO (Figure 3). It is a finding associated with alveolar edema and interstitial inflammation. (5) It is a finding that demonstrates disease progression in COVID-19 and emerges on days 5-9 defined as the progressive phase. (12)

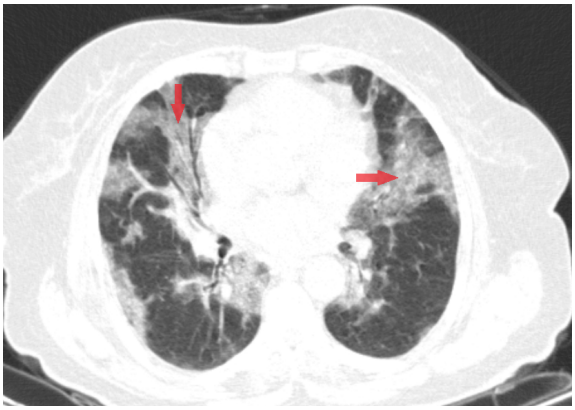

Figure 3: CT image shows bilateral GGOs with prominent intralobular lines and interlobular septal thickening, resulting in a crazy-paving pattern (red arrow).

2.1.4. Air Bronchogram and Airway Changes

Air bronchogram is high density because the lung tissue around the bronchi is filled with soft tissue instead of air and the bronchial lumens are seen as black in the high density lung parenchyma. (5) (Figure 4). In autopsy studies conducted with COVID-19, it was found that the low density in bronchial lumens was not caused by air, but by the sticky mucus in the bronchi. (13)

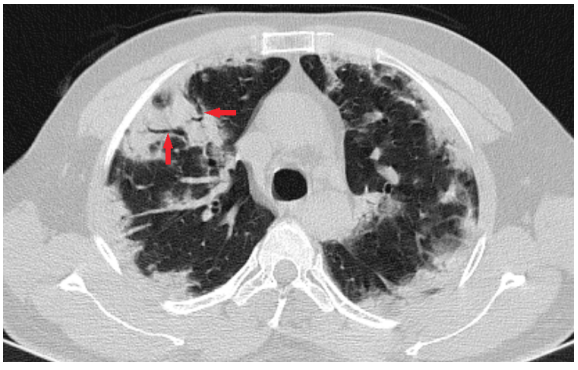

Figure 4: Consolidation with air bronchogram sign (red arrow) in the right upper lobe.

Other airway changes seen in COVID-19 patients are bronchial mucus plugs, bronchiectasis, bronchioletasia and bronchial wall thickening. (2,8,10) Bronchial wall thickening was found to be associated with poor prognosis and it was found to be more common in severe and critical patients. (14)

2.1.5. Pulmonary Vascular Enlargement

Pulmonary vascular enlargement (PVE) is the enlargement of subsegmental vessels in or around the parenchymal lesions and its diameter becoming ≥3 mm (Figure 5). PVE has been found to be more common in COVID- 19 pneumonia than other pneumonias and therefore PVE is a valuable finding in the diagnosis of COVID- 19. (15)

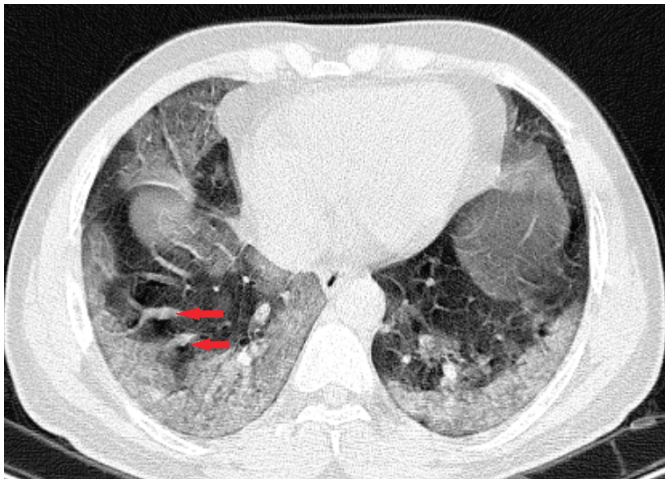

Figure 5: Focal vascular enlargement (red arrow) is seen in the GGO in the right lobe.

2.1.6. Reticular Pattern and Linear Opacification

Reticular pattern occurs with the thickening of interstitial structures such as interlobular septal and intralobular lines. (5) (Figure 6) It is frequently seen with consolidation and ground glass opacity and it is one of the late findings of the disease. (16) It has been shown that reticular opacities may be permanent in patients who recover from COVID 19 pneumonia. (17)

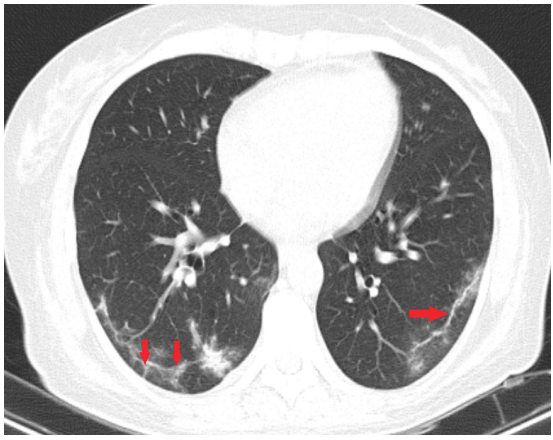

Figure 6: Subpleural curvilinear lines and interlobular septal thickening (red arrow) , with GGOs in both lower lobes.

2.1.7. Pulmonary Thromboembolism

Pulmonary thromboembolism is an important finding that can be seen together with parenchymal findings in COVID-19 patients. Pulmonary thromboembolism has been reported in 22-30% of patients and it has been found more frequently especially in intensive care patients who require mechanical ventilation. (18,19)

2.1.8. Nodules and Halo/Reversed Halo Sign

A nodule is an opacity smaller than 3 cm with regular or irregular borders in the lung parenchyma. It is a common sign in viral pneumonia and it has been reported with a rate of 6% in COVID-19 pneumonia. (20) Multifocal, solid, irregularly circumscribed nodules can be seen in these patients (Figure 7). “Halo sign” and “reverse Halo sign” can also be seen with the nodules.

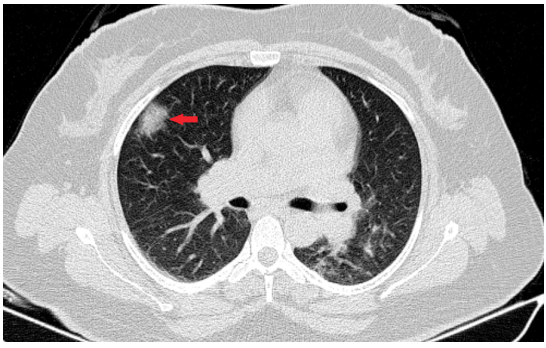

Figure 7: Axial chest CT demonstrated a nodule with halo sign in the right middle lobe (red arrow).

Halo sign is defined as ground glass opacity around the nodule or mass. It occurs due to bleeding or spread of the lesion to the surrounding interstitium. It is commonly seen in invasive fungal infection, haemorrhagic pulmonary metastasis and organized pneumonia (5). Halo sign is observed in 10-14% of COVID – 19 patients. (7,20) Reverse halo or Atoll sign is defined as a dense ring-like consolidation surrounding ground glass opacity. (5) This sign, which is specifically seen in cryptogenic organized pneumonia, has been shown in 2-15% of COVID-19 patients. (21,22,23) Pathophysiologically, it indicates consolidation in resolution or newly developing consolidation around GGO as a progressive lesion. (24)

2.2. Unusual Computed Tomography Findings

CT findings defined as unusual and rarely detected are lymphadenopathy, pleural effusion, pericardial effusion and cavitation. Lobar consolidation and tree-in-bud pattern nodules are also among unusual findings. If one of these rare findings in COVID-19 is present in a RT-PCR positive patient, accompanying bacterial infection should be considered. (25)

3. Conclusion

In COVID-19 pneumonia, early diagnosis is important for treatment and preventing the spread of the disease. CT is significant in early diagnosis in patients who have a negative RT-PCR test but clinical suspicion. In patients with a positive RT-PCR test, radiological data are significant in the follow-up of the disease. Common CT findings in COVID-19should be known because of the importance of CT in diagnosis and follow-up.

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CHAPTER IV

THE EFFECT OF COVID-19 ON THE ANATOMY OF THE CARDIOVASCULAR SYSTEM

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1. Introduction

2019 novel coronavirus (2019-nCoV), or now known as severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), originated from the city of Wuhan in China's Hubei province and spread quickly to the rest of the world. From the emergence of the disease to February 2020, approximately 415.092.856 coronavirus cases and 5.849.435 deaths have been reported. The future course of this disease is not known yet. Coronaviruses are enveloped positive-stranded ribonucleic acid (RNA) viruses which range from 60 nm and 140 nm in diameter, which have pointed protrusions on the surface and which have a crown-like appearance under electron microscope. (1)

Infection is generally transmitted through large droplets that occur while coughing or sneezing by symptomatic patients; however, transmission by asymptomatic individuals has also been reported. Studies have shown no difference between symptomatic and asymptomatic individuals in terms of viral load and a higher viral load in the nasal cavity than the throat.(2) Incubation period ranges from 2 to 14 days (5 days on average) .(3)

Clinical manifestations of Covid-19 are fever, cough, sore throat, fatigue, muscle pain and shortness of breath. (4) Although chest X-ray is normal in the early stage of the disease, it usually shows bilateral infiltration. Computed tomography (CT) is used extensively in the diagnosis of Covid-19 because it is more sensitive. In Covid-19, it is generally known as ground glass appearance and lower segment consolidation on CT lung image.(4)

ACE2 has been defined as a functional receptor for Covid-19. This receptor plays a role in the functions of the heart and the development of hypertension (HT) and diabetes mellitus (DM).(5) Symptoms are more severe in patients with cardiovascular disease (CVD). This is thought to be caused by increased ACE2 secretion in individuals with CVD. ACE2 affects not only lungs but also the cardiovascular system to a great extent. Therefore, cardiac damage in ACE2 related signalling pathways may play an important role.

Other mechanisms implicated in myocardial damage include damage to myocardial cells by cytokine storm triggered with an unbalanced response of type 1 and type 2 auxiliary cells, respiratory dysfunction and hypoxemia. Myocardial damage caused by infection with these viruses undoubtedly increases the difficulty and complexity of treating patients.(6) Patients with CVD constitute a great majority of deaths from Covid-19. In one study, it was shown that 58% of the patients with severe COVID-19 symptoms had HT and 44% had arrhythmia. (7)For this reason, particular attention should be paid to cardiovascular protection during the treatment of COVID-19.

2. CORONARY ANATOMY

Coronary arteries are veins that come out of the coronary sinus and navigate in the epicardial area and supply the heart. They are grouped in two as the right and the left coronary arteries. The right coronary supplies the myocardium only in the diastole, while the left coronary artery supplies the myocardium both in the diastole and the systole. (8) The left main coronary artery (LMCA) originates from the left aortic sinus and passes between the pulmonary trunk and the left atrium. Its diameter is 3-6 mm, while its length is 10-15 mm. (9) In two thirds of individuals, LMCA is divided in two as the left anterior descending artery (LAD) and circumflex artery (CX), while in the remaining one third, it has three parts by giving the ramus intermedius branch in addition to these two veins. Some cases do not have LMCA, LAD and CX are separated from the left aortic sinus with separate ostia. Sometimes there may not be LMCA at all, in such a case, LAD and CX originate from separate ostia. (10, 11)

LAD courses through the interventricular sulcus on the anterior surface of the heart and progresses to the apex, giving its diagonal and septal branches. Diagonal arteries supply the anterior and anterolateral of the left ventricular (LV) free wall and the inner 1/3 of the anterior right ventricular (RV) free wall. Septal branches originate from the LAD at an angle of 90 degrees and supply

the anterior 2/3 of the interventricular septum, the bundle of His and supply the right and anterior left bundle branches. (8, 11, 12) CX passes anterior to the left atrial appendage and proceeds to the posterior side of the heart in the left atrioventricular sulcus. It gives off left marginal artery and left atrial branches. CX supplies the lateral of LV free wall, a part of the anterolateral mitral papillary muscle and the lateral and posterior side of the left atrium. Cx is dominant in 10% of human beings. Cx dominance is determined by giving off the posterior descending artery (PDA). 80% of the population has right coronary artery (RCA) dominance, while the remaining 10% has co-dominance. (13) RCA originates from the right aortic sinus, and advances along the right atrioventricular sulcus to the "crux" by returning to the posterior side of the heart. The first branch RCA gives off is the conus branch. In 50% of the cases, it originates from a different ostium and supplies the right ventricular outflow tract. The second branch RCA gives off is the artery supplying the sinoatrial node. Several acute marginal branches leave off the middle segment of RCA and these branches supply the anterior wall of the right ventricle. In addition, these marginal branches together with the conus artery play a role in the collateral formation that occurs in LAD occlusion. RCA gives off the post-crux PDA and posterolateral (PL) branch. This way, ARC supplies the right atrium, RV anterior wall, 2/3 part of the interventricular septum inferior, inferior of LV free wall and posteromedial mitral papillary muscle. (10, 12)(Figure 1, 2)

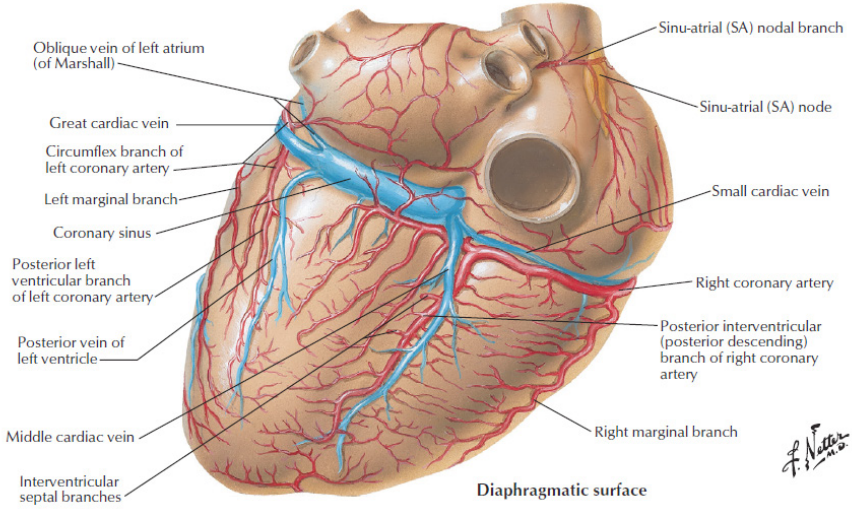

Figure 1: Coronary artery anatomy (Diaphragmatic surface). (14)

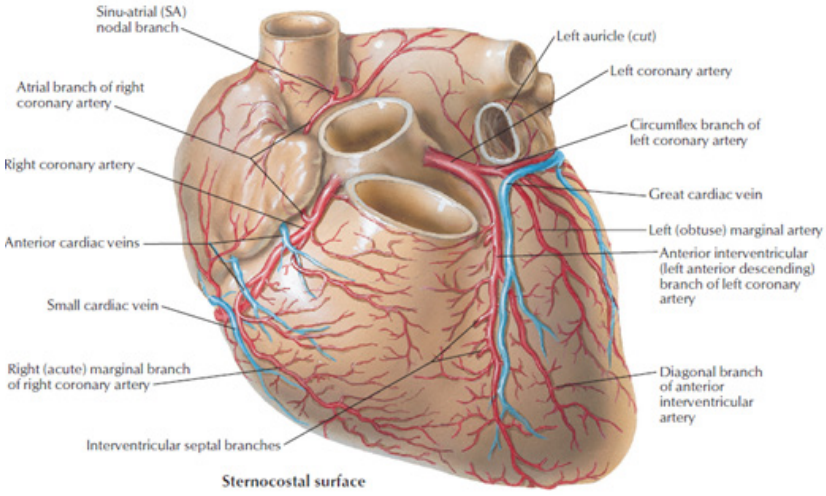

Figure 1: Coronary artery anatomy (sternocostal surface).(14)

2.1. Acute Coronary Syndromes

The clinical spectrum of acute coronary syndromes (ACS) is very broad. While it may have a painless course on admission, it may progress to chest pain, pulmonary oedema, cardiogenic shock and even cardiac arrest. In patients with ACS suspicion, the most important symptom starting the diagnosis and treatment process is acute chest discomfort described as pain, pressure, tightness and burning. Other symptoms equivalent to chest pain may be dyspnea, epigastric pain and pain in the left arm. (15)

2.2. Pathophysiology of coronary artery disease

2.2.1. Atherosclerosis

Atherosclerosis is a repetitive process that primarily affects the intima of medium and large arteries and then the media and adventita layers that is based on endothelium dysfunction and progresses with lipid accumulation and inflammation. Coronary arteries, carotid arteries and branching points of distal abdominal aorta are involved most frequently in atherosclerosis.(11)

The period of atherosclerosis formation includes many stages. The first stage of atherosclerosis is endothelial dysfunction that occurs due to a large number of risk factors such as HT, DM, hyperlipidemia, smoking and genetics. The process that starts with endothelial dysfunction continues with the transportation and storage of the released adhesion molecules and monocytes

loaded with oxidized LDL from the circulation to the intima layer. (12, 16) As macrophages phagocytize oxidized LDL in the intima, a foam cell forms and it is observed as streaks under the intima layer. These lesions, which do not cause narrowing of the lumen, are called fatty streaks and they are the first lesion of atherosclerosis.

As accumulation increases, LDL cholesterol also increases inflammatory response. Monocytes transform into macrophages. Macrophages secrete inflammatory mediators with lipid accumulation. Immune response increases further with inflammatory mediators and T lymphocytes attracted to the area. With the effect of increased immune response, vascular smooth muscles that migrate to intima proliferate and cause the plaque to grow by producing extracellular matrix. Fatty streak turns into atheroma plaque after this stage. Atherosclerotic plaque consists of a lipid-rich nucleus, surrounding intimal smooth muscle cells and inflammatory cells, and outer fibrous cap. (9, 16) Atherosclerotic plaques are grouped in two in terms of their content:

Vulnerable plaque: these are plaques with a thin fibrous cap rich in lipid content. These plaques are rich in terms of smooth muscle cell and they are more likely to be complicated. Stable plaques are plaques with low lipid content and thick fibrous content. They cause symptoms if they enlarge to cause significant narrowing in the lumen.

3. COVID-19 INFECTION

3.1. Epidemiology

SARS-Cov-2 spread rapidly in the world after it emerged in China in December 2019. Throughout the world, cases were reported from all continents after Antarctica. As of February 2020, WHO named the disease Covid-19, Coronavirus disease 2019.

According to WHO, the first cases in America and European countries began to be seen in January 2020. Following this, as of February 2020, the pandemic was seen in a large number of countries and continents, especially Italy, England, Brazil, Spain and Iran. While the pandemic was declared by WHO on March 10, 2020, the first case was declared on the same day by the Ministry of Health in Turkey. (17)

In terms of the demographic characteristics of the disease, in a report including an average of 44.500 confirmed Covid-19 patients in China Disease Control and Prevention Centre, 87% of the patients were between the ages of 30 and 79. (18)

Covid-19 infection is transmitted through large droplets formed by coughing and sneezing of patients. (19) Studies have reported a higher viral load in the nasal cavity compared to the throat, and no difference in viral load between symptomatic and asymptomatic individuals. (20) In Covid-19, the disease can be contagious as long as symptoms persist and even during clinical recovery. While the virus can survive on surfaces in suitable atmospheric conditions, it can be destroyed in less than a minute with commonly used disinfectants such as sodium hypochlorite and hydrogen peroxide. (21) Infection occurs by breathing in these droplets or touching a contaminated surface or touching the nose, mouth or eyes. The virus is also found in feces. (22) According to existing information, transplacental transmission from pregnantwomen to foetus has not been described. However, neonatal disease associated with postpartum transmission has been described. Incubation period varies between 2 and 14 days (5 days on average). Studies have described ACE2 as the receptor through which the virus enters the respiratory mucosa. (Figure 3)(23)

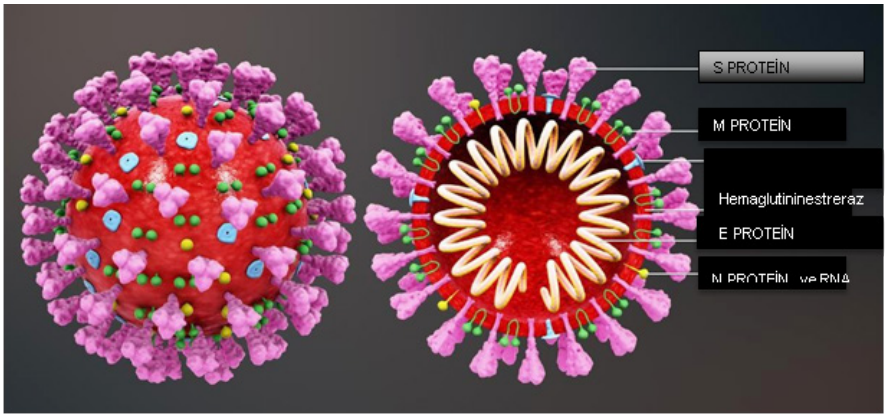

Figure 3: The structure and proteins of Coronaviridea.(23)

3.2. Pathophysiology

The pathophysiology of Covid-19 disease is not fully understood yet; however, the most important mechanism is thought to occur through the attachment of the virus to ACE-2 receptors.

ACE-2 enzyme is an enzyme that causes the formation of Angiotensin 1, which is found in the vascular endothelium and type 2 alveolar cell membranes of lungs and causes a decrease in blood pressure in the body, vasodilation and inflammation.

This enzyme is a component of the Renin- Angiotensin system (RAS), which plays a very important role in the body's blood pressure system. ACE-2 does its job in the body through converting Angiotensin 2 (Ang-2) to Ang 1-7. With ACE, which acts opposite to ACE-2, ACE-2 enzyme maintains RAS balance in the body. While ACE hormone leads to Acute Respiratory Distress Syndrome in the lungs by causing vasoconstriction, bronchoconstriction and fibrosis through stimulating inflammation in the body, ACE-2 shows opposite effects. It is thought that disruption of this balance plays a major role in the pathogenesis of COVID-19. (24, 25) (Figure 4) As a result of the activation of serine protease -2 in the transmembrane of the patient cell by attaching to ACE-2 receptor on the surface of the patient cell with the S protein in the Covid-19 virus membrane, which provides the spiky appearance of the virus, fusion develops between the viral envelope and cell membrane and thus the virus enters the cell. It is thought that the disease is initiated by suppressing the ACE-2 system of the sick individual after fusion. (26) In the light of a study conducted on mice infected with Covid-19, it was found that decreased level of ACE-2 played a role in the exacerbation of lung failure. (27) It has been found that excessive amount of Ang-2 in sick individuals due to decreased ACE-2 and as a result its excessive binding to AT-1 receptor compared to the past caused the progress to ARDS; it was even thought that ARDS development could be slowed by administrating AT-1 receptor blocker to sick mice. (28)

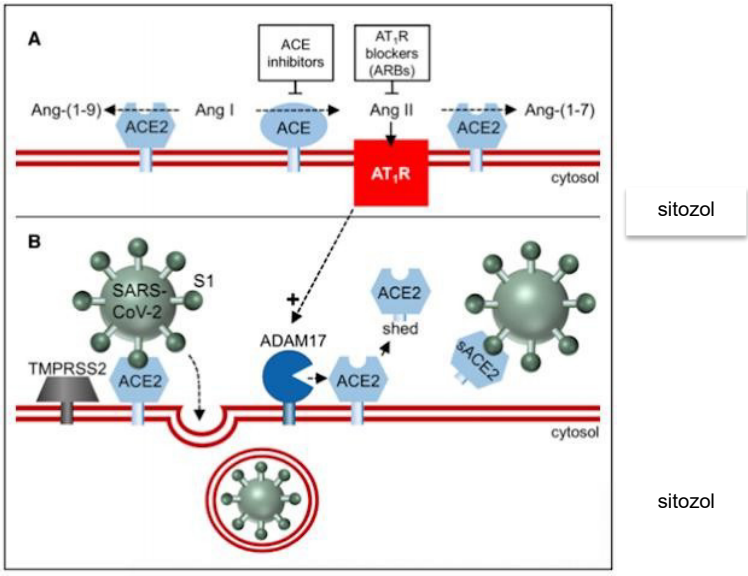

Figure 4: Coronavirus Pathogenesis. (29)

In the early stages of SARS-CoV and MERS-CoV infections, which previously caused epidemics, delayed IFN response was found after the penetration of the virus into the diseased cell. The reason for this was that the patient host was not able to form a full immune to the virus. (30) In addition to this, in the light of studies on MERS patients, a large number of neutrophils and monocytes were found in the lung cells of patients and these cells were found to play a role in lung damage. (31)

It was found that a similar mechanism was also found to be present in novel coronavirus disease and in accordance with the studies conducted, "cytokine storm" was found to play a role in progression to ARDS in severe cases. (32) After the virus enters the cell in sick individuals, weak interferon (IFN) response occurs and then T lymphocyte is activated by releasing proinflammatory cytokines. In some individuals, this immune response of the patient's body to the damage by the virus can be very severe. After the formation of large amounts of proinflammatory cytokine and chemokines against the virus, macrophages and neutrophils are activated and these cells go to the lung tissue quickly. This is called cytokine storm. (33) As a result of cytokine storm, large amount of cytokine released in the body causes apoptosis in lung epithelial and vascular endothelial cells and cause these cells to accumulate in the pulmonary microvascular bed, vascular damage and vascular leakage. Thus, ARDS clinic occurs after alveolar oedema and hypoxia. (34)

In patients infected with COVID-19 who are followed in intensive care and who are having a severe disease, macrophage chemotactic factor (MCP), granulocyte colony stimulating factor (G- CSF), IFN-gamma, IL-1, IL-7, IL-8, IL-10 and tumour necrosis factor alpha (TNF alpha) levels were higher in blood samples when compared with the patients followed in the service. (35)

3.3. Clinical Course

Covid-19 leads to broad spectrum clinic. While it causes some of the patients to be asymptomatic carriers, it has a more severe course in some others and causes acute respiratory dysfunction. Covid-19 disease is grouped in four as severe, asymptomatic, mildly-moderately severe and critical. (18)

The most important factor in the mortality of the disease is age and it increases rapidly with advanced age. In Turkey, mortality rate is very low when compared with many European countries and America and it was reported as 2.4% by the Ministry of Health as of September 2020. In a study conducted in China, it was found that mortality increased approximately 3 times in patients

aged 80 and older. (36) In Italy, it was reported that 83% of the cases in which the disease resulted in death were cases older than 70 years of age. (37) While studies conducted in Korea found the mortality of the disease as 0.9% in all patients, this rate was found to be higher in patients older than 80 years of age (9.3%). (38)

There are a number of studies about the course of the disease and it has been reported to have a worse prognosis in some patient groups and in case of some risk factors accompanying. In summary, it has been found that in the presence of diabetes mellitus, essential hypertension, atherosclerosis heart disease, chronic obstructive pulmonary diseases, comorbid malignancy and smoking, the risk of getting infected with Covid-19 and mortality after infection was found to be higher when compared with the other individuals in the population. (39)

It has been stated that demographically, gender as well as age is another factor emphasized that affects the course of disease. Although the number of total cases was equal in both genders, it was found that especially the need for intensive care or mortality rate was higher in male patients; for example, it was found that the number of patients followed in intensive care in Italy and France was 4 and 3 times higher, respectively in men when compared with women. (40)

In another study conducted in China, while the number of mild and moderate course COVID-19 cases was higher in women, the majority of intensive care patients were men. In the same study, of the 37 cases which resulted with mortality, 70.3% were men, while 29.7% were women. (41)

Symptoms of the disease have a wide spectrum, ranging from cough and fatigue, which are seen in a simple respiratory tract infection to hypoxic pneumonia in more severe presentations. Most common symptoms are dry cough, fatigue, fever and myalgia. More severe cases have chest heaviness, feeling of tightness in the chest and dyspnea. In a study conducted in America with approximately 370.000 patients, most common findings were cough, fever and myalgia, respectively (50%, 43% and 36%, respectively). (42)

In another Covid-19 patient group with atypical presentation, the patients' complaints were gastrointestinal system findings and these were mainly nausea, vomiting and even diarrhoea in some patients. (43)

While mild symptoms are similar to classical upper respiratory tract flu infections, the complaints in more severe cases are different. Most of the patients in need of intensive care are patients with advanced age and comorbid diseases. When patients with more severe Covid-19 infection are examined, it can be seen that the most common comorbidities are diabetes mellitus and hypertension.

(44)Critical patients followed in the intensive care often develop hypoxemic respiratory failure (there are also cases accompanied with hypercapnia) and ARDS (60%) afterwards. Studies conducted have shown septic shock to develop in 30% of the patients and acute renal failure in 10-30%. (45) In a study conducted in China, in almost half of the 2087 critical patients, the disease had a mortal course. In another study with fewer patients, 97% of the patients who were on artificial respiratory device died. (46)

3.4. Laboratory Findings

In addition to helping Covid-19 diagnosis, laboratory examinations also give information about mortality and association with poor prognosis in the course of the disease with some parameters. In patients with Covid-19 infection, the parameter most associated with mortality is lymphocyte count. In most of the patients, independent of leukocyte count, a decrease in lymphocyte count and lymphopenia were observed. (47) Some studies have reported that the diagnostic value of lymphopenia is weak. (48) The over-released anti-inflammatory cytokines against the Covid-19 virus cause apoptosis and decrease the number of lymphocyte cells, which is one of the underlying mechanisms of lymphopenia. (49)

Another important parameter NLR (neutrophil-lymphocyte ratio – NLR) has come to the fore with the high rate of migration of neutrophils to the lungs and therefore with the increase in the number of neutrophils circulating in the blood and due to deep lymphopenia in these patients.(50) Although cut-off limit value is 3 for NLR in some studies while cut-off values are more different in others, the common view in all studies is the fact that high NLR value increases mortality and is an indicator of poor prognosis.

Other parameters are C-reactive protein (CRP) and procalcitonin. It has been found that high values of both, especially CRP, are correlated with the disease and they show poor diagnosis. In another study conducted with 140 patients in China, in first admission blood values of patients, 65% of the patients were found to have high CRP, while 5.7% were found to have high procalcitonin and high levels of both were found to get even higher in patients with a severe course. (51)

Another pathophysiological mechanism of the disease process caused by Covid-19 virus infection in the body has been reported as hypercoagulability. (52) Another parameter associated with mortality and poor prognosis is high D-dimer level. (53) In the meta-analysis of 25 studies including 5350 patients, it

was found that high d-dimer levels indicated high mortality although they were not found to be associated with intensive care hospitalization. (54)

Ferritin is a positive acute phase reactant and it has been found to be elevated in Covid-19 patients. In 10 different studies retrospectively examining its association with mortality, elevated ferritin level was found to be a poor prognostic biomarker and the levels were found to be even higher in patients in the intensive care and in those who died. (55)

3.5. Radiological Findings

In Covid-19 pneumonia, diagnostic value of direct X-ray graph is between 30-40% and this rate is much lower than tomography. (56)Although no pathology is found in direct graph, there are patients who have involvement in tomography. (57)

3.6. Diagnosis

In studies conducted so far, gold standard method for Covid -19 diagnosis is the detection of viral RNA by using reverse transcriptase polymerase chain reaction (RT-PCR) method in samples taken with swab from nasal and oral cavities of sick individuals. (58)

The main thoracic findings suggesting Covid-19 pneumonia are unilateral and mostly bilateral consolidated areas or ground glass densities in the periphery and basal of especially the lung tissue. Ground glass and consolidations are seen together in some patients.

The table below shows the classification of thoracic CT findings by British Society of Thoracic Imaging. (3) (Table 1).

Table 1: Classification of thoracic CT findings by British Society of Thoracic Imaging. (3)

Diagnosis	**Tomographic pathology**
Typical COVID-19 100% compatible	• Peripherally located; diffuse, multiple, bilateral ground glass density increases in lower lobes • Paving stone appearance • Air bronchograms • Peripheral consolidations with organized pneumonia • Reverse halo appearance/perilobular pattern
Possible COVID-19 71-99% compatible	• Peripherally located, diffuse bronchocentric consolidations in lower lobes • Limited ground glass appearance • perilobular pattern
Suspected COVID-19 <70% compatible	• Patients not compatible with the other three groups • Patients with compatible radiological image, but another diagnosis (interstitial pulmonary disease, etc.)
Excluded COVID-19	• Lobar pneumonia • Cavitation • Lymphadenopathy • Tree appearance of buds • Pleural effusion • Advanced pulmonary fibrosis

In a study conducted prospectively in China with 1014 patients, while the sensitivity of 1014 CT in Covid diagnosis was found as 97%, the sensitivity of Covid PCR tests used frequently in diagnosis was found as 60-70% (57). In a study conducted in Italy, the sensitivity of bilateral multilobar peripheral ground glass image in tomography, which is considered as typical involvement, was found as 97%, while its specificity was found as 56%. (3) (Figure 5)

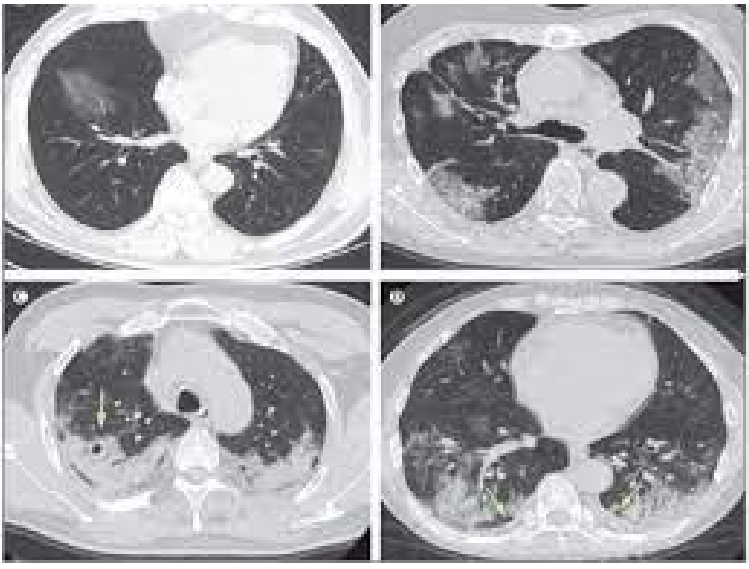

Figure 5: Sample CT and X-ray images in Covid -19 patients.(3)

3.7. Treatment

Studies on the treatment of Covid-19 are still continuing and there is no clear treatment with proven efficacy yet; however, some treatments predicted to be beneficial have been suggested in our country and in the world. These are mainly chloroquin / hydroxychloroquine, favipiravir, lopinavir / ritonavir, remdesivir, corticosteroids, IL-6 receptor antagonists, anakinra, intravenous immunoglobulin (IVIG), and convalescing plasma (46).

3.8. Immunization

Vaccine is considered as the most effective treatment for Covid-19 infection. With this purpose, vaccine studies have started in many countries since the beginning of Covid-19 pandemic. Currently, vaccines such as BNT162b2 (Pfizer-BioNTech Covid-19), mRNA 1273 (Moderna Covid-19 vaccine), CoronaVac (Sinovac) have started to be applied in many countries with the indication of emergency use.

4. Cardiovascular system and Covid-19

CVDs are commonly seen comorbidities in patients infected with SARS or MERS. This has been described clearly in a series of reports regarding the

clinical features of patients with Covid-19. The prevalence of ICU in critical patients and the prevalence of cardiovascular states in patients who die are very high. In a single-centre cohort study including 138 patients hospitalized with Covid-19 in Wuhan, 31% of the patients had HT (58% of the patients in ICU), while 15% (25% of the patients in ICU) had other CVDs. General mortality rate of cases with CVD was 10.5% {the highest among those with a comorbidity including chronic respiratory disease (6.3%) or cancer (5.6%). (47)

4.1. Myocardial injury and myocarditis

In Covid-19 studies in China, myocardial damage proven with high cardiac biomarker levels or electrocardiogram anomalies were reported in 7-20% of the patients. (58) Presence of myocardial damage has been associated with worse prognosis significantly. Another study conducted supported this finding. It reported that mortality rate was 37.5% in patients with high cardiac troponin T levels and elevated cardiac troponin T levels in patients with underlying cardiovascular comorbidities almost doubled mortality (69. 4%). (59) There is limited histological evidence of myocardial damage or myocarditis in Covid-19. When all these findings are evaluated together, it can be seen that myocardial damage is not only a common symptom of Covid-19, it is also a risk factor for poor prognosis.

4.2. Acute Coronary Syndrome

As in other contagious diseases, Covid-19 may also trigger ACS. The mechanisms underlying ACS induced by Covid-19 may include plaque rupture, coronary spasm or microthrombus due to systemic inflammation or cytokine storm. (60)

4.3. Heart failure

With its 24% incidence in all patients and 49% incidence in patients who die, heart failure is one of the most common complications of Covid-19. High amino-terminal pro-B-type natriuretic peptide (NTpro-BNP) levels have been found in 49% of all patients (85% of those who die). Especially in old patients who have decreased diastolic functioning, preserved ejection fraction heart failure may develop during the course of Covid-19 and this can be triggered with high fever, tachycardia, extreme hydration and impaired renal functions. (60)

4.4. Arrhythmia and sudden cardiac arrest

One of the common symptoms of Covid-19 is Arrhythmias and sudden cardiac arrest. The contribution of Covid-19 to cardiac arrhythmia is uncertain; however, myocardial damage or other systemic causes such as fever, sepsis, hypoxia and electrolyte abnormalities may trigger the infection. In addition, Covid-19 patients are mostly treated with antiviral drugs and antibiotics that are determined to cause arrhythmia in some patients. (61)

4.5. Coagulation Disorders and Thrombosis

Covid-19 is associated with coagulation anomalies that can cause thromboembolic events. The results show that a significant proportion of Covid-19 patients have coagulation anomalies that do not typically meet the criteria for common intravascular coagulation set by the International Society for Thrombosis and Hemostasis, and that Covid-19 may contribute to the development of various cardiovascular symptoms. The mechanisms underlying coagulation anomalies, particularly hypercoagulation, are unclear. Severe inflammatory response and endothelial damage caused by Covid-19 and underlying comorbidities may predispose patients to hypercoagulable state. Some antiviral drugs and investigational treatments given to these patients can cause thrombosis or bleeding through the interaction of anticoagulants and drugs. (62)

4.6. Covid-19 and Hypertension

It is unclear whether hypertension is a risk factor for susceptibility to SARS-CoV-2 infection. In line with the high strain rates (N30) in the general population, available data show prevalence rates of 15-40%. At first glance, hypertension is more common in patients with a more severe course of discomfort. A recent analysis in China reported that it was present in 13.4% of those without severe disease and in 23.7% of those with severe disease. In a study of 44 672 patients with CVD in China, the prevalence of hypertension was reported as 12.8% in all patient groups and 39.7% in patients who died. (63)

4.7. Covid-19 and ischemic heart disease

Although little is known about the effects of Covid-19 on ACS, various paths regarding viral diseases may contribute to imbalance of plaques in Covid-19 patients. Patients with cardiac failure are under high risk in terms of acute events or exacerbation; viral disease can potentially destabilize atherosclerotic

plaques through systematic inflammatory responses, cytokine storm and specific changes of immune cell polarization towards more unstable phenotypes. All of these have been observed in Covid-19. Acute MI has been observed in two of five deaths in early reports in case of SARS and MERS. (64)

4.8. Venous Thromboembolism

Laboratory results of Covid-19 patients confirm coagulation anomalies. Reports, decreased number of thrombocytes, high D-dimer and fibrinogen levels and elongated prothrombin time explain a poor prognosis. Excessive procoagulant production causes severe hypoxia and inflammation causes hypercoagulation. While pulmonary artery thrombosis is rate in other coronavirus infections, it is more common in SARS-CoV-2. In one study conducted on Covid-19 patients, deep vein thrombosis was found in 7 of the 12 cases who were suspected of deep vein thrombosis. (65)

5. ACE-2 and Cardiovascular symptoms

It has been reported that ACE-2 expression in Covid-19 is one of the main factors in the biological mechanism underlying the infection. As with SARS-CoV, SARS-CoV infection is triggered by the binding of the viral S protein to human ACE-2. Animal models of ACE inhibitors and angiotensin receptor blockers (ARB) have also been reported to increase ACE2 expression. Considering the widespread use of both ACE inhibitors and ARBs in the treatment of hypertension and other cardiovascular diseases, it has become an important question whether these drugs should be discontinued during the Covid-19 pandemic. (65)

6. Treatment

In general, suggestions about the treatment of cardiovascular complications in Covid-19 patients are not different from pre- Covid-19 period. For example, mechanic ventilation was used when necessary in severe patients with low blood saturation, vasopressor catecholamines were given to increase the decreased blood pressure in case of shock and drugs and specific procedures were used in many other clinical situations. Although pandemic creates new difficulties about the treatment of myocardial infarction, main treatment method should not be changed. Zheng et al. reported that drug induced cardiac damage is of concern during Covid-19 treatment and especially antiviral drug use should be followed. These types of drugs are known to induce various cardiovascular disorders;

cardiac failure and arrhythmias including sinus syndrome have been observed in patients after interferon and ribavirin use. For this reason, in order to prevent cardiac toxicity, antiviral drugs and side effects should be kept under control especially in patients with previous CVD. (65)

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CHAPTER V

EFFECTS OF COVID -19 INFECTION ON CENTRAL AND PERIPHERAL NERVOUS SYSTEM ANATOMY

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1. Introduction

Coronaviruses are a large family of viruses with high infectious properties that can cause respiratory tract infections and more severe infection states, can be transmitted from animal to human and from human to human.

Coronaviruses have an enveloped and single-stranded RNA genome. Since there are protrusions in the structure of glycoprotein, which allows them to look like a crown in an electron microscope on their outer surface, this family of viruses is called “corona” in Latin, which means “crown” or “ring of light”. They have a large genome, which stands out among all RNA viruses with a base length of 30 kilograms. They are common in humans and animals. (1) Just as there are various subtypes of coronaviruses that can be easily transmitted from human to human, there are also subtypes (SARS-CoV, MERS-CoV) that are found in animals and are transmitted from animal to human. (2) Considering their genetic characteristics, coronaviruses are divided into four groups as alpha-coronaviruses, beta-coronaviruses, delta-corona viruses and gamma-coronaviruses. (3)

In 2003, a new coronavirus emerged for the first time in China as a causative agent of SARS (severe acute respiratory syndrome). (4) Coronaviruses have caused outbreaks three times (SARS, MERS and COVID-19) to date,

including the first in 2003. Genetic and phylogenetic analyses of the virus that caused the Covid -19 outbreak show that this virus phylogenetically belongs to the Coronaviridae family and has a strong relationship with these outbreaks that occurred in previous years. (5) The causative virus of Covid19 has been named SARS-CoV-2 due to its great similarity with SARS CoV, the causative virus of SARS that caused the outbreak in 2003(6). SARS-CoV2 is a novel beta coronavirus that can infect humans quickly. (7)

Covid -19 is a contagious disease that first appeared in Wuhan, China. Due to the high transmission rate of the causative virus, it was declared a pandemic by the World Health Organization in March 2020 by affecting the whole world in a short time. (8) According to the World Health Organization data, more than 521 million Covid-19 cases were detected in the period from 11 March 2020, the beginning of the pandemic, to 20.05.2022.

In addition, there have been 6.2 million deaths due to Covid-19. (9) The factors affecting the person-to-person transmission of Covid-19 disease include the amount of virus in the respiratory tract of the infected person, taking preventive measures, the type and duration of contact with the infected person. The person infected with this disease, which spreads quickly and easily, can be infected by close contact with other people through droplets during coughing and talking. (10) The disease is usually manifested by an asymptomatic infection, which may also be accompanied by mild pneumonia. However, it can sometimes cause severe hypoxic respiratory failure accompanied by multiple organ dysfunction. (11) In COVID-19 disease, in 80-90% of cases, the disease is mild or asymptomatic. (12)

The most common symptoms of the disease are high fever, sore throat, weakness and fatigue. Chest pain, cough with phlegm, loss of appetite, abdominal pain, nausea, vomiting, diarrhea and headache and joint pains may also occur. In more severe cases, pneumonia, acute cardiac problems and multiple organ failure may occur. The mortality rate is in the range of 2-5%. (13) With the increase of scientific studies, we see that coronavirus infections affect many organs and systems as well as the respiratory system. (14) Spiratory, cardiac and neurological complications may worsen the prognosis. According to observational studies, the presence of headache, nausea, vomiting, myalgia, dizziness, hyposmia and altered consciousness in SARS-CoV-2 infected patients indicates nervous system involvement. (15)

According to studies, 35% of patients develop neurological symptoms, and in a group of patients, some neurological symptoms may appear before

the common symptoms of COVID-19. (16, 27) Neurological symptoms in COVID-19 patients may be due to the entry of the virus into the central nervous system, invasion of endothelial cells in the cannacerene barrier, invasion of epithelial cells in the blood-cerebrospinal fluid (CSF) barrier, invasion of inflammatory cells that can enter the central nervous system, or retrograde axonal transport (from olfactor, respiratory or enteric nervous system networks) and clinical pictures after interaction with ACE-2 receptors located in the central nervous system. (17,18) Direct invasion damage, hematogenous pathway, neuronal pathway, hypoxic damage, immune damage and ACE2 pathway have been shown in the nervous system damage mechanisms of coronavirus infections. (19)

2. Neural Invasion of SARS-CoV2 and Possible Routes of Transmission

2.1. Neuronal Pathway

The human coronavirus has been shown to spread to the central nervous system in less than a week and has been detected not only in neurons, but also in neuroglial cells. (20)

The olfactory nerve is the neural pathway most commonly blamed for reaching the CNS by respiratory tract viruses. It is thought that the olfactor, which is part of the nasal mucosa, passes through the olfactory nerve in the mucosa. It is thought that the virus, which attaches to the cell through ACE-2 receptors located in the olfactory mucosa, multiplies here, causes inflammation and local cytokine storm, and reaches the CNS through the ethmoid cribriform layer. (21) Retrograde axonal transport of the virus through receptors in the olfactory bulbus is observed more frequently. (22)

Another neuronal pathway was focused on the tenth cranial nerve, the nervus vagus, and it was thought that the virus infecting the lungs could reach the brain stem and respiratory center from the lungs through the vagus nerve. (23)

2.2. Hematogenous Pathway

It has been suspected that SARS may benefit from the blood brain barrier permeability of cytokines released after viral infection of the respiratory tract, whose main task is to ensure mobility and communication between leukocytes, and chemokines that mediate its migration to a specific region. (24)

2.3. Target Cell

The target receptor of SARS and SARS-CoV2 is the ACE2 enzyme. ACE2 is greatly expressed in the circulatory and excretory system, especially in the heart and kidneys. The ACE2 receptor, located in the capillary endothelium of the brain, provides the entry of the virus into the CNS after virus interaction with the ACE2 receptor during viremia. (25) Therefore, it has been emphasized that SARS and SARS-CoV2 can directly target neurons and spread. It has been emphasized that the expression of the ACE2 enzyme in the nervous system can lead to neurological symptoms by indirectly or directly affecting the mechanisms in the nervous system, and in the autopsy results of patients who died with Covid-19, it was shown that the brain tissue was hyperemic and edematous and some neurons were degenerate. Patients with Covid-19 who applied to the hospital to investigate the effects of Covid-19 on the nervous system were evaluated neurologically, and in these patients with severe infection, neurological symptoms were also very severe. During this research, SARS-CoV2 was also detected in patients admitted to the hospital with only neurological findings. (26) According to studies, 35% of patients develop neurological symptoms, and in a group of patients, some neurological symptoms may appear before the common symptoms of COVID-19. (27, 16)

3. Covid 19 and Nervous System Symptoms

SARS-CoV2 has a characteristic of rapid spread and rapid mutation. In addition to the specific clinical symptoms that affect the respiratory system and cause severe respiratory distress, the neurological symptoms seen in various case reports can be classified as follows.

1. Central nervous system symptoms
2. Peripheral nervous system symptoms
3. Neuromuscular symptoms

3.1. Central Nervous System Symptoms

In patients with COVID-19, the incidence of nervous system symptoms is higher in patients with high severity of respiratory infection. As Covid-19 continues to spread rapidly, it has emerged that the SARS-CoV-2 virus infects many organs, showing various neurological manifestations, including acute cerebrovascular disease and epilepsy. Possible theories are based on the fact that the spread of

SARS-CoV-2 to the central nervous system can occur either by hematogenous route or through nerve endings.

The possible mechanism of neurological symptoms observed in infected patients is developed with the virus being linked to neurological and psychiatric symptoms. (28) Studies have found that as high as 36% of patients with COVID-19 have neurological symptoms. (29) When neurological and neuropsychiatric symptoms were reported, the most common symptoms were 62%, followed by cerebrovascular events in 31% (28). Neurological symptoms include a mild headache or "brain fog". (30, 31) Guillain-Barre syndrome varies to more serious complications such as encephalitis. (32) Arterial and venous problems are common. (33, 34)

3.2. Peripheral Nervous System Symptoms

Odor and Taste Disorders; It is the most common peripheral nerve involvement of COVID-19 patients. In the nasal cavity, which is the entrance gate of respiratory tract viruses, it is found in three types of mucosa: squamous, respiratory, olfactory mucosa. The ACE-2 receptor is specifically expressed in the olfactory mucosa. As it is known, SARS-CoV2 enters the cell through this receptor. The virus attaches to the receptor and replicates. Inability to smell is caused either directly by the virus or by olfactory nerve dysfunction due to local cytokine storm and inflammation that develops in the mucosa. (35) ACE-2 receptors are more concentrated in the tongue than in the cheek mucosa and gums. The virus that binds to the receptor multiplies and leads to local inflammation. It is thought that the inability to taste develops accordingly. There is no exact information about how long the inability to smell and taste will last, whether it is permanent or not. It has been reported that it improves at different times in some patients, while it does not improve in others. (36)

In the literature, as a result of peripheral nervous system involvement reported to occur in relation to COVID-19, diplopia, taste disturbance, bilateral abdusens paralysis, Miller-Fisher syndrome with areflexia, decrease or loss of sense of smell and/or taste accompanying bilateral facial paralysis are developed. (37-39)

3.3. Neuromuscular Symptoms

Some motor symptoms such as muscle pain, ataxia, skeletal muscle damage and myopathic changes have been detected in COVID-19 disease. Staying in the hospital and intensive care unit, long recovery processes increased muscle problems. (40)

Covid -19 patients may also experience motor function losses due to prolonged inactivity during the intensive care period and due to the lack of necessary physical therapy and rehabilitation. A comprehensive rehabilitation program is needed to improve the motor functionality and overall health status of these patients. (41)

4. Result

Patients who recover after acute COVID-19 and are discharged from the hospital have an increased risk of multiple organ dysfunction and mortality. (42) This uncertainty and the fact that Corona viruses exhibit neuroinvasive properties, increase neurological symptoms, cause cytokine storms, and also consider cytokine storm as an underlying mechanism of neurodegenerative diseases; The question mark of what kind of profile awaits patients infected with SARS-CoV2. In addition, the increase in the severity of neurological symptoms according to the severity of the infection shows that SARS-CoV2 has an effect on the nervous system.

In line with this information, it is necessary to follow up the infected patients and recover forward, and to take serious measures against this infection, which is also our life. More studies need to be done and more concrete data need to be obtained in this area in order to make researchers more understandable the possible mechanisms of action of coronaviruses on the nervous system.

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CHAPTER VI

THE ANATOMICAL APPROACH TO SARS-COV-2 AND STROKE

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1. The relationship between SARS-CoV-2 and central nervous system

In the literature, investigations have been suggested that there may be viral encephalitis associated with SARS-CoV-2 and virus attacks against the central nervous system (CNS), and this has led to the consideration of SARS-CoV-2 may cause nervous system injuries. (1) The high similarity of neuronal infection between SARS-CoV-1 and SARS-CoV-2 and the neurotropic characteristics of SARS-CoV-2 suggests that this virus has neurological damage. (2) In addition, in the literature, neurological symptoms such as headache, epilepsy, and loss of consciousness, together with early neurological symptoms without respiratory symptoms, have been reported in many Covid19 patients. (3,4)

We may examine the neurological complications of Covid19 in 3 main sections. The stroke reasons are potential immune-mediated complications after infection, pulmonary and systemic diseases, and encephalitis in the central nervous system that is directly affected by a coronavirus. (5,6) The effect of Covid19 on the central nervous system as viral encephalitis was first described in a study on March 4, 2020. Wu et al. suggested that the Covid19 virus potentially causes central nervous system damage as a result of the genome sequencing method in cerebrospinal fluid. (2)

Xu et al. determined the presence of enveloped virus particles with a diameter of 80-90 nm. in the electron microscopy of the brain tissue taken from the patient showing symptoms of SARS-CoV and in a cDNA fragment estimated to be associated with the virus and stated that SARS-CoV has the ability to infect the central nervous system. (7) Lau et al. determined

positive SARS-CoV findings in cerebrospinal fluid in a 32-year-old woman infected with SARS. (8) These findings are supported by experiments on mice, and various Covid viruses have been indicated to have the ability to infect the central nervous system. (9–11) However, the association between immune dysfunction and exposure to the disease has increased the release of catecholamine secondary to anxiety and stress. Wang et al. have also reported that this condition causes severe cases of symptoms seen when the Covid19 virus infects the central nervous system. (12)

Another study of the opposite opinion states that SARS-CoV-2 indicates similar characteristic features as SARS-CoV, and statistical data and neurological symptoms related to both viruses. (3)

Due to these studies, we suggest that SARS-CoV-2 has a connection with the central nervous system, but its extrapulmonary pathogenesis is not clearly known. This situation creates a debate about the effect of SARS-CoV-2 on the CNS.

2. Stroke

According to the definition by the World Health Organization, stroke; is a clinical syndrome characterized by rapid localization of signs and symptoms of focal loss of cerebral function without a significant cause more than other vascular causes. Symptoms duration may be longer than twenty-four hours or may result in death. The syndromes indicate extensive variability that includes healing within one or two days, partial healing, severe disability, and mortality possibility. Stroke is the second cause of mortality in the world. At the same time, it ranks first in disability and occupies an essential place in hospital admissions and health expenditures in industrialized societies. (13) Thrombosis or embolism causes cerebral infarction and cerebrovascular events, while intracranial hemorrhage is another common cause of morbidity and mortality. (14) Stroke mortality is especially high in eastern Europe and Asia, while a stroke is observed on average every 40 seconds in America. There are various factors that increase the risk of ischemic stroke. Aging, male gender, ethnic and family history, stroke history, low physical activity, low social status, smoking, alcohol and drug use habits, arterial hypertension, dyslipidemia, heart diseases, carotid artery disease, diabetes, hyperhomocysteinemia, atrial fibrillation and left ventricular hypertrophy are the most common reasons of stroke. (15) Yu et al. listed the complications of stroke as the most common ones. The

complications are hypertension (49.6%), diabetes (26.9%), hyperlipidemia (23.5%), coronary artery disease (10.1%), atrial fibrillation (10.9%), prior stroke (% 5), reported previous valvular diseases (1.7%), and previous cancers (3.4%). (16)

In this section, we aimed to determine the alteration in stroke incidence during the Covid19 pandemic period and the correlations of SARS-CoV-2 with ischemic and hemorrhagic stroke, and also we investigated the relationship of the mechanisms in the light of the studies and clinical anatomy.

2.1. The Anatomical approach to stroke

The knowledge of the vascular territories and neuroanatomical pathways is effective in interpretation of brain imaging and determining the functional deficiency. In addition, clinical anatomy knowledge is effective in understanding the mechanism and prognosis of stroke. The anterior circulation consists of a. cerebri anterior and a.cerebri posterior, which are the branches of a. carotis interna.

The complete proximal occlusion of a. cerebri media usually occurs from the cardiac embolism, and this situation indicates contralateral hemiparesis, loss of hemisensory, the deficiency of visual field, hemineglect, and afasia. The damage of the superior part of a. cerebri media indicates contralateral hemiplegia, hemisensorial loss, and Broca's afasia on the dominant side of the body. The addition of a. cerebri media's inferior branches damages usually indicates hemianopsia and Wernicke's aphasia if the damage is on the left side of the body.

The damage of distal tip generates the infarcts of the primary somatomotor area, and this situation indicates a 'cortical hand sign'. The left and right a. vertebralis generate the basillary artery, and the basillary artery generates the posterior cerebral artery. The posterior cerebral artery supplies the occipital cortex, thus this artery infarction cause hemianopsia. The diagnosis of stroke, which is generated after a vertebrobasillar territory problem, has a challenge due to accompanies of various clinical symptoms.

For instance, while the brainstem ischemia indicates opposite signs, the basillar ischemia may conclude hemiplegia, loss of sense, vision deficiency, and 'locked-in syndrome bilaterally.

Small subcortical infarcts generate by the occlusion of small perforating arteries and usually indicate asymptomatically signs. Occlusions developing within eloquent brain regions cause lacunar syndromes. (17)

3. The relationship between stroke and SARS-CoV-2

3.1. The relationship between stroke and circulation in patients with SARS-CoV-2

Hypertension or other stroke factors are frequently involved in cerebrovascular patients associated with SARS-CoV-2. In addition, there are proinflammatory changes that occur during SARS-CoV-2 and are a risk factor for stroke. These inflammatory changes are reported to be associated with leukocyte activation and a subsequent increase in cerebrovascular thrombosis. An increase in inflammatory immune cells in the vascular wall leads to the disintegration of the blood-brain barrier, and the fact that this process is also caused by thrombosis leads to an increased risk of stroke. (18)

Greenberg et al. have determined occlusion and ischemic on large vessels with neuroimaging findings on 954 Covid-19 and ischemic stroke patients with a rate of %59.9 (Greenberg et al., 2021). Baudin et al. reported a high correlation between microangiopathic-associated stroke and the occlusion of the distal large vessels. (19)

Kazemi et al. suggested that SARS-CoV-2 infection causes stroke in some cases and stated vasculopathy of SARS-CoV-2 related endothelial damage in small vessels, viral infection-induced platelet dysfunction, or thrombocytopenia, activation of proinflammatory hence these alterations leading to consumption coagulopathy may be the reason of this situation. The possible mechanism in ischemic stroke patients is that the presence of ACE2 receptors in neurons plays a key host cellular receptor role in SARS-CoV-2 disease, in addition to dysregulation of ACE2-related physiologic functions, cerebral endothelial and arterial smooth muscle dysfunction, coagulopathy, and thrombo-inflammation of Covid 19 may be associated with SARS-CoV-2. (20) In addition, increasing evidence in the literature indicates that SARS-CoV-2 infection causes acute cerebrovascular disease by causing cytokine storm syndromes. (21,22)

Kazemi et al. reported a correlation between SARS-CoV-2 infection and stroke besides they stated that the supported mechanism of hemorrhagic stroke might be the association of the damage to small vessels of the endothelium and vasculopathy. Kazemi also stated that the stimulation of thrombocytopenia or platelet dysfunction caused viral infection and suggested that proinflammatory effects cause activation of coagulopathy. The most obvious strategy for this is extracorporeal membrane oxygenation in some patients with elevated d-dimer or thrombus due to SARS-CoV-2 infection. (20)

3.2. The relationship of biomarkers with stroke in SARS-CoV-2

In the biomarker analysis of Covid19 patients, Channappanavar & Perlman stated that this virus may be associated with stroke. Inflammatory monocytes-macrophages (IMMs) and neutrophils are the main sources of cytokines and chemokines, and they include pathogens of SARS-CoV-2. (23) Napoli et al., reported that the increase in the concentration of serum C-reactive protein (CRP) is a marker of inflammation, and the results of ICH may be an independent estimate in the diagnosis. (24) However, it is thought that interethnic genome differences may affect CRP status and that there are estimated values of different stroke phenotypes. Another marker is proteins from the lipocalin family called serum neutrophil gelatinase-associated lipocalin (NGAL) that may be transported by small hydrophobic molecules. These proteins play an important role in the immune response, providing an independent prediction of outcomes in the follow-up of hemorrhagic stroke. (25) These mentioned biomarkers suggest that the cytopathic effects seen in SARS-CoV-2 may be related to hemorrhagic stroke outcomes. In particular, reduced peripheral lymphocyte appears as data in many Covid19 cases. (12) Chan et al. performed a pathological examination on lung, liver, heart biopsies, and blood cell analyses of patients who died due to Covid19 and reported that lymphopenia may be widely seen in these patients and may be associated with proinflammatory phenotypic switching in T cell subsets and that this situation may be associated with mortality or severe progression of Covid19. (26,27) In addition, Wanh et al. have reported that SARS-CoV and SARS-CoV-2 may also play a role in lymphocytes in the respiratory mucosa, and decreased peripheral blood lymphocytes accompanying cytokine storm, and this effect may cause dysfunction in cellular immune function. When these disorders are accompanied by diabetes, hypertension, and cerebrovascular diseases, the Covid19 prognosis gets worse. (12)

Another factor that causes delays in patients with Covid19 who have had strokes. The delay is about contacting of people to the emergency service because of the anxiety of the risk of transmission. (28) In particular, the application of reperfusion therapy in acute ischemic stroke provides effective healing results in a timely and effective transfer to a hospital. (29,30) In addition, the examination of these biomarkers will be effective in reducing the risk of stroke. Thus, Covid19 patients should not neglect the necessary treatments with various concerns.

3.3. The relationship of cytokine storm with stroke in SARS-CoV-2

The investigations have been reported that coagulopathy, ACE2 expression on the central nervous system, the interaction of SARS-CoV-2 with endothelial dysfunction, microthrombosis, and cytokine storm are the causes of cerebrovascular diseases associated with Covid19. (31–33) One possible mechanism of SARS-CoV-2-associated stroke is the proinflammatory cytokine storm phenomenon. In this mechanism, different viruses trigger hypercytokinemia with various mechanisms. (34) Many inflammatory cytokines are released as a result of brain injuries associated with SARS-CoV-2, which triggers thrombosis and stroke. (35) The similarity of SARS-CoV-2 to the influenza virus may aggravate the ischemic brain injury prognosis by increasing the risk of triggering a cytokine storm. (36) In this context, the occurrence of cytokine storms after SARS-CoV-2 reinforces the view that SARS-CoV-2 causes cerebral diseases. (20)

3.4. The relationship between stress with stroke in SARS-CoV-2

The Covid19 pandemic has undoubtedly increased anxiety, fear, and stress exposure in many people worldwide. Since social stress, anxiety, and depression are potential risk factors for hemorrhagic stroke, keeping these factors in the appropriate ratio is the primary preventive method in cerebrovascular diseases. (37,38) The locus coeruleus, a part of the brain stem, contains adrenergic neurons that play a critical role in anxiety genes, and locus coeruleus neurons have a critical mission in releasing catecholamines during the stress response. (39) Studies report that severe vasospasm and microcirculation disorder occurs as a result of over-stimulation of adrenergic stimulus with catecholamines. This overstimulation may increase the risk of hemorrhagic stroke. (40)

On the other hand, Nalleballe et al. stated that there is no obvious result in the increase and decrease of the Covid19 frequency. The consequences have been determined some relationships between SARS-CoV-2 infection and stroke suggested that this relationship arises from a social and psychological origin and has no pathophysiology. (41)

4. Discussion

ACE2 is an important host cellular receptor for the virus in SARS-CoV-2-associated ischemic stroke. ACE2 is associated with psychological functions, thrombo-inflammation, coagulopathy, and coagulation abnormalities associated with Sars-CoV-2. (20) The pathogenesis of ischemic stroke in patients with

Covid19 is an endothelial injury caused by regional and systemic inflammation and thrombosis due to hypercoagulability. (42) The incidence of stroke is reported to be between 0.5 and 4.5% in multicenter and meta-analysis studies conducted in patients with Covid19. (42–44)

Oxley et al. have been determined that the rate of stroke is approximately 5% among 55-year-old covid19 patients hospitalized in Wuhan, China. (29) This has led to speculation that the infection has an effect on the development of stroke. (3,45) Mao et al. identified acute stroke in 5% of 214 patients admitted to the hospital with the diagnosis of Covid19. (3) Another study reported that 5.9% of 221 Covid19 patients developed acute cerebrovascular events, 5% developed acute ischemic stroke, and 0.5% developed cerebrovascular thrombus and intracerebral hemorrhage. (16)

Li et al. investigated 221 patients after the covid19 infection between the ages of 57-91 and reported that cerebrovascular disease developed in 13 patients (5.9%), and 11 of these patients (%84.6) ischemic stroke, 1% (7.7%) cerebral venous sinus thrombosis, one patient (7.7%) diagnosed with cerebral hemorrhage besides Li et al. have indicated hypercoability and increased inflammatory response in all patients. (45) In a study conducted on 214 patients with severe course of Covid19, it was reported that acute cerebrovascular disease developed in 5 patients (5.7%), ischemic stroke in 4 patients (4.6%), and cerebral hemorrhage in one patient (1.1%). (3) In a recent large-scale cohort study, Katsanos et al. reported that 1.3% of 67,845 Covid19 patients were hospitalized due to a cerebrovascular event, of which 1.1% had an ischemic stroke, and 0.2% had a hemorrhagic stroke. (46)

Similarly, we determined in the literature that SARS-CoV-2 infection indicates an increased risk of the development of ischemic stroke compared to other neurological problems. In a retrospective case series study in a Wuhan hospital, 78 of 214 hospitalized patients had nervous system dysfunctions such as central nervous system, peripheral nervous system, and musculoskeletal system. Besides this, 6 of 78 patients had an ischemic stroke. (3) Helms et al. reported an unidentified encephalopathic prognosis in 13 of 58 Covid19 patients. (47) In another study, stroke symptoms were determined in 4 patients as a result of neurological imaging of 17 Covid19 patients. (48) In addition, Ashrafi et al. reported the complication of stroke in moderate-intensity Covid19 young patients. Regarding this, Ashrafi et al. reported that 11 Covid19 patients under the age of 55 with minimal respiration developed ischemic stroke in large vessels. (29,49,50) In a 33-year-old patient with Covid19 infection, thrombosis

was observed in the left vertebral artery after occipital pain, nausea, vomiting, and balance problem symptoms. (50) In another study, a 52-year-old male patient with a history of hypertension was discharged after antibiotic treatment. Days later, the patient experienced stroke associated with occlusion from the left arteria carotis interna. (51)

There are also studies in the literature in which stroke rates in patients with Covid19 are high. Yu et al. investigated in 167 patients who experienced cerebrovascular accidents after Covid19 in their review and indicated that acute ischemic stroke in 119 (71.2%), cerebral hemorrhage in 33 (19.8%), a subarachnoid hemorrhage in 3 (1.8%), and cerebrovascular thrombus in 12. (16) Dhamoon et al. In the analysis of 277 stroke patients, 105 (38%) suffered from Covid19, and Covid19-positive patients were more prone to cryptogenic stroke injuries (51.8% vs. 22.3%, $P < 0.0001$); it has been reported that the incidence of stroke is higher as a result of injuries to the temporal, parietal, occipital and cerebellar regions.

The results of Covid19 positive patients were found to be worse and to have longer hospital stays, higher intensive care needs, and neurological deterioration. In addition, Dhamoon et al. have been reported that hospital deaths are 33% in Covid19-positive patients. (52)

Morassi et al. reported that the prognosis and outcomes of cases with both Covid19 and stroke patients are often worse than other types of stroke, and stroke is frequently seen in people with severe pneumonia and multiple organ failure and reported that outcomes are poor. (53)

The cortical affected areas of patients who had a stroke after Covid19 were evaluated from an anatomical perspective. Yu et al. examined the localization of stroke developing after Covid19 and reported that the injury was seen in the frontal lobe 33.3%, parietal and temporal lobe 15.2%, brain cells, and ganglia 12.1%, cerebral hemisphere 6.1%. (16) Dhamoon et al. stated that the incidence of stroke due to injury was higher in the temporal, parietal, occipital, and cerebellar regions. Besides, the outcomes of Covid19 positive patients were worse, and longer hospital stays, greater need for intensive care, and greater neurological deterioration reported that hospital deaths are 33% in Covid19 positive patients. (52)

5. Conclusion

Based on the above data, some cautions should be taken to reduce the rate of stroke cases after Covid19, and more attention should be paid to the elderly

individuals in the risky age group. Regarding this, Yaghi et al. have reported that the risk of cerebrovascular diseases is higher in elderly people who are affected by Covid19 and that risk factors should be considered in elderly people. (54)

The greatly increased risk of hemorrhagic stroke in hypertension patients affected by Covid19 may also affect the increased release of anxiety and stress adrenergic. This situation causes vasospasm and microcirculation disorder. Inflammation biomarkers in Covid19 patients should be evaluated together with central nervous system symptoms in light of these data. These clinical examinations may reduce the risk of encountering irreversible results in diagnosis and treatment. (12) The neurological symptoms that occur increasingly in many patients associated with the Covid19 infection. (3,47) However, clinical data are still insufficient. There is still an insufficient consensus that Covid19 may be a triggering risk for the onset of hemorrhagic stroke. (12)

In the light of the mentioned studies, we suggest that there is a relationship between Covid19 and stroke, however there is no clear ratio. Patients's awareness of this relationship and awareness of symptoms may reduce this risk. The patients who suspect to SARS-CoV-2, should not ignore these related cautions. The patients may decrease the risk of stroke by these cautions even if they don't have symptoms of stroke, nearbye it is essential to have a cardipulmonary treatment while in Covid19 stage.

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CHAPTER VII

EFFECTS OF THE COVID-19 PANDEMIC ON ORTHOPEDICS AND TRAUMATOLOGY

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1. General Information About Covid - 19

Covid-19 disease first appeared in Wuhan, Republic of China in December 2019 and spread all over the world in a short time. (1) The pandemic initially emerged with a new Cov, then a subspecies detected in animals, named SARS-Cov-2 because it caused severe acute respiratory syndrome (SARS, Severe Acute Respiratory Syndrome). While most subtypes progress with mild complaints such as the common cold in humans, SARS-Cov-2 has led to a pandemic picture that puts the health system in a difficult situation in the world. (2,3)

Knowing the infection chain and transmission characteristics of the disease is important in terms of carrying out health services.

Chain of infection is source, transmission path, and host. The source is presumed to be wild animals sold. With a mutation that occurred later, the source turned into a human.

The route of transmission is droplets that occur through coughing, sneezing or speaking. After contact with these droplets, the virus clings to the mucous membranes and completes the disease.

Covid-19 is resistant to alcohol, disinfectant and external environment. It can survive on surfaces for 24-72 hours.

80% of people have the disease without the need for any medical intervention. Diseases with chronic events such as diabetes and heart diseases tend to be more serious. Initial symptoms are fever, cough, and shortness of

breath. Patients with a moderate clinical condition can be managed with supportive treatments. In severe cases, pneumonia, shock, multi-organ failure and acute respiratory distress syndrome (ARDS) may develop and advanced supportive treatments are required.

2. Covid-19 Pandemic in Turkey

The first Covid-19 case in Turkey was announced on March 11 by the Ministry of Health. As of this date, education was suspended in schools, collective worship was prohibited, and a curfew was imposed on citizens over the age of 65 and with chronic diseases. There has been a decrease in orthopedic cases with the decrease in activities with social and collective lives. As of March 17, elective surgical procedures have been postponed. The Ministry of Health has started the New Normalization Period as of June 1, 2020.

3. New Pre-Normalization Approaches

As of 20 March 2020, hospitals in Turkey that have at least two specialists in infectious diseases and clinical microbiology, internal medicine and chest diseases and have tertiary adult intensive care units have been accepted as 'pandemic hospitals' by the Ministry of Health. With the postponement of elective cases, all physicians, including orthopedic surgeons, joined the pandemic patient management. The fact that anesthesia and reanimation specialists do not take part in elective surgical procedures and undertake intensive care management has made great contributions to the management of the pandemic.

4. New Normalization Period Approaches

As of June 1, 2020, the new normalization process has started. Health service management was provided during the pandemic by the Coronavirus Science Board and Operations Center established under the Ministry of Health. (4)

Orthopedics and Traumatology branch association also presented the necessary measures for the new normalization to orthopedic physicians. (5)

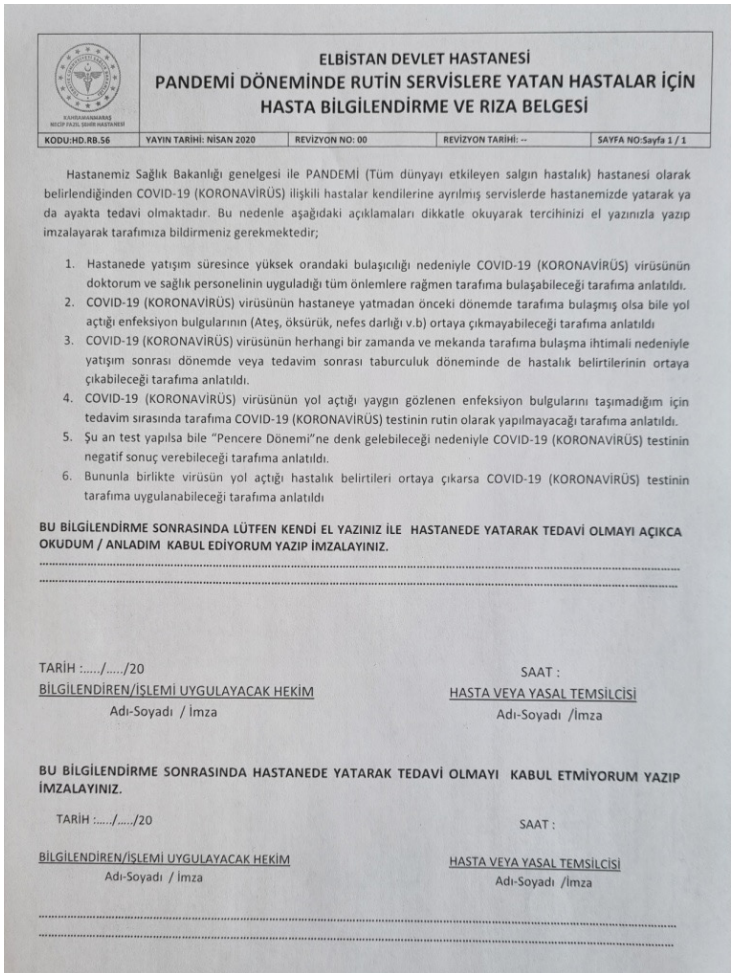
5. Management of Patients in Orthopedics and Traumatology during the Covid-19 Pandemic Process

Orthopedic surgeons took part in the treatment of pandemic patients as well as in their own departments during the pandemic. During the pandemic, they

participated in up-to-date training and kept their knowledge up to date. Up-to-date information on the management of orthopedic cases admitted to the emergency department or polyclinic was constantly followed.

Every patient who applies to the orthopedic unit is questioned in terms of Covid-19. It is important that the patient and his/her companion are masked and that the accompanying person is a person. Fever, sore throat, shortness of breath and cough should be questioned.

From the very beginning, the patient should be prevented from spending extra time in the unit. Along with the patient's consent for the surgical procedure, it is also important to obtain consent for Covid-19. (Figure 1)



ELBİSTAN DEVLET HASTANESİ
PANDEMİ DÖNEMİNDE RUTİN SERVİSLERE YATAN HASTALAR İÇİN HASTA BİLGİLENDİRME VE RIZA BELGESİ

KODU:HD.RB.56	YAYIN TARİHİ: NİSAN 2020	REVİZYON NO: 00	REVİZYON TARİHİ: --	SAYFA NO:Sayfa 1 / 1

Hastanemiz Sağlık Bakanlığı genelgesi ile PANDEMİ (Tüm dünyayı etkileyen salgın hastalık) hastanesi olarak belirlendiğinden COVID-19 (KORONAVİRÜS) ilişkili hastalar kendilerine ayrılmış servislerde hastanemizde yatarak ya da ayakta tedavi olmaktadır. Bu nedenle aşağıdaki açıklamaları dikkatle okuyarak tercihinizi el yazınızla yazıp imzalayarak tarafımıza bildirmeniz gerekmektedir;

1. Hastanede yatışım süresince yüksek orandaki bulaşıcılığı nedeniyle COVID-19 (KORONAVİRÜS) virüsünün doktorum ve sağlık personelinin uyguladığı tüm önlemlere rağmen tarafıma bulaşabileceği tarafıma anlatıldı.
2. COVID-19 (KORONAVİRÜS) virüsünün hastaneye yatmadan önceki dönemde tarafıma bulaşmış olsa bile yol açtığı enfeksiyon bulgularının (Ateş, öksürük, nefes darlığı v.b) ortaya çıkmayabileceği tarafıma anlatıldı
3. COVID-19 (KORONAVİRÜS) virüsünün herhangi bir zamanda ve mekanda tarafıma bulaşma ihtimali nedeniyle yatışım sonrası dönemde veya tedavim sonrası taburculuk döneminde de hastalık belirtilerinin ortaya çıkabileceği tarafıma anlatıldı.
4. COVID-19 (KORONAVİRÜS) virüsünün yol açtığı yaygın gözlenen enfeksiyon bulgularını taşımadığım için tedavim sırasında tarafıma COVID-19 (KORONAVİRÜS) testinin rutin olarak yapılmayacağı tarafıma anlatıldı.
5. Şu an test yapılsa bile "Pencere Dönemi"ne denk gelebileceği nedeniyle COVID-19 (KORONAVİRÜS) testinin negatif sonuç verebileceği tarafıma anlatıldı.
6. Bununla birlikte virüsün yol açtığı hastalık belirtileri ortaya çıkarsa COVID-19 (KORONAVİRÜS) testinin tarafıma uygulanabileceği tarafıma anlatıldı

BU BİLGİLENDİRME SONRASINDA LÜTFEN KENDİ EL YAZINIZ İLE HASTANEDE YATARAK TEDAVİ OLMAYI AÇIKCA OKUDUM / ANLADIM KABUL EDİYORUM YAZIP İMZALAYINIZ.

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TARİH :...../...../20
BİLGİLENDİREN/İŞLEMİ UYGULAYACAK HEKİM
Adı-Soyadı / İmza

SAAT :
HASTA VEYA YASAL TEMSİLCİSİ
Adı-Soyadı /İmza

BU BİLGİLENDİRME SONRASINDA HASTANEDE YATARAK TEDAVİ OLMAYI KABUL ETMİYORUM YAZIP İMZALAYINIZ.

TARİH :...../...../20

SAAT :

BİLGİLENDİREN/İŞLEMİ UYGULAYACAK HEKİM
Adı-Soyadı / İmza

HASTA VEYA YASAL TEMSİLCİSİ
Adı-Soyadı /İmza

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Figure 1: Consent form obtained before admission.
Orthopedic cases in the Covid - 19 pandemic:

5.1. Emergent cases

Compartment Syndrome, major traumas associated with hemodynamic instability, replantations, septic arthritis, dislocations, open fractures. For these cases, surgical procedures should be applied quickly without waiting for the PCR test result.

5.2. Urgent cases

Closed fractures, circulatory-protected hand and finger injuries, cancer cases and prosthetic infections. These cases should also be taken early, but the PCR test result should be awaited.

5.3. Elective cases

Arthroscopy, arthroplasty and scoliosis surgeries. In order for these cases to be made, the end of the pandemic period should be waited. (6)

During the pandemic period, it is recommended that the operating room rooms be with negative pressure. All materials should be prepared in advance, entrances and exits should be minimized and it should be ensured that cleaning is done in a sufficient time. Ensure that the protective equipment is ready for the entire team and is in accordance with the procedures. (6) (Figure 2)

The patient should be taken directly to the operating room and spinal anesthesia should be preferred. The number of people in the surgical team should be kept as low as possible. The use of cautery should be as little as possible and cautery fumes should be aspirated. Reamers and cutters that will cause droplet formation should be used carefully and a protective equipment should be wear during this period. (7) (Figure3) After the surgery is completed, protective equipment should be removed in the patient's room in accordance with the procedures. (8)

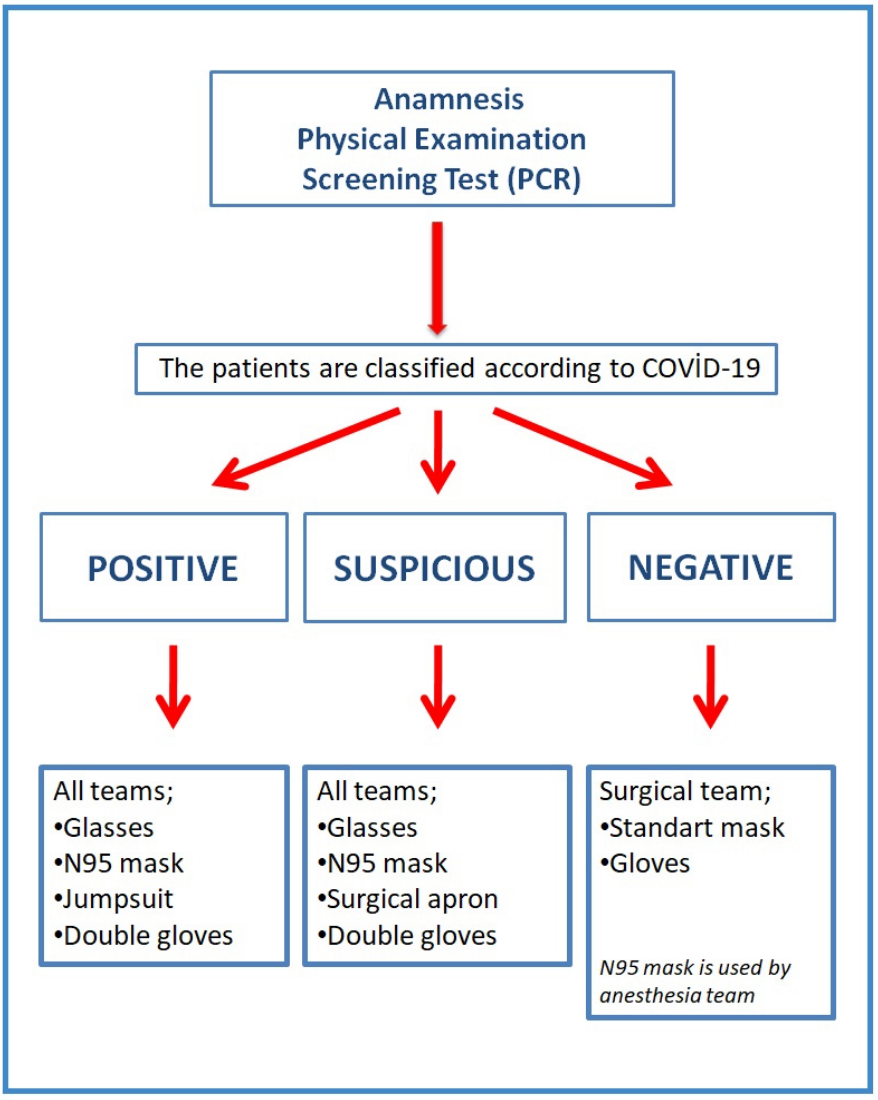

Figure 2: Equipment to be used in the operating room. (6)

Fever, respiratory distress and low blood oxygen values should be followed up after the operation. Whether these symptoms occur due to surgery or covid 19 should be investigated and their treatment should be planned.

Figure 3: Precautions taken in the operating room when operating on a Covid-19 positive patient with a femoral shaft fracture.

6. Conclusion and Discussion

Orthopedic surgeons are physicians who provide health services in the emergency room and polyclinic. They take part in the health team that performs the first interventions in all trauma cases. During the Covid-19 pandemic period, while working for the treatment of the pandemic disease, they continued surgical procedures and most of them operated on trauma patients with Covid-19. In this process, taking all protective measures is important for orthopedic surgeons to prevent contamination.

The pandemic process has also led to significant effects in the field of orthopedics. The decrease in social life and the bans applied caused a decrease in the number of trauma cases and operations. In a study, it was stated that the operation rates decreased by 76% during the pandemic. (6) Conservative treatment methods have come to the fore again, especially in order to reduce hospital stays and therefore prevent the spread of the virus. (9)

For orthopedic surgeons, it should be applied optimally and quickly, especially for fractured patients, and all precautions should be followed to prevent infection. (10)

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CHAPTER VIII

DIABETES AND COVID-19

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1. Introduction

Coronavirus (COVID-19) is a human-to-human disease characterized by severe acute respiratory syndrome (SARS). This disease was caused by coronavirus 2 (SARS-CoV-2) (1). SARS-CoV-2 is a β-coronavirus with single-stranded RNA. (2). The disease was first described in December 2019 in Wuhan, China. Covit 19 spread very quickly and caused a pandemic in the world. The disease is transmitted through the respiratory tract. The transmission of airborne contaminated droplets from person to person is the main source of transmission. Virus particles contained in the secretions of an infected person are transmitted through direct contact with the mucous membranes. (3).

Typical symptoms of the disease are dry cough, shortness of breath, fever, fatigue, muscle pain, normal or decreased leukocyte counts, and radiographic evidence of pneumonia. Radiologic symptoms such as thrombocytopenia, lymphopenia, and ground glass opacities have been described in some patients. (4).

The genome sequence of SARS-CoV-2 was determined to be the same as that of a bat. According to the virus genome results, the bat is thought to be the natural host of the virus. It is known that SARS-CoV-2 can be transmitted from bats to humans through unknown intermediate hosts. (5).

The epidemiology of COVID-19 is influenced by advanced age (mean age of death 75 years) and gender (male gender), as well as underlying causes such as cardiovascular disorders, diabetes mellitus, immunodeficiency, chronic respiratory disease, and hypertension. (6-8).

Some known mechanisms in diabetes may leave diabetics vulnerable to COVID-19. Diabetes is associated with decreased T cell function, chemotaxis

in neutrophils, decreased phagocytic activity, and innate low adaptive immunity. (9-11).

The hereditary material of the coronavirus is a single-stranded RNA molecule surrounded by nucleoproteins (12).

The coronavirus genome encodes four structural proteins: spike (S), membrane (M), nucleocapsid (N), and envelope (E) proteins. SARS-CoV-2 attaches to the angiotensin-converting enzyme-2 (ACE-2) receptor in the host cell by means of the spike protein. ACE and ACE-2 receptors are transmembrane proteins. ACE converts Ang-1 to Ang-2. Ang-2 is converted to Ang (1-7) by ACE-2. The S protein enters the cell via ACE-2. (13, 14).

Possible dysfunctions occur when SARS-CoV-2 binds to the ACE-2 receptor. Under the infection condition Ang (1-7) is no longer synthesized, Ang 2 causes both tissue damage (especially heart, pancreas and lung) and proinflammatory signals that trigger hypertension.

Studies have shown that the risk of infection with the virus is reduced in mice with reduced ACE-2 expression. After virus binding, ACE-2 expression on the cell surface decreases. This decrease decreases the conversion of Ang2 to Ang (1-7) in the cell and increases the amount of Ang2 (15). This situation has further increased the clinical and scientific importance of ACE-2.

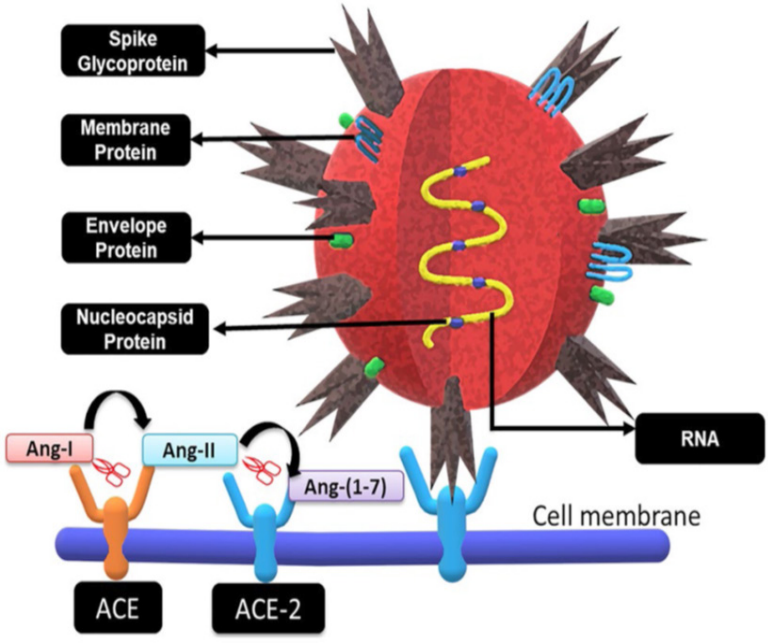


Figure 1. Binding of SARS-CoV-2 to the ACE-2 receptor (16)

ACE and ACE-2 receptors are transmembrane proteins. ACE converts Ang-I to Ang-II. Ang-II is cleaved to Ang-(1-7) by ACE-2. SARS-COV-2 Covid-19 viral RNA encodes 4 structural proteins as transmembrane Spike glycoprotein (S), Nucleocapsid protein (N), envelope (E), membrane (M).

Diabetes mellitus (DM) is a metabolic syndrome characterized by hyperglycemia resulting from a defect in carbohydrate, fat, and protein metabolism, or insulin secretion or secretion, or both. (17).

DM is one of the most common metabolic and chronic diseases with a prevalence of 9.3% in the world and is often associated with other comorbidities in the form of metabolic syndrome. (18). In studies, it has been stated that diabetics show severe lung pathologies due to disorders in the immune system. Thus, they are more susceptible to Middle East Respiratory Syndrome (MERS) and SARS infection. (19).

Studies have been conducted on the mechanisms of the relationship between COVID-19 and DM. DM complications were found to be strongly associated with mortality and morbidity in coronavirus patients. (20). Studies have shown that the severity of COVID-19 disease increases in individuals with diabetes. COVID-19 may predispose patients to hyperglycemia. Hyperglycemia can modulate inflammatory and immune responses along with diabetes complications. Thus, the severe course of the disease and consequences such as death occur. Inflammation, potential relationships between COVID-19 and DM include effects on immune status and activation of the renin-angiotensin aldosterone system. (21).

2. Possible potential mechanisms in diabetes mellitus and COVID-19

1. Angiotensin-converting enzyme-2 (ACE-2) mediated mechanisms
2. Impaired T cell response
3. inflammatory environment (cytokine storm)
4. Furin level increase
5. Comorbidities

The degree of hyperglycemia in diabetes mellitus, indicate some pathophysiological mechanisms that lead to increased mortality known complications of diabetes mellitus (chronic kidney disease, heart failure and CVD) and presence of COVID-19

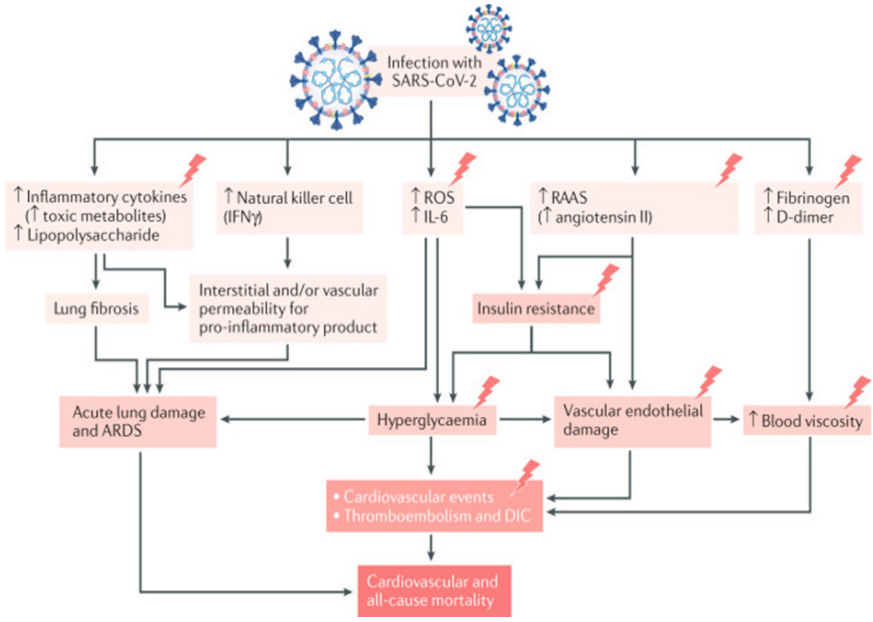


Figure 2: Potential mechanisms in T2DM and COVID-19 patients (21)

SARS-CoV-2 may cause an increase in toxic metabolites and inflammatory cytokines. (22). Increased natural killer cell activity (IFNy) may increase proinflammatory products vascular permeability (23-25). SARS-CoV-2 causes increased production of reactive oxygen species (ROS) (24, 26). Cytokines and ROS cause acute lung injury, lung fibrosis, and acute respiratory distress syndrome (ARDS) (27). ROS and viral activation of the renin-angiotensin-aldosterone system (RAAS) (via increased expression of angiotensin II), hyperglycemia, and vascular endothelial damage lead to disseminated intravascular coagulation (DIC), thromboembolism, and cardiovascular events (28-30). Infection causes an increase in fibrinogen and D-dimer. (23, 24, 31).

Red arrows indicate mechanisms highlighted in patients with type 2 diabetes (T2DM). Activation of ROS and RAAS causes vascular endothelial damage, hyperglycemia, insulin resistance, which contributes to cardiovascular events, thromboembolism and DIC. An increase in fibrinogen and D-dimer occurs, and cardiovascular events, thromboembolism, and DIC occur, associated with increased blood viscosity and damage to the vascular endothelium. Patients with diabetes had higher angiotensin-converting enzyme-2 (ACE-2) levels than the general population (28). It has been shown that SARS-CoV-2 can use the receptor, ACE-2, to infect humans (7). ACE-2 is an important regulator of the

renin-angiotensin-aldosterone system (RAAS). SARS-CoV-2 causes disruption of ACE/ACE2 balance and activation of RAAS. It leads to the progression of the disease in people with cardiovascular disease, hypertension, diabetes mellitus. (28).

ACE-2 expression is decreased in people with diabetes. ACE-2 is found in the kidneys, pancreas, vascular system, lungs, and plays a role in anti-inflammation. When people with diabetes are infected with COVID-19 while the impaired physiological state is worse, it increases the risk of serious lung injury, such as acute respiratory distress syndrome (ARDS). (27). COVID-19 binds to the S protein and causes downregulation of ACE-2. Endothelial and epithelial apoptosis, which occurs after viral replication in organs as a result of regulation, releases proinflammatory cytokines and creates a systemic response. Increased vascular permeability as a result of down-regulation of pulmonary ACE-2 function increases pulmonary edema and accelerates ARDS. SARCoV-2 binds to ACE-2 and enters the pancreatic islets and causes acute beta-cell dysfunction. Damage to the pancreas impairs insulin secretion. As a result, hyperglycemia is observed even in patients without diabetes. (32-35).

The causes of ketoacidosis are thought to be the entry of SARS-CoV-2 into pancreatic islet cells, inducing beta cell damage, down-regulation of ACE-2, increased anijotensin-II, and decreased insulin secretion. (35, 36).

Hypo- or hyperglycemia is a typical complication of COVID-19 in people with impaired glucose regulation or diabetes. One study showed that SARS-CoV-2 infection in diabetics using insulin creates a need for high-dose insulin. This points to its relationship with the levels of inflammatory cytokines (37, 38).

The susceptibility to infections and complications increases in diabetes. As a result of impaired epithelial-endothelial-barrier functions in diabetes, proinflammatory coagulation occurs and COVID-19 progresses more severely. Bacterial and viral respiratory tract infections in diabetics are caused by weakened immunity, decreased T cell response and neutrophil dysfunction. Interferons, which protect the body against viruses and bacteria, are very important. The early interferon response is suppressed in infected individuals. A cytokine storm occurs that causes organ damage. (39, 40).

The imbalance of TH1/TH2 cells in the immune response is associated with the diabetic state. The SARS-CoV2 infection causes T cell imbalance. This imbalance exacerbates diabetic ketoacidosis. As a result of ketoacidosis, IL-6, D-dimer, and TNF alpha cytokine levels increase (41).

These inflammatory factors are thought to be the cause of the COVID-19 susceptibility of patients with diabetes. (42, 43).

Cytokine storm is believed to promote the inflammatory process in T2DM patients. Angiotensin 2 receptor inhibitors (ARB) and ACE inhibitors (ACEI) are used in the treatment of heart and kidney diseases associated with diabetes and hypertension. ARB and ACEI drugs are thought to increase the risk of COVID-19, as the ACE-2 receptor allows SARS-CoV-2 to enter cells. (44).

An increase in Furin levels has been observed in COVID-19 and Diabetes. Furin, known as a type 1 membrane-bound protease, facilitates the entry of SARS-CoV-2 into the cell. Increased levels of furin have been reported in diabetics. (45).

In addition, the imbalance in the immune system leads to beta dysfunction in SARS-CoV-2 infection, causing new-onset diabetes.

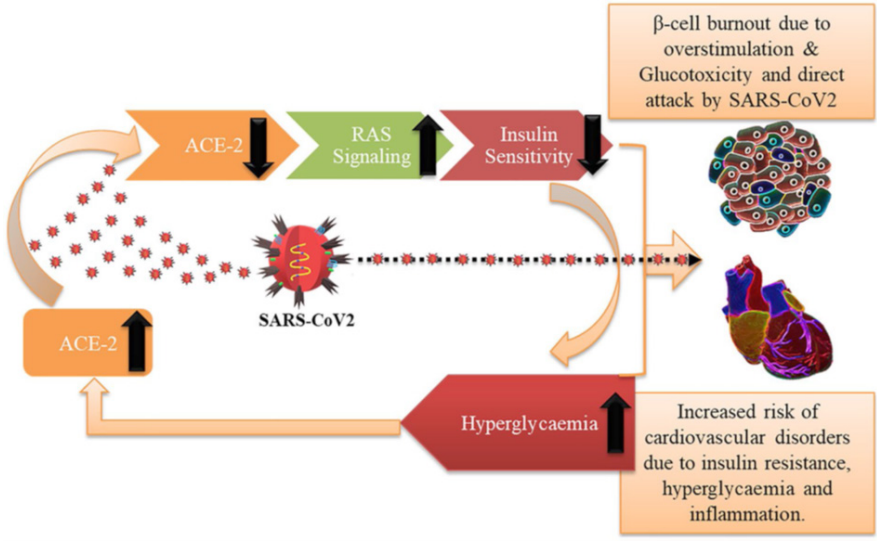
3. COVID-19 and New-Onset Diabetes

It is thought that there is a bidirectional relationship between diabetes and SARS-CoV2. While the course of the disease worsens in patients with diabetes, new-onset diabetes can be seen after SARS-CoV2 infection. (46).

Diabetes is associated with an increased risk of severe COVID-19. The use of high insulin doses in cases of diabetic ketoacidosis, new-onset diabetes and hyperosmolarity in COVID-19 patients has shown that existing diabetes creates serious metabolic complications. (47, 48).

It was stated that insulin resistance was associated with a metabolic disorder. Severe patients infected with SARS-CoV-2 have insulin resistance. Some studies have reported that there may be a relationship between the renin-angiotensin system (RAAS) and the pathogenesis of insulin resistance. Ang-2 has effects on adipogenesis, insulin signaling pathways, and oxidative stress. Thus, there are studies suggesting that it may affect glucose metabolism (49). SARS-CoV2 activates the RAAS pathway to induce inflammation and oxidative stress (14). RAAS responds to proinflammatory stimulation. It also helps to develop insulin resistance. (50). Insulin resistance may increase circulating free fatty acids to reduce HDL and increase LDL (51). Activation of the RAAS pathway causes vasoconstriction and elevation in blood pressure. Hyperglycemia is associated with increased disease severity and death in COVID-19 (52). In the case of hyperglycemia, β-cell dysfunction, diabetic cardiomyopathy, and long-term high blood sugar are seen. (53, 54). Studies show that high glucose will cause an increase in ACE-2 expression in insulin-producing cells. As a result, it

has been reported that the risk of hypertension and cardiovascular complications due to hyperglycemia and insulin resistance increases. The figure describes the worsening condition in diabetic patients infected with SarS-CoV2. (16).



Figüre 3. Reasons for increased risk of cardiovascular disease in diabetics with SARS-CoV-2 (16)

In SARS-CoV-2, impairment in ACE-2/RAS signaling progresses to hyperglycemia, insulin sensitivity, and cardiac and β-cell dysfunction. A vicious circle ensues. A cycle in which SARS-CoV2 enters ACE-2 receptors increases hyperglycemia and insulin resistance. The risk of cardiovascular complications increases. increased hyperglycemia may modulate the ACE-2 receptor response, thereby increasing vulnerability to SARSCoV2 attack..

4. Diabetes Management During the COVID-19 Pandemic Process

During the pandemic process, regular follow-up, treatment and self-care of patients in health units became difficult due to obligations such as curfews and social isolation During this period, it is important to monitor blood sugar and glycemic status at home, since regular exercise, regular drug use, diabetes management, and attention to nutrition become insufficient. Except for emergencies, routine controls should be provided with technological communication as much as possible and hospitalizations of patients should be reduced as much as possible. (55, 56)

4.1. Evaluation of People with Diabetes and COVID-19 Infection

People with diabetes are at high risk for COVID-19 infection and diabetes complications. Therefore, it is necessary to be sensitive in the diagnosis, follow-up and treatment of COVID-19. Diabetic people with COVIT must first be diagnosed and confirmed. If the patient shows minimal symptoms, hospitalization is not mandatory. However, due to the increased risk of morbidity and mortality, it is recommended that diabetic patients with COVID-19 be treated and followed up in the hospital (55). Hospitalization is mandatory because diabetic patients need intensive care and mechanical ventilation compared to non-diabetic patients. In diabetic patients with COVID-19, blood sugar levels, HbA1c values, and glycemic status should be checked. Diabetes complications should be investigated.

4.2. Glycemic Controls

It is necessary to prevent complications in order to reduce morbidity and mortality related to diabetes. For this, glycemic control should be provided (57).

If glycemic control is good and infection severity is low, it can be followed at home. As long as people can take adequate food and fluid intake, they can be followed up with the glucose-lowering agents they used before. If glycemic control is not achieved and the severity of the infection has increased, medical treatment is applied. Oral antidiabetic treatments are discontinued and insulin therapy is started for those who have respiratory distress or need mechanical ventilation. (55, 56, 58).

4.3. Blood Sugar Controls

Blood glucose should be monitored for glycemic control. Glucose measurements should be performed more frequently in patients receiving intravenous insulin than in patients receiving subcutaneous insulin. Studies have shown that glucose levels below 180 mg/dl reduce mortality and result in less ARDS, septic shock, acute heart and kidney damage, and DIC. For this reason, if the blood sugar is >180 mg/dl in hospitalized patients, insulin therapy should be started. However, in patients without risk of hypoglycemia, the glycemic target can be reduced to 110 mg/dl. (56, 59, 60).

4.4. Antidiabetic Agents

4.4.1. Dipeptidyl peptidase -4 (DPP4) inhibitors

Dipeptidyl peptidase -4 (DPP4) is a peptide that provides control of chemokines, growth factors, bioactive peptides and T cell activation. They play a role in the regulation of glucose metabolism. Also known as CD26(61). Glucagon-like peptide-1 (GLP1) and glucose-dependent insulinotropic polypeptide (GIP) are the two most important incretin hormones (62). DPP-4 inhibitors inactivate circulating incretin hormones by inhibiting the DPP-4 enzyme. They prolong the duration of action of GLP-1 and improve the response of the alpha and beta cells of the pancreas to glucose. (63, 64). SARS-CoV-2 uses the CD26 pathway to enter T cells. DPP-4 inhibitors (such as vildagliptin, sitagliptin, linagliptin) used as anti-diabetic agents in COVID-19 are thought to be very effective in blocking the CD26 pathway (65, 66). It has also been suggested that the enzyme dipeptidyl-peptidase 4 (DPP4) is responsible for the cytokine storm in COVID-19 patients with diabetes. (67).

4.4.2. Glucagon-like peptide 1 (GLP-1) Receptor Agonists

GLP-1 Receptor Agonists increase glucose-dependent insulin secretion and inhibit glucagon secretion. Thus, they lower blood sugar (68). GLP-1 receptor antagonists reduce cardiovascular complications in diabetes patients. It is known to have an anti-inflammatory effect that may be beneficial for diabetes management in diabetics with COVID-19. (69, 70).

4.4.3. Sodium-glucose cotransporter 2 (SGLT2) inhibitor

SGLT2 inhibitors block the SGLT2 receptor in the renal proximal tubules. They prevent the reabsorption of glucose. They increase urinary glucose excretion and lower blood sugar independently of insulin. In diabetic patients, treatment should be reviewed using an SGLT2 inhibitor. The drug should be discontinued in patients with impaired renal function, as it may cause inhibitory osmotic diuresis. (71, 72).

4.4.4. Thiazolidinediones (TZD)

Thiazolidinediones (TZD) act by activating nuclear receptors. These receptors cause increased insulin sensitivity in the liver, muscle, and adipose tissue. This drug has been reported to inhibit proinflammatory cytokines. Therefore, it is thought to be a supportive treatment for COVID-19 (73).

4.4.5. Insulin

Hyperglycemia, insulin resistance, and associated inflammatory disorders caused by COVID-19 may increase the pancreatic β-cell load in patients with diabetes (74). However, insulin requirements are higher in diabetic patients hospitalized in the ICU due to the presence of a pre-existing inflammatory condition and cardiometabolic comorbidities. In people with diabetes with COVID-19, insulin should be continued throughout the illness. The most reliable and effective method in the management of hyperglycemia in intensive care patients is insulin infusion (75).

5. Conclusion

The COVID-19 pandemic is associated with high mortality. The mechanisms in COVID-19 and Diabetes Mellitus increase the severity and course of the disease. SARS-CoV-2 infection disrupts the ACE/ACE-2 balance. Ang-2 receptor pathways are activated. As a result, serious complications occur. In the pancreas, various disorders occur as a result of COVID-19 infection. Hyperglycemia and insulin resistance and occur. There is a strong link between the poor prognosis of COVID-19 and diabetes. Strong diabetes management procedures such as nutritional control, glycemic controls, and appropriate treatments are necessary to minimize adverse effects in people with diabetes.

CHAPTER IX

COVID-19 AND HUMAN FERTILITY

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Introduction

A new coronavirus (CoV), named severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in December 2019 in Wuhan, China (1). The infection has rapidly evolved into a global epidemic and it has been determined that the virus belongs to the subgroup of β-coronaviruses within an enveloped nucleocapsid (2, 3). The viral structure includes the N protein that forms the nucleocapsid, the envelope (E) and membrane (M) proteins that help viral assembly, and the protein spikes (S) that protrude from virion surfaces and permit viral cell entrance (2). The S protein consists of two subunits, S1 and S2, and mediates viral transfer to host cells. While the S2 is is responsible of fusing the virus to the host cell membranes, the S1 is involved in the attachment of the virus to the host cell membrane (4). There are numerous receptors involved in the S1 protein's interaction with host cells in the human cell membrane have been identified (2). One of these receptors is Angiotensin translation enzyme 2 (ACE2) receptor. Binding of the SARS-COV2 virus to ACE2 receptors facilitates the entry into the cell and replication of the virüs (Figure 1). Therefore, in cells with high levels of ACE2 expression, it increases the potential of the virus to target and damage these cells (5). SARS-Cov2 virus binds to ACE2 receptors and enters cells to complete the replication cycle (5). Viruses replicating intracellularly release mature virions and infect target cells (6). Besides ACE2 receptors, entry of SARS-COV-2 into the cell also occurs via transmembrane protease serine 2 (TMPRSS2), which is involved in viral entry of human coronaviruses by cleaving the S protein (4) (Fig. 1). Basigin (BSG)

is another cellular receptor of COVID-19 that can mediate virus entry into host cells (7).

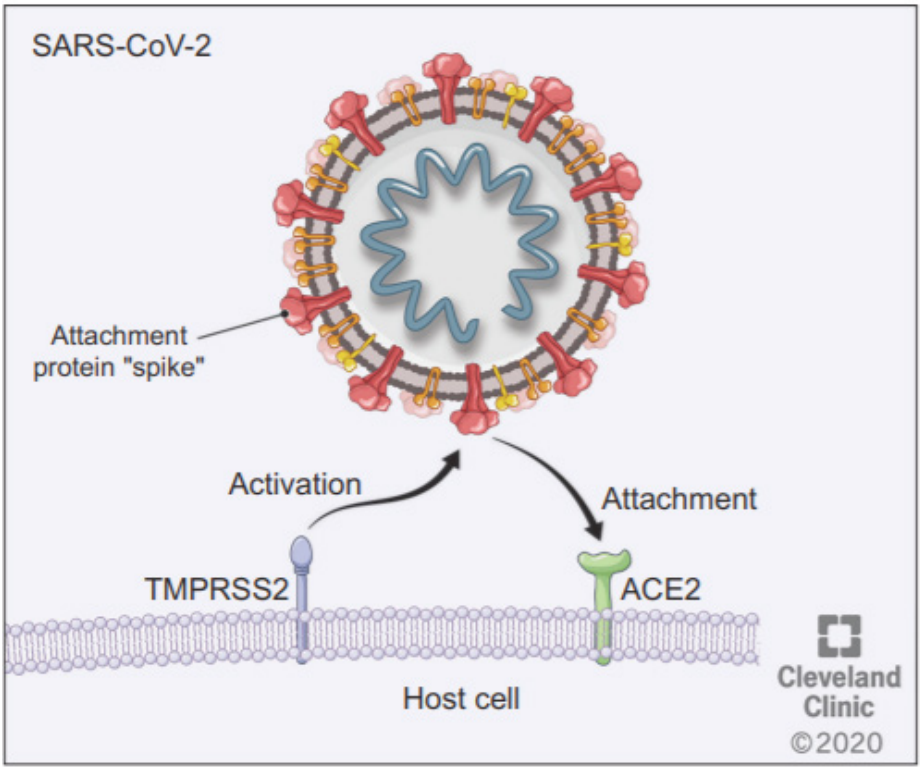

Fig. 1. SARS-CoV-2's cellular entry mechanism. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection is mediated by binding between viral spike proteins and the angiotensin converting enzyme 2 (ACE2) cellular receptor, and proteolytic cleavage and activation of spike proteins by transmembrane protease serine 2 (TMPRSS2) (8).

COVID-19 and Human Fertility

An important issue that may be of close interest to the community regarding COVID-19 is its impact on the reproductive system. SARS-CoV-2 has been shown to have negative effects on the reproductive system and leading to a potential decrease in fertility (9). Many young individuals have shown sexual and reproductive health issues related to the COVID-19 pandemic (10). However, it has been shown that there are sex-specific differences in disease

severity and mortality, raising the possibility that sex hormones play a part in how the body reacts to SARS-CoV-2 infection (11). The majority of SARS-COV2 infected individuals are men, which indicates that one of the risk factors for COVID-19 is male gender (12). This sexual dimorphism demonstrated that testosterone, the male sex hormone, may be a risk factor associated with the severity of COVID-19, whereas estrogen may be protective (9). The expression of ACE2 mRNA and protein is almost highest in the testes compared to other body tissues, while ovarian cells express ACE2 at comparatively low levels, suggesting that male gonadal function impairment and fertility caused by SARS-CoV-2 is more sensitive to this virus (5, 13). This may also be due, in part, to activation of the androgen receptor, which increases the expression of TMPRSS-2, a protease responsible for the preparation of the S1 protein required for host cell infection by binding with ACE-2 (4, 14). The course of COVID-19 disease has been linked to androgen sensitivity in some investigations (15), and a hyperandrogenic phenotype may be linked to higher viral loads, larger viral dissemination, and more severe pulmonary involvement (14). In actuality, testosterone (T) increases the expression of critical cell-surface receptors, such as ACE-2, on pneumocytes leading to an increase in the likelihood of infection in men. Interleukin 6 (IL-6) and tumor necrosis factor (TNF) activity is inhibited by T, preventing the "Cytokine storm," which is the main cause of COVID-19 death. Consequently, the steady decrease in T levels associated with aging may account for the greater mortality rate in older males (16).

COVID-19 is also reported to form a new invasion pathway by binding of the S protein to BSG, which invades host cells (17). It is hypothesized that BSG is required for normal fertility in both men and women, and with respect to the invasion pathway of COVID-19 mediated by BSG, COVID-19 infection could potentially affect reproduction (18).

COVID-19 and Male Fertility

The brain and testicles are among the various organs that are damaged by the huge inflammatory cytokines storm brought on by SARS-CoV-2. SARS-CoV-2 infection may result in to change sperm parameters and have a negative impact on male fertility. These effects can be brought on by a variety of causes, consisting of germ cell invasion caused directly by viruses, viral impact on reproductive hormones, inflammatory response, and finally infection-triggered fever that disturbs normal reproductive physiology (19). The negative effects of the virus

occur by binding to ACE2 and TMPRSS2 in testicular tissue. In particular, expression of ACE2 in the testis has been demonstrated in seminiferous duct cells, as well as in spermatogonia, Sertoli and Leydig cells, and is associated with potential risks related with SARS-CoV-2 infection in the reproductive tract (20). In addition to ACE2, TMPRSS2 also offers the potential entry route for SARS-COV-2 in spermatogonia, prostate, Sertoli and Leydig cells (20, 21). Overall, SARS-CoV-2 has been linked to issues with the reproductive system such as scrotal discomfort, seminiferous tubular damage, low sperm motility, and oligo-crypto-azoospermia in many male patients (22).

COVID-19 and Sex Hormone Abnormalities

According to reports, the blood-brain barrier (BBB) is permeable to SARS-CoV-2 and SARS-CoV-2 can infect ACE2-expressing glial cells and neurons causing neuropathogenesis and neuroinflammation in regions of the brain like the hypothalamus, which regulates a number of physiological processes such as body temperature and hormone balance (23). Reporting of a hyperintense signal indicating an enlarged pituitary gland as well as hypothalamic lesions in neuroimaging findings (23) suggests that involvement of the hypothalamus in COVID-19 patients may change the control of gonadotropin release, which in turn causes testosterone levels to drop (24). It was discovered that COVID-19 patients had much less testosterone, higher luteinizing hormone (LH), prolactin, and a comparable level of follicle stimulating hormone (FSH) (25). The average levels of circulating LH and FSH have been seen to rise as COVID-19 severity increases (26), which may point to a momentary activation of gonadotropin-producing cells brought on by inflammatory reactions (24). (Fig. 2)

Testicular infection causes significant hormonal repercussions, including hypergonadotropic hypogonadism due to the loss of Leydig cells, which lowers T levels while raising LH levels, resulting in a state of hypergonadotropic hypogonadism (27), which in COVID-19 patients is followed by a worse prognosis (28). These abnormalities show how the COVID-19 disease affects the secretion of sex hormones. While testicular pathology and HPG axis dysregulation, testosterone, FSH, and LH are associated with physiological regulation of the reproductive system have been linked to the onset and progression of sexual problems and infertility, (29). Therefore, COVID-19 survivors will have a higher risk of having sexual abnormalities and and issues connected to infertility (Fig.2).

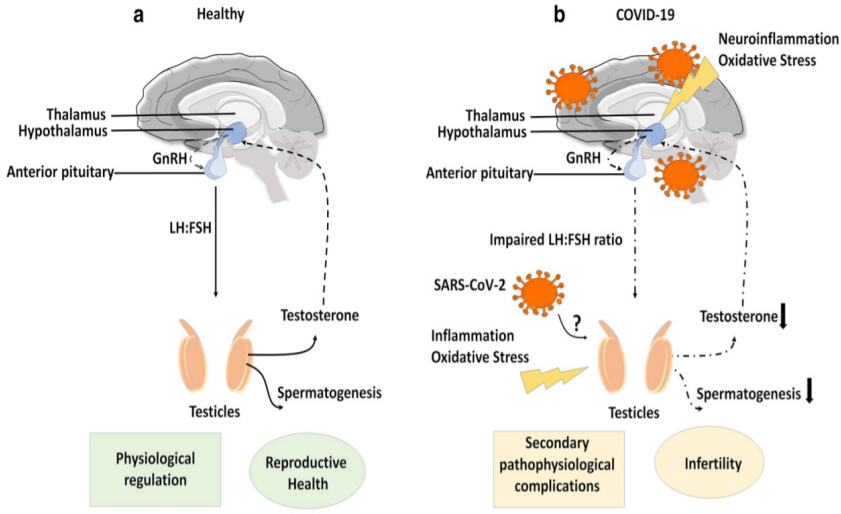

Fig. 2. Schematic representation of HPG axis regulation in healthy and person with COVID-19 infection. a. It represents the healthy human brain and testicles along with the HPG axis. b. It represents human brain and testicles infected with SARS-CoV-2 with neuroinflammation and due to testicular inflammation and oxidative stress, the HPG axis is dysregulated, which results in reduced steroidogenesis and spermatogenesis. (24).

During critical illness in COVID-19 patients, potential activation of the aromatase enzyme in adipose tissue brought on by inflammatory cytokines may result in a large increase in the conversion of testosterone to estradiol during critical illness in COVID-19 patients (30). In line with this, a higher estradiol/testosterone ratio was linked to higher levels of inflammatory cytokines, COVID-19 severity, the need for a ventilator, Intensive Care Unit (ICU) hospitalization, and mortality (31).

COVID-19 and Testicular Dysfunction

It has been noted that testicular damage and eventual male infertility following SARS-COV-2 infection can result from either a direct viral invasion via ACE-2 receptors or an indirect immune response that is inflammatory (32). Since ACE2 expression is high in the testicles, It was determined that SARS-COV-2 enters the interstitial space of the testicles during viremia and and Leydig cells may be one of the first targets of the virus (30). Furthermore, testicular ACE2 expression is age-related, with the highest expression of ACE2 observed in patients in their

30s and the lowest in patients in their 60s (33). Therefore, testicular damage was found to be significantly higher in young men with COVID-19 compared to older men. When the autopsy results of individuals affected by SARS-CoV-2 infection are examined, interstitial edema, inflammation, congestion, and red blood cell exudation in the testicles and epididymis was shown. Additionally, it has been noted that there are more apoptotic cells in the seminiferous tubules and a higher concentration of leukocytes in the interstitial cells of the testicular tissue (34). Although testicular pathology associated with hyperthermia is known, it has been reported that there is a significant decrease in semen concentration and motility due to fever seen in COVID-19 patients (35).

According to reports, COVID-19's pathogenic progression is aided by the proinflammatory cytokines that are circulated as a result of SARS-CoV-2 infection (36, 37). The testicles are among a number of organs that are particularly susceptible to oxidative stress brought on by free radicals and an increase in inflammatory chemicals (38, 39). Pro-inflammatory cytokines (C-reactive protein (CRP) and Interferon-gamma (IFN-γ)) and oxidative stress is extremely harmful to the production of steroid hormones and sperm by causing degeneration of the cellular components of the testicles and thus can seriously affect fertility (38, 39) (Figure 2). The observed enormous cytokine storm results in structural and functional impairment in the testicles independent of direct infection by SARS-CoV-2.

In particular, IL-1β, IL-1α, IL-6, Monocyte Chemoattractant Protein-1 (MCP-1) and TNF-α, are specifically upregulated during testicular inflammation, which has a negative impact on germ cells and creates inflammatory conditions in the testicles that disrupt the spermatogenesis process (34, 40). In COVID-19, lower testosterone levels and decreased spermatogenesis have also been linked to ongoing fever, increased pro-inflammatory molecule levels, and a subsequent immunological reaction in the testicles (41, 42). Additionally, the hypothalamus of the brain appears to be affected by SARS-CoV-2 infection, which is in charge of sensing sex steroid hormones derived from the testicles. This hypothalamus is responsible for controlling the HPG axis, and testicular abnormalities may result in lower amounts of sex hormones, which may be related to faulty HPG axis regulation.

In Leydig cells, ACE2 can disrupt local microvascular flows and permeability, promote inflammation, and impair Leydig cell function. This reduces the production of testosterone and harms seminiferous tubular cells (43). However, the infection is expected to last only a few days because of the testicles' superior immunological condition (44). It is well known that testicular

macrophages and sertoli cells have immunosuppressive characteristics that are particularly important for minimizing virally-induced testicular damage and lowering inflammation. However, the inflammation brought on by COVID-19 may temporarily affect the blood-testicular barrier's (BTB) integrity, which could have a negative impact on spermatogenesis (20). Proinflammatory cytokines released by Leydig and Sertoli cells can result in autoimmune orchitis by injuring the epithelium of seminiferous and provoking the autoimmune response (43). As a result, testes cannot be protected from the body's immune reaction despite their privileged immunological position. Leukocyte, CD3+ T lymphocyte, and CD68+ macrophage infiltration into the interstitial tissue of the testis might result in the generation of interferons, which can also decrease testosterone synthesis (45).

COVID-19 and Spermatogenesis

Seminiferous tubules constitute 90% of human testicular tissues, where ACE2 expression seen in germ and sertoli cells indicates that these tissues are potential sites for SARS-Cov-2 infection and may affect spermatogenesis. Seminiferous duct cells, Leydig cells, spermatogonia, Sertoli cells and primordial germ cells show the highest ACE2 mRNA levels in testicular cells. Seminiferous tubule damage, decreased Leydig cell count, and mild lymphocyte inflammatory response have been reported in COVID-19 patients (46, 47). Additionally, COVID-19 male patient samples that underwent histological analysis revealed impaired spermatogenesis. The inverse relationship between elevated ACE2 levels and compromised spermatogenesis in immunofluorescent analyzes performed in COVID-19 patients indicates the possible mechanism of infection of the testicles with SARS-Cov-2 (48). However, reports of decreased circulating testosterone levels in cases of COVID-19 strongly suggest that aberrant spermatogenesis, which can result in infertility and may be predominantly caused by testicular inflammation, may be a possibility.

SARS-CoV-2 in Semen Samples

The incidence of SARS-CoV-2 in semen samples was found to be very low. According to reports, those who had the virus in their semen were either in the early stages of infection or were recovering from serious disease (44, 49). However, in another study examining semen samples taken during the early stage of infection, SARS-CoV2 was not detected in semen (50). SARS-CoV-2 RNA was not found in the semen of patients with acute COVID-19 infection,

according to a different investigation. However, deterioration in sperm quality and semen parameters was observed in individuals with moderate infection (51). These results are consistent with several other investigations in which semen samples from COVID-19 patients did not include SARS-CoV-2 RNA (52). Low sperm count and poor sperm motility were observed in semen samples from those recovering with mild to moderate COVID-19, but no viral particles were found in the semen (51). It has been shown that semen test positivity is lower in patients with clinical recovery compared to patients in the acute infection stage. This result shows that the virus is gradually cleared with recovery (53).

COVID-19 and Erectile Dysfunction

It is believed that COVID-19 may cause extensive endothelial dysfunction in erectile tissue of the peniles has many endothelium-lined blood vessels (54). The cause of erectile dysfunction is the TMPRSS-2 and ACE-2 genes expression in endothelial cells caused by COVID-19 infection (55). Immunothrombosis has the ability to impact penile vessels, causing vascular function to be compromised, which promotes the progression of erectile dysfunction that are more severe. Cardiomyopathy and myocarditis the other cardiovascular complications of COVID-19, can lead to erectile dysfunction even after the acute phase has passed. A sign of the potential negative consequences of COVID-19 on sexual health is pulmonary fibrosis, which causes the penile vascular bed to be hypoxic and may contribute to the deterioration in erectile performance in COVID-19 patients. When compared to individuals who tested negative for COVID-19, immunohistochemistry analyses revealed reduced gene expression of endothelial Nitric oxide synthase (eNOS) in COVID-19 positive men's corpora cavernosa (55). Similar to this, Sansone et al. hypothesized that COVID-19 infection could result in both short- and long-term complications related to erectile dysfunction. In this study, participants who tested positive for COVID-19 had a higher prevalence of erectile dysfunction than those who tested negative (56). Decreased T secretion from the affected testis may possibly contribute to the effects of COVID-19 on erection because T also controls endothelial function (52).

COVID-19 and Female Fertility

SARS-CoV-2 has been demonstrated to have an impact on female fertility and negatively impact female reproductive processes (57, 58). SARS-CoV-2 can infect target cells and consequently impact female fertility via binding to

the ACE2 receptor. The ovaries, vagina, uterus, and placenta of rats as well as granulosa cells, stromal cells, and immature oocytes have all been reported to express ACE2 (57, 59). It has been shown that COVID-19 can infect the ovaries, vagina and uterus, through ACE2 expression, thereby impairing female reproductive functions and leading to menstrual irregularity and infertility (57). ACE2 regulates luteal angiogenesis and degeneration, follicular development, and ovulation and plays a reproductive regulatory role by influencing regular endometrial tissue changes and embryo development (60). These factors give SARS-CoV-2 the ability to affect female fertility by damaging endometrial epithelial cells or granulosa cells and ovarian tissue (58). In the expression ratio of ACE2/TMPRSS2, no significant difference was observed between old and young ovaries, and high and low ovarian reserve (61).

SARS-CoV-2 on Endometrium and Menstrual Cycle

Endometrium plays an important role in embryo implantation and human reproduction. Studies have shown that low expression of the ACE transcription and TMPRSS4 and BSG genes in the endometrium (62). The expression of these genes changes throughout the menstrual cycle. They concluded that because of the low presence of ACE2 and the moderate presence of TMPRSS2, the endometrium may be protected from TMPRSS2-mediated SARS-CoV-2 infection. Since TMPRSS4 increases significantly in the mid-secretory phase, the endometrium may be affected by TMPRSS4-mediated SARS-CoV-2, particularly in the early and mid-secretory phases (63). The increase in ACE2 from early to mid-secretory phases implies a high risk of viral infection at this stage of the menstrual cycle (63). BSG is an alternative receptor whose expression alters throughout the menstrual cycle, and it shares a mechanism of activation with TMPRSS2 and ACE2 and is highly expressed most of the cycle (63). High expression of BSG explain SARS-CoV-2 infection, through processes other than ACE2 (63). SARS-CoV-2 RNA expression was not observed in endometrial biopsy samples (64).

In a review, it was shown that there are significant changes in the menstrual cycle related to COVID-19, but these changes are reversible (65). The main menstrual cycle findings are changes in menstruel volume, primarily decreased volume, delayed menstrual cycle, altered menstrual onset, deterioration of premenstrual symptoms, missed periods, and lower libido. Statistical analysis showed no significant difference in menstrual volume changes between mild and severe patients. In contrast, significant differences in menstrual length were found (66). However, Ding et al. discovered that the more severe group had a

higher flow (67). It should be remembered that being in the hospital can be a stressful experience that can result in irregular menstruation (68).

The Effects of SARS-CoV-2 on Ovarian Reserve and Hormones

A review showed a slight change in ovarian reserve and hormonal balance in relation to COVID-19 (65). In the study published by Li et al., no significant difference could be found the concentrations of Anti Müllerian Hormone (AMH) and sex hormones (estrogen, progesterone, testosterone, LH, FSH) between the individuals with COVID-19 and the control group. However, reporting increased levels of FSH and LH in the early follicular phase, in some women may indicate suppression of ovarian function. Correlation results of serum concentrations showed little or no effect on female fertility and ovarian reserve (66). Similar findings relating FSH, AMH, and antral follicle count (AFC) levels were reported in a different study. No difference was observed between women with COVID-19 and the control group (69). A study investigating AMH levels in hospitalized women also found no difference (66). Progesterone and estradiol levels were similar in both groups (70). Compared to pre-pandemic levels, women undergoing in vitro fertilization (IVF) procedures had higher FSH levels at the start of the cycle (71). Lower pregnancy rates have been linked to elevated FSH levels. In terms of hormonal ovarian status, Ding et al. found that women with COVID-19 had lower AMH levels, higher FSH levels, and greater levels of testosterone and prolactin compared to the same-age control group. One of the most reliable indicators of ovarian reserve is AMH. According to this study's findings, ovarian reserve may be impacted by SARS-CoV-2 infection (67).

COVID-19 and Follicular Fluid, Oocytes and Embryos

In SARS CoV-2 positive women, the number and quality of oocytes did not significantly differ compared to the control group and the presence of SARS-CoV-2 RNA in the follicular fluid was not reported (70, 72, 73). However, considerably fewer recovered and mature oocytes were found (69, 74). All of the women having IVF after COVID-19 infection had anti-SARS-CoV-2 IgG and low levels of vascular endothelial growth factor (VEGF) and IL-1β in their follicular fluid, according to Herrero et al. (74). The follicular fluid's compounds reflects the quality of the oocytes (75), therefore a change in its composition could have a negative impact on reproductive function. This study demonstrated low levels of VEGF, which can adversely affect the blood supply of the ovary, reduce the nutrient supply for the follicles, and ultimately result in poor oocyte

quality. In addition, low levels of the cytokine IL-1β, which are involved in regulating folliculogenesis and atresia (76, 77), may adversely affect oocyte quality (74). SARS-CoV-2 infection had the most negative effect on fertility in terms of lower embryo number and quality. Positive SARS-CoV-2 IgG levels were seen in the follicular fluid in all COVID-19 recovered patients. In the vast majority of studies, the quantity of blastocysts, high-quality embryos, and euploid embryos was impacted (65).

SARS-Cov-2 Infection in Pregnancy and Intrauterine Transmission

To tolerate a fetus with a different genetic characteristic, a pregnant person's immune system must adapt during pregnancy. Compared to the general population, pregnant women are thought to be more susceptible to COVID-19 infection and less tolerant of hypoxia because of their immunological condition and the physiological changes that pregnancy brings about (edema of the respiratory tract mucosa, decreased total lung volume, increased oxygen consumption, etc.). These immune system modifications, together with adjustments to the heart, lungs, and other systems, could make a pregnant woman more susceptible to infection or raise her risk of morbidity and mortality (78). The level of pathogen exposure also affects a woman's susceptibility to infection while she is pregnant. An increased risk of serious illness has been associated with pregnancy, according to studies comparing pregnant women to women of reproductive age who are not pregnant (79). In contrast to women of reproductive age who are not pregnant, intensive care unit (ICU) admission rates, the requirement for invasive ventilation, and the need for extracorporeal membrane oxygenation are higher in pregnant subjects (80).

High levels of IL-6, IL-8, TNF-α, and other cytokines are frequently linked to COVID-19, and these cytokines cause a procoagulant state that is harmful to the growth of the blastocyst or fetus in a healthy human uterus (81). Coronaviruses can have adverse effectson fetuses and newborns, causing intrauterine growth restriction, early birth, spontaneous abortion, and even death, according to an epidemiological study (82). Additionally, research has shown that SARS-CoV-2 is present in the placenta, even in pregnant women who have mild COVID-19 disease, and that it may cause fetal growth limitation and other pregnancy complications (83). In addition, conditions such as thrombosis, infarction and remodeling of the vascular walls have developed in the endothelium of the placental chorionic villi and decidua. This suggests maternal and fetal vascular hypoperfusion, which some studies have linked to

oligohydramnios, fetal growth limitation, premature birth, and stillbirth (84). SARS-CoV-2 infection during pregnancy has been linked to an increased risk of pregnancy problems, while COVID-19 has been linked to a higher risk of preeclampsia, premature birth, and stillbirth (85). In addition, preeclampsia seen in pregnancy; it has been shown to have severe features such as eclampsia, low platelet count, hemolysis, and elevated liver enzymes (86). Compared to the mild form of the disease, severe cases had higher rates of gestational diabetes, preeclampsia, low birth weight, cesarean section, preterm birth, and neonatal ICU admission (85). Cesarean section rates were found to be higher in SARS-CoV-2 infected pregnancies compared to uninfected pregnancies (22).

When a newborn baby tests positive for SARS-CoV-2, it might be difficult to determine whether transmission happened intrauterine (during pregnancy and before labor begins), intrapartum (after delivery), postpartum, via breastfeeding, or through other pathways. SARS-CoV-2 transmission in the uterus has been described, however it is uncommon (87). The reasons for the low incidence of SARS-CoV-2 intrauterine transmission are not fully understood, and although not all studies are consistent (88) this may be associated with lower levels of viremia in SARS-CoV-2 infection (89). It may also be due to the lack of co-expression of the ACE2 and TMPRSS2 receptors in the placenta, which facilitates the entry of SARS-CoV-2 into cells (90, 91).

Conclusion

The COVID-19 virus is brought on by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become an important public health problem, spreading rapidly around the world, resulting in severe issues with health systems of several countries and tens of thousands of deaths. It has been demonstrated that COVID-19 may harm the reproductive system and result in sterility, either directly by viral invasion or indirectly through a secondary immunological or inflammatory response. The data obtained show that COVID-19 affects male and female fertility, but more studies are needed to reveal the acute and delayed consequences of these effects. According to studies, SARS-CoV-2 infection affects male patients slightly more than female patients. Despite the fact that the way SARS-CoV-2 enters cells has been explained, there is insufficient evidence to support this important sensitivity of the male reproductive system. Given that more study is need to establish conclusive proof of potential COVID-19 effects on reproductive outcomes, it is important to be alert to possible interventions and delays in care that could have lasting effects on fertility. Going forward, it is

of great importance to monitor the reproductive functions of all male and female patients recovering from COVID-19, and investigating the potential long-term reproductive implications of their treatments and vaccines.

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CHAPTER X

COVID-19 PRESENTATION IN CHILDREN

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1. Introduction

SARS CoV-2 is a virus spreading universally and it can affect children of all ages, regardless of gender. Beyond the disease and its rare presentations in children, the negative impact of Covid-19 pandemic on children and adolescents' education, social development and emotional well-being is undeniable. Clinically, the course of Covid-19 is observed to be better in children. In a comprehensive study, it was found that 112 of 2143 children showed a severe picture, only 13 of these children experienced ARDS, multiple organ failure and respiratory dysfunction. The only death reported in this study was a 14-year-old child (1). According to data from American Academy of Paediatrics, it was reported that 5.3% - 32.3% of the positive cases in the country on a state basis were children until April 8, 2021. The rate of hospitalization due to Covid-19 was between 0.1% - 1.9% in children, while the rate of death was between 0.0% and 0.19% (2).

1.1. Covid-19 symptoms and contamination in children

Children may have various disease symptoms, or they may not show symptoms. Most cases recover within 1-2 weeks. Lower respiratory tract involvement is rare (3). Severe symptoms such as ARDS, coagulation disorders and septic shock, which are observed in adults from the first week of illness, are very rare in children. 6-day symptoms in a severe case reported from Wuhan Children's Hospital were vomiting and diarrhoea and high fever and respiratory distress in the last two hours. Pneumatic infiltration was observed in the patient's right lung and the patient was intubated. 10 days later, the patient recovered and was removed from intubation. This showed that children may show severe presentations, although rare (4).

Contamination occurs through droplets. The first reported case was a family contact (5). The first infant case was reported from Xiaogan of Hubei

state (6). Although virus has been reported in the stools of some sick children, it is not clear that the virus is transmitted in this way (7). Children whose Covid-19 tests are positive may be clinically asymptomatic or they may show symptoms such as dry cough, fever, and malaise. Symptoms related with the gastrointestinal system have also been reported in some cases. In children, the course of the disease is usually mild, the prognosis is good, and the process lasts for 1-2 weeks (6, 8, 9).

A study conducted in China reported that children between the ages of 0 and 1 were 2.20 times more likely to catch the disease when compared with children between the ages of 2 and 2.5 and 1.53 times more likely when compared with children between the ages of 6 and 12. In addition, according to this report, people younger than 20 years of age were 1.58 times more likely to transmit the disease when compared with individuals older than 60 years of age (10).

When asymptomatic children were compared with symptomatic children and adults, they were found to have same or higher viral load. In this case, it can be thought that children and adults are not different from each other in terms of transmitting the infectiousness (11, 12). It can be said that ways of transmission in children are important in terms of the epidemic (13).

1.2. Diagnosis and interventions

While applying triage and diagnostic methods in children, their symptoms such as fever, cough and respiratory distress should be taken into consideration. Children should be taken to isolation areas reserved for Covid-19 and they should be observed by clinicians using personal protective equipment. Contact history should be taken from the patient and family and their physical examination should be performed. Cardiopulmonary support should be provided to patients whose general conditions are not stable and they should be transferred to the relevant service (14). Upper respiratory tract swab samples are taken from those who are suspected to have Covid-19 and RT-PCR test is performed for SARS-CoV-2. With the start of symptoms, the test can give positive result within 1-2 days. Test positivity may take up to 2 weeks in some cases, depending on severity. It is recommended to take PCR sample from the children of pregnant women diagnosed with Covid-19 within 24 hours of delivery (15). It will be useful to repeat tests to confirm the diagnosis (16).

1.3. Pregnancy

There is not enough information about transmission of SARS-CoV-2 from mother to child during pregnancy. In a study conducted on 9 pregnant women with positive Covid-19 test, pneumonia was not observed in any of

the pregnant women, while typical multiple patchy ground-glass sections were found in the CT examinations of 8 of the pregnant women (8). Although it is not clear how mother's having Covid-19 in the early periods of pregnancy affects the baby, studies conducted have not reported transmission from mother to baby after birth (17). There are various symptoms reported about Covid-19 presentation in newborns, while there is not enough information in literature (13). It has been reported that SARS-CoV-2 does not transmit to babies from mother's milk (8). WHO has not indicated any problems about breastfeeding of mothers with Covid-19, but has recommended for necessary hygiene rules to be followed (18).

1.4. Why are the symptoms milder in children?

Experimental studies conducted on mice with other types of coronaviruses have suggested that acute lung damage develops as a result of immune system reaction and therefore acute respiratory failure is triggered (19). Since immune response develops more in adults when compared with children, this can explain the milder course of presentation in children. Reasons such as immune system's being more active in children, absence of different concomitant diseases, distributions and functions of viral receptors and frequent exposure to viral infections can explain the good prognosis (20).

It is known that SARS CoV-2 uses ACE2 receptor to enter the cell (21). Studies conducted with mice have reported that this receptor decreases rapidly with age. These experiments show that the reason why prognosis is good in children is not associated with the ACE2 receptor. However, it can be thought that the protective effect of ACE2 for lungs is effective in good presentation (20). Another reason for milder course of Covid-19 in children may be the effect of melatonin. Melatonin production decreases with increasing age. The effect of melatonin reducing inflammatory cell migration to lungs can be shown as a reason for this (21).

In some countries vaccinated with Bacillus Calmette-Guérin (BCG), SARS-CoV-2 related mortality rates were found to be lower (22). Studies have indicated that BCG vaccination makes the spread of Covid-19 difficult and decreases mortality. However, it is not clear whether BCG vaccination will be effective for elderly individuals (22). Randomized controlled studies are required to state clearly that BCG vaccination can protect.

In a comprehensive study conducted in China, 2143 child cases were examined. However, in this study 65.9% of the cases were accepted as possible Covid-19. The remarkable situation in this data was that the prognosis of the disease was more severe as the age decreased (1). Children who have

immunodeficiency and a history of disease related with lungs always have a higher probability to have severe Covid-19 (23).

In a review conducted in the USA, it was reported that symptoms of fever, cough, and shortness of breath, which were observed with a rate of 93% in adults, were observed with a rate of 76% in children. In this study, adults had higher need for hospitalization and intensive care when compared with children. It was found that children younger than 1 year old had higher need for hospitalization and intensive care when compared with children between the ages of 1 and 17. 3 of the 2572 children examined died and their underlying disease states were not known (24).

1.5. Laboratory tests and treatment

Data regarding the laboratory examinations of children are not sufficient. In a study conducted on 66 pediatric patients, leukocyte counts were examined and values with a normal count were found in 69.2%, while values with an increased count were found in 15.2% and values with a decreased count were found in 15.5%. High CRP value was found in 13.6% of the cases, while high procalcitonin value was found in 10.6% (25). Although lymphopenia is observed in adults, especially in those with a severe course, it may not be observed in infants because their immune system is not yet mature compared to adults. CRP values are lower in children when compared with adults (26). It is thought that increased IL-6 level indicates a condition associated with severe pneumonia for pediatric patients (4). As a result, laboratory examinations may differ in children, they may even be in normal levels.

In children, pulmonary CT findings may be normal in the early periods of the disease. In studies conducted, ground glass opacities were found in 1/3 of the CT images of pediatric cases. In the same study, more than half of the cases were diagnosed with pneumonia (27). In general, ground glass opacities, unilateral or bilateral patchy appearance, consolidation, interlobular septal thickening, halo sign and subpleural findings were observed in children on CT (27, 28). Although lymphadenopathy and pleural effusion are rare, ground-glass opacities may turn into consolidation in the future (14).

There is no set treatment procedure for children. Usually, symptomatic treatment is applied according to the patient's condition. Although drugs such as lopinavir-ritonavir, azithromycin, hydroxychloroquine are generally used as pharmacotherapy, the efficacy of none of these is not known yet. Cardiotoxic effects of especially azithromycin and hydroxychloroquine should be considered (29-31).

Conditions that require observation and follow-up in the hospital for children can be listed as follows:

1. Respiratory difficulty
2. Oxygen saturation below 92%
3. Shock/ Poor peripheral perfusion (cyanosis)
4. Poor oral feeding, especially in infants
5. Lethargy, especially infants and small age groups
6. Seizures or encephalitis (32).

In children who are hospitalized, discharge may be considered in cases where fever decreases and is stable for 3 days and there are no respiratory complaints. It is recommended to comply with the rules of home isolation for 14 days after discharge (26, 33).

2. Discussion and Conclusion

Recently conducted studies have reported that admission to intensive care, invasive mechanic ventilation and deaths are experienced in hospitalizations due to covid-19 (34). In children under 2 years of age who had severe disease course, cardiovascular disorders, chronic pulmonary disease, neurological diseases, prematurity, and respiratory airway anomalies were the comorbidities. Diabetes mellitus, obesity, and tube-related nutritional status draw attention in children between the ages of 2 and 17 who have a severe disease course (34). It has been reported that allergic diseases and allergic reactions observed in children during the Covid-19 pandemic have a milder course (35). Epidemiological characteristics of airway viruses have changed during the pandemic. It was thought that the reason for this was not directly the SARS-CoV-2 virus, but the pandemic measures applied by the countries. It can be said that the measures taken by the individuals on their own contribute to this (36). However, since countries have different measures and different vaccination, we cannot express a universally clear view about this process.

According to CDC data in the USA, it was reported that almost two thirds of children who developed multiple organ damage due to Covid-19 were treated in intensive care for an average of 5 days. 36 of 3185 children who developed multiple organ failure until March 29, 2021, resulted in death (11).

In a study conducted in Italy on 19 children who had covid-19, it was found that 41.8% of the children had recovered completely and they did not have any symptoms. The rate of children who had one or two symptoms after they recovered was 35.7%, while the rate of those who had more than two

symptoms was 22.5%. The symptoms were mainly insomnia with a rate of 18.6%, respiratory symptoms such as pain and tightness in chest with a rate of 14.7%, nasal congestion with a rate of 12.4%, fatigue with a rate of 10.8%, muscle and joint pain with a rate of 6.9% and concentration disorder with a rate of 10.1% (38).

In a study conducted on 5 children who were diagnosed with covid-19 at least 2 months ago, it was reported that the children's symptoms continued for 6-8 months and one of these children had been hospitalized due to pericarditis. All of the five children had complaints of fatigue, shortness of breath, heart palpitations or chest pain, while four had headaches, difficulty in concentrating, muscle weakness, dizziness and sore throat. Some of the children were found to have improvements, while all of them suffered from fatigue and none of them could make a full return to school (39). This study is important in terms of knowing the long-term effects of the disease in children who had Covid-19.

According to state level fata from American Academy of Paediatrics, by July 14, 2021, a total of 6.8 million children, 38% of whom were between 16 and 17 years of age and 25% of whom were between 12 and 15 years of age, had been vaccinated fully in the USA. In addition, 8.8 million American children under the age of 18 (46% between 16 and 17 years of age and 34% between 12 and 15 years of age) had received at least one dose of COVID-19 vaccination (40).

Studies on COVID-19 vaccination for children are progressing slowly, but the non-replicated structure of Astra-Zeneca vaccine is thought to be relatively safer for children. The manufacturers of the vaccine included children up to 12 years of age in the second phase of their clinical trials (41). On January 23, 2021, Israel began to vaccinate children between the ages of 16 and 18 with Astra-Zeneca vaccine and by March 10, approximately 600 children younger than 16 with underlying diseases had been vaccinated (42). Previous Astra-Zeneca vaccine trials in adults showed that the vaccine was safe; it could create a strong immune system reaction and had high efficiency. A United Kingdom study was started on February 12, 2021, to evaluate whether healthy children between the ages of 6 and 17 showed a good immune reaction to Astra-Zeneca vaccine. The study is being carried out by Oxford University and three common sites in London, Southampton, and Bristol. 300 children between the ages of 6 and 17 were included in the study. The process related to this study is still on-going (43).

By January 16, 2021, manufacturers of Chinese CNBG COVID-19 vaccine had previously completed clinical trials for children who were 17 years

of age and older and had finished Phase I and II clinical trials on 3-5, 5-12- and 12-17-years old children. In this experiment, immune response and safety data showed good results for children between 3 and 17 years of age. This vaccine is expected to cover all patients older than 3 years of age (44).

CoronaVac is an inactivated SARS-CoV-2 vaccine tried for the first time in children. According to the results of the clinical study published on this subject, it was reported that the vaccine triggered humoral immune response in individuals between the ages of 3 and 17, it was reliable and tolerable (45). Although it was found in this study that immune response is better in children when compared with adults, it should be kept in mind that fever and allergic conditions because of excessive immunity may occur more often than adults. In addition, the need to balance the side effects that may occur, and overreactions of the immune system is obvious. Long term effects of vaccines on the development of children should also be examined well.

Children usually have low immunity, and some show a long period of incubation after SARS-CoV-2 infection. For this reason, children's contact with crowded and complex environments should be avoided as much as possible so that children are not infected by potential contagious agents (6).

According to the Phase III trial of Pfizer vaccine administered to children between the ages of 12 and 15, it was reported that side effects were consistent with adults, whereas the vaccine led to strong antibody response (46).

The most common adverse reactions reported so far after vaccination were pain, redness and swelling or itching at the injection site. The most common systemic adverse reactions were fatigue, fever, headache, cough, muscle pain, chills, nausea, vomiting and diarrhoea (47). Myocarditis has been reported as a rare complication of Covid-19 mRNA vaccine in young adults and adolescent men especially after second dose Covid-19 mRNA vaccination. In the United States of America, as of June 11, 2021, rough recording rates for myocarditis or pericarditis cases following Covid-19 mRNA vaccination in children aged between 12 and 17 years of age were 4.2 per million doses in females and 32.4 per million doses in males. The US Vaccine Adverse Event Reporting System received 1226 myocarditis and pericarditis reports after approximately 300 million doses of Pfizer and Moderna vaccine (48, 49).

In Israel, 275 myocarditis cases were reported in five million vaccinated individuals and most of these cases were men between the ages of 16 and 19 who had received their second dose vaccine. It is not known for sure why myocarditis occurs predominantly more in men. However, explanations regarding the

conditions that cause myocarditis stated that it could be associated with the differences in immune reaction and gender hormone. In short, it is clear that the differences in long term efficacy, safety and dosage, age and process of various COVID-19 vaccines should be confirmed by further studies (50).

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CHAPTER XI

NEUROLOGICAL FINDINGS OF COVID-19 IN CHILDREN AND EFFECTS ON CHILDREN WITH NEUROMUSCULAR DISEASE

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1. Introduction

The Novel Coronavirus Disease, which affected the whole world, affected health, education, economy and social order in many countries with the emergence of the first case on 31 December 2019 in Wuhan, China's Hubei province. It has been accepted as a global epidemic on March 11, 2020 by the World Health Organization, as it causes very serious health problems in the World. (1)

While most of the patients have symptoms similar to influenza infection, they are often admitted to the hospital with the complaints of sore throat, fever and cough. Although most of the patients show mild symptoms, severe pictures can also be seen in which many organs and systems in the body are affected. (2)

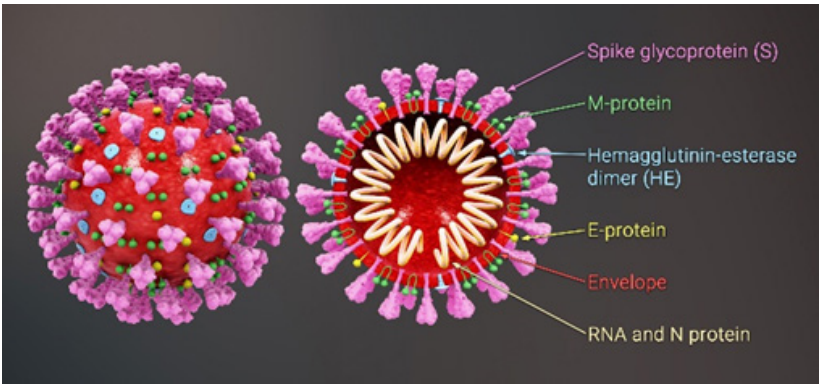
The disease is more likely to show serious symptoms in adults. However, people of all ages can be affected differently by the disease. Studies have emphasized that children show milder symptoms and the disease is mostly asymptomatic. (3)

COVID-19 not only affects a single system, but also can cause damage to many organs and systems in patients of all ages. In this section, we aimed to review the neurological findings in children diagnosed with COVID-19 and the findings in pediatric patients with neuromuscular disease.

2. COVID- 19

Coronaviruses are 40-60 nm in diameter, weak, single-stranded RNA viruses from the coronaviridae family. (Figure 1) All coronaviruses are pleomorphic. Coronaviruses have a crown shaped structure (corona) composed of tuber like peplomers. Subgroups gamma and delta-coronaviruses infect birds, while mammals are infected by alpha- and beta-coronaviruses. (4)

The new virus was named SARS-CoV-2 because of its close genetic similarity to SARS CoV. The definition for the new coronavirus (2019- nCoV) was used. Based on all these definitions, the disease has taken its place in the literature as COVID-19. (5,6)



Figüre 1. Coronavirus Structure (7)

Symptoms such as upper and lower respiratory tract infection, cough, fever, loss of appetite, abdominal pain and diarrhea are seen in patients infected with COVID-19. Apart from that, neurological findings such as headache and confusion may also occur. Other remarkable findings have been reported as sudden loss of smell and taste. (8)

The main mode of transmission of the disease is through droplets. It is transmitted by direct contact of other people with the droplets spread by sick people by coughing or sneezing, or by carrying this virus to organs such as mouth, nose and eyes with their hands. The highest risk of transmission is in the first 5 days after the onset of symptoms. Since asymptomatic patients who do not show any symptoms can also be contagious, care should always be taken in terms of transmission. (9)

Diagnostic method of COVID-19 is a quantitative real-time polymerase chain reaction (qRT-PCR) test with nasopharyngeal swab taken from patients.

Although this diagnostic method is very sensitive and reliable, thoracic CT is also important in terms of determining the course of the disease and the clinical picture that may arise. (10)

There are various treatment protocols for the disease. But the most important thing is the clinical course and findings of the disease. The most important issue is the measures to be taken to prevent the disease. Medical mask, staying away from patients and cleaning is the gold standard for reducing the spread. Regular vaccination is also very important in the fight against the disease. (9)

3. COVID- 19 in Children

It has been revealed that COVID-19, which affects the whole world, is not seen very often in pediatric patients, and it does not usually show a severe picture in infected children. The first child case of COVID-19 exists on January 20, 2020. He is a 10-year-old boy living in Shenzhen, China. (12)

When the studies are evaluated, many case series are encountered. The smallest case encountered was a baby born 30 hours ago, the oldest was 18 years old. (13)

When the literature was examined, the mean age of pediatric patients with Covid-19 ranged from 7 to 3.3 years. Most cases were seen in children over 1 year old. When the gender distribution of the patients was investigated, although many studies showed different results, the rate of male patients was high. (14)

In a study, 2135 pediatric patients were examined and it was stated that the majority of them showed mild symptoms or were asymptomatic. Complaints such as acute kidney injury, encephalopathy, myocardial damage, coagulation dysfunction and acute respiratory failure were reported in only 5.8% of the cases. (3)

In a study conducted in Bingöl between March-December 2020 in our country, 1431 case information was evaluated. Only 0.1% of them were reported to be in poor condition. (14)

In another study conducted in our country, 262 pediatric patients with Covid-19 were evaluated. 50.4% of these patients were mild; It was reported that 0.8% of them were severe. While it was reported that the rate of needing intensive care among all patients was 4.27%, it was observed that 80% of them were under 1 year old. (15)

Although the reason why COVID-19 is not severe in children cannot be fully explained, factors such as less exposure to viruses, more protection against cigarette smoke and air pollution are of great importance. In addition,

regular childhood vaccinations can play a protective role against this virus. Another factor may be that children's immune systems are still developing, have different responses to pathological conditions, and have more antibodies than adults. (16,17)

The incubation period of the disease in children varies between 1-14 days, but the average duration is 5-6 days. Generally, cough, sore throat, fever and fatigue symptoms are seen in children. In some children, symptoms such as runny nose, nasal congestion, diarrhea, vomiting have also been reported. (12) The majority of pediatric patients recover after 2 weeks at the latest. However, in cases where the lower respiratory tract is infected, this period may increase and cause a severe clinical picture. (6)

In a study conducted in the USA in which 2572 children were evaluated; the mean age was reported as 11 years. The age group with the highest number of patients was between the ages of 15-17, respiratory distress, cough, and fever symptoms were observed in 73% of the patients. (17)

When the laboratory findings in pediatric patients were evaluated, it was observed that the white blood cells were within normal values in the blood count, the C-reactive protein (CRP) level may be normal or increased in some cases. In addition, in more severe cases, an increase in creatine kinase (CPK), lactate dehydrogenase (LDH), transaminase, myoglobin, procalcitonin, and ferritin levels can be observed. (18, 20) Many health boards have also deemed it appropriate to carry out these examinations in pediatric cases. (18)

Considering the clinical situation in pediatric patients, low-dose chest radiography or computed tomography (CT) findings may be used in the presence of respiratory distress. In the literature, CT was requested for children whose condition worsened or with different underlying diseases, and findings such as milder ground glass opacities and bilateral multilobar consolidation were found compared to the findings of adult patients. (19,20)

It cannot be said that there is no definite data about the treatment in pediatric patients with COVID-19. However, considering the clinical picture in children, it can be said that the treatments applied reduce the symptoms of the disease. (18) The treatment protocols given are also changing day by day. Accordingly, the recommended treatment steps for patients are updated. (21)

In line with the information obtained from SARS and influenza among the general common treatment methods, it is considered beneficial to initiate antiviral drugs and treatments at the right time. Despite all this, it should not be forgotten that the treatment should be planned individually in each case and the possible side effects of drugs should not be ignored. (9)

4. Neurological Findings in Children

Although the symptoms of COVID-19 in children are generally mild, it has been observed that many different systems, including the central and peripheral nervous system, are affected in some cases and severe clinical pictures occur. (8)

Headache, the frequency of which varies between 13.8% and 66%, is one of the most common neurological findings in adult patients. The severity differs from person to person. It has been observed in studies that it is more common in patients with severe disease. (8, 17) In addition, neurological findings such as dizziness, seizures, encephalopathy, encephalitis, ataxia, impaired consciousness, acute cerebrovascular disease are also seen in patients with COVID-19 infection. (2)

It is assumed that the mechanisms by which COVID-19 affects the nervous system develop in different ways. (Figure 2) The first occurs when the virus, which crosses the blood-brain barrier in different ways, enters the nervous system. The second possible mechanism is the post-infectious immune-mediated condition seen after many viral infection states. (22,23) In another mechanism, the virus, which affects the respiratory system, can cause damage to the lungs and affect many functions by disrupting the nutrition of the brain. In another proposed mechanism, the immune response increases; The levels of chemokines and cytokines increase, which leads to the emergence of neurological findings, especially in children. This condition is also called cytokine storm. (24,25)

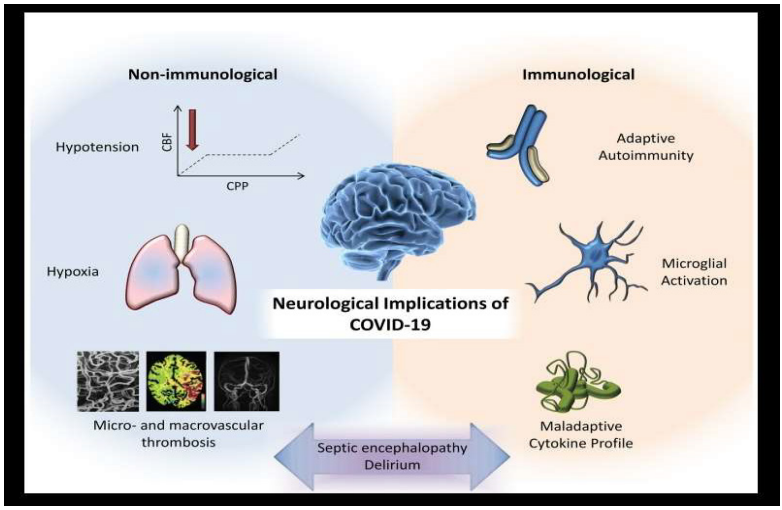


Figure 2. Mechanism of COVID-19 Neurological Findings (19)

When studies in pediatric patients were examined, it was seen that there were fewer publications with neurological findings at the beginning. However, severe neurological symptoms were observed in children who had a severe disease, although not very often. (16)

The most common neurological finding in pediatric cases with COVID-19 is headache. In addition, symptoms such as seizures, fatigue, encephalitis, impaired consciousness, ataxia are also encountered. (26, 27)

A study conducted in 2020 evaluated 171 children with COVID-19 infection and showed no neurological findings. (28) However, as time passed, pediatric patients with increasing neurological findings were encountered. In later research, loss of smell and taste was observed in 6% of the patients, while symptoms such as fatigue, headache, muscle and joint pain were found at a rate of 16.7%. (29,30)

When the 5 years old male patient who was admitted to the hospital with the complaints of vomiting, headache, loss of appetite and weakness, who was 5 years old and did not have any comorbidities before, some neurological findings were observed. In the brain MRI examination, signal increases consistent with cytotoxic edema showing diffusion restriction in the bilateral periventricular deep white matter were observed, the CSF distance around the brain stem was erased, and the edema secondary to the edema described in the cerebral parenchyma was reduced. (31)

COVID-19 infection affects the CNS, causing acute neurological findings. This brings along CNS damages such as consciousness disorders, cerebrovascular diseases, hypoxic-ischemic encephalopathy, acute hemorrhagic necrotizing encephalitis, corticospinal findings that cause neurological syndromes. Although these findings are not very severe in children, it is thought that it may cause an increase in neurodegenerative diseases in future generations. Therefore, neurological evaluation and follow-up of children, adolescents and young adults who have had the disease is very important. (29,30)

5. COVID-19 in Children with Neurological Disease

Although most children survive the COVID-19 infection mildly or without symptoms, the disease progresses more severely in those with neurological or neurodevelopmental diseases (cerebral palsy, spina bfida, epilepsy, DMD, genetic metabolic diseases) and under 1 year old. (16, 32, 19)

Neuromuscular diseases are progressive, inherited and degenerative conditions that occur in body muscles. Although different findings may occur

in these patients according to the type, course, age and general condition of the patient, there are mostly loss of strength, atrophy in the muscles, contractures in the joints, deformities in the extremities and becoming dependent as a result. (33)

In neuromuscular diseases, symptoms such as musculoskeletal problems, loss of walking, spinal deformities, swallowing disorders, respiratory muscle weakness and accordingly respiratory failure are observed. One of the most common causes of morbidity and mortality is respiratory failure. (34)

Treatment of neuromuscular diseases also varies from patient to patient. The age of onset, level of progression and general findings of the disease are important. Therefore, each patient should be evaluated individually and the treatment plan should be determined accordingly. The main purpose of treatment; preserving and increasing muscle strength, delaying atrophy, reducing spasticity, preventing edema and contractures. (35)

Neuromuscular diseases may worsen with COVID-19. In addition, new neuromuscular diseases may occur. Infection is a triggering factor for exacerbation and progression of almost all neuromuscular diseases. (36)

In diseases such as Dravet syndrome, cerebral palsy, Down syndrome, the course of the disease may be aggravated depending on the existing conditions such as respiratory difficulties, lung infections, scoliosis, difficulty in swallowing. (35)

People with neuromuscular disease who use immunosuppressive drugs in treatment are more likely to get COVID-19 infection and have a more severe risk of having the disease. Therefore, pediatric patients with neuromuscular disease are a group of patients at serious risk due to decreased respiratory capacity and immunosuppressant treatments, and care should be taken in their isolation. (37)

When patients diagnosed with epilepsy encounter COVID-19 infection, the results may be different. It has been observed that exposure to COVID-19 is riskier, especially in patients with fever and infection triggering seizures. For this reason, it is imperative for these patients to take the necessary precautions to prevent the disease and to increase the isolation as much as possible. (38)

Studies have proven that there is aggravation of seizures at rates ranging from 8.6% to 29.5%. For this, it should be kept in mind that antiepileptic drugs do not suppress the immune system and patients should not discontinue their anti-epileptic drugs due to fear of COVID-19. (39)

COVID-19 may cause worsening of motor symptoms. For this reason, the effects of COVID-19 are felt more in neurological diseases with psychomotor effects such as cerebral palsy. (38)

In general, the effects of the disease on the CNS may occur as direct neurological involvement, worsening of the pre-existing neurological picture or an increase in existing neurodegenerative findings. (40)

Weakness of the thoracic region and diaphragm muscles is very common among children with neurological diseases. As a result, respiratory problems arise. In the case of COVID-19, these findings are exacerbated. In addition to these findings, sudden increase in complaints and rhabdomyolysis due to conditions such as scoliosis, respiratory support and tracheostomy, inadequate coughing and oropharyngeal weakness, failure to clear the airway, heart muscle involvement (or those using cardiac drugs), infection, hunger, fever. The presence of diabetes and obesity, steroids or drugs that adversely affect the immune system (immunosuppressive), the disease progresses more severely. (41)

6. Conclusion

Children are affected differently by COVID-19 and the resulting findings are in different ways. Although very severe findings are not observed in children who have had the disease, it has been observed that neurological involvement and neurodegenerative diseases may occur in these children in the future. In addition, long-term follow-up of these children is necessary and very important, since the disease can be severe and cause serious life problems in children with neurodegenerative diseases. (40)

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CHAPTER XII

A CURRENT APPROACH TO COVID-19 INFECTION AND MIS-C SYNDROME IN CHILDREN

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1. Introdactıon

Coronaviruses, which were first identified in 1967, have gained importance recently due to the pandemic in humans in all age groups. Due to the increase in advanced lung infection cases in Wuhan, China, and when these cases were evaluated, it was announced by the Chinese authorities in December 2019 that there were live animal market contact cases (1). The causative agent was produced in the samples taken from the lung, and it was determined that an acute respiratory distress factor was encountered, which had not been seen before, and diagnostic tests were started to be studied in the laboratories (2). The virus was named as SARS-CoV-2 when it was noticed that the microorganism, which was named as ovelcoronavirus 2019 when first detected, was similar to SARS coronovirus due to its genetic structure (3). A state of emergency was declared all over the world by the World Health Organization in January 2020, and the epidemic was described as a pandemic in March 2020 (3). Cases began to be identified in Turkey as of March (4). Although adult patients were predominantly seen in the first period of the pandemic process, as the process progressed, cases began to be seen in the pediatric age group as well, and their number is increasing day by day. Recently, the number of literatures in which pediatric case series are presented has increased and it has been observed that children can be infected with SARS CoV2 as much as adults, though the severity and mortality rates of the cases are lower.

Various theories such as the number of angiotensin converting enzyme 2 (ACE2) receptor, which is the receptor that the virus binds to the cell, is low in children, the cytokine storm is milder or less frequent due to the incomplete maturation of the immune system in children, and the antibodies developed due to frequent viral infections in children are protective by reaction have been put forward in order to explain the reasons why children have a milder disease (5, 6).

Pediatric patients are generally infected by domestic contact. In a study, it was found that 65% of pediatric cases were diagnosed with Covid-19 after contact with positive family members. While respiratory findings are milder in pediatric patients than in adult patients, high fever and other system complaints also occur (7, 8).

During the pandemic period, febrile pediatric cases with multisystem involvement have been described from many countries. This condition, which was likened to Kawasaki disease in the first period, was defined as multisystemic inflammatory syndrome (MIS-C) detected in children associated with Covid-19 by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) (8). Cases in children who had Covid-19 disease or had contact with it, whose inflammation was confirmed by laboratory tests, who had a clinic that was severe enough to require hospitalization or intensive care, and who had at least two system involvements, were considered MIS-C if they could not be explained by any other clinical condition.

With the progress of the pandemic process and the increase in pediatric covid-19 patients, it has gained great importance to establish diagnostic and treatment criteria for pediatric patients. The severity of the disease was classified into five groups as asymptomatic, mild, moderate, severe and critical, according to clinical signs, laboratory parameters and imaging findings (9-11).

1. Asymptomatic case: Covid-19 test positive cases without clinical symptoms.
2. Mild case: Cases with acute upper respiratory tract symptoms, pharyngeal symptoms detected in physical examination, and normal lung listening findings.
3. Moderate case: Cases with pneumonia, frequent fever, cough, non-hypoxemia and clinically asymptomatic lesions on lung computed tomography.
4. Severe case: Cases where the disease usually progresses within one week and the oxygen saturation falls below 92% in which dyspnea occurs with central cyanosis.

5. Critical case: Cases that develop shock, encephalopathy, myocardial involvement or cardiac failure, bleeding disorder, acute renal injury and organ dysfunction, which rapidly progress to acute respiratory distress syndrome or respiratory failure.

When evaluated according to the severity of the disease, it was seen that more than 95% of the cases were in the middle and lower groups, and the number of severe and critical patients was very low (9-11).

2. Mıcrobıologıcal Propertties and Pathogenesıs

The Covid-19 virus is thought to be of animal origin. Coronaviruses are divided into four groups: alpha beta, gamma and delta. 2019 nCoV is in the beta coronavirus group together with bat-SARS-like (SL)-CoVZC45, bat-SL-CoVZXC21, SARS-CoV and MERS-CoV (12). It has been determined that the Covid-19 virus has more than 80% similarity with SarsCoV and more than 50% similarity with MERS (13).

The Covid-19 virus is spread by contact with droplets or surfaces contaminated by these droplets. Although not fully confirmed, it has been claimed that pediatric cases have been reported in which test positivity persisted in stool samples of other types of contamination such as fecal and oral contamination, and that negative polymerase chain reaction (PCR) tests in rectal swab and stool samples, as well as nasopharyngeal samples, may be useful in determining the isolation process in order to determine the isolation period in these cases, (14).

It has been determined that the Covid-19 virus enters the cell by binding to the ACE-2 receptors in the body cells with its spiny protrusions on its surface. ACE-2 receptors are found in lung, skin, gastrointestinal organs, kidneys and cardiac cells (15,16). After the microorganism is presented to T lymphocytes via antigen presenting cells, the inflammatory pathway continues with the release of proinflammatory cytokines. It has been determined that the release of indecytokines is important in the pathogenesis of the disease. In a study, it was shown that IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-A and TNF-alpha levels are associated with disease severity in cases followed in the intensive care unit (17).

3. Dıagnosıs and Clınıc

All age groups are at risk from the Covid-19 virus. For children, the main source of infection is usually the presence of positive cases in the family. Contact status

is especially important in the story. Although it has been shown in many studies that domestic contact is at the forefront, the number of out-of-home contact cases has been increasing with the removal of restrictions, the opening of social areas and the start of face-to-face education in the last period. Patients are mostly detected by PCR controls made due to contact individuals or by PCR testing as a result of admission to the hospital asymptomatically.

As clinical findings, upper respiratory tract infection symptoms are usually in the foreground. Most of the cases are asymptomatic and do not produce clinical findings. Mild cases may include fever, sore throat, stuffy or runny nose, cough, and headache. In addition, muscle-joint pain can be seen in mild cases. In moderate and severe cases, respiratory distress due to organ involvement, hypoxia, and hemodynamic disorders, diarrhea-vomiting may occur. In critical and Mis-C cases, findings related to multiorgan failure and shock findings can be seen.

Probable and definitive case definitions have been constantly updated in the light of the edited data, with the guidelines updated at various date intervals since the first case was seen. The diagnosis of Covid-19 is made by history, clinic, laboratory and imaging in pediatric cases as well as in adults. Especially contact history and PCR positivity are important for diagnosis. It is important to exclude other micro-organisms causing upper respiratory tract infections in the differential diagnosis. It was stated by the CDC that nasopharyngeal swab should be preferred primarily, and if an oropharyngeal swab is to be taken as a sample, it would be more appropriate to take it together with a nasopharyngeal swab (18). In cases where the PCR sample is negative but clinically suspected, repeat samples should be taken, and samples should be taken from the lower respiratory tract if possible. Producing Covid-19 in cell cultures is technically difficult and is often used for vaccine and therapeutic agent studies. Serological methods working on antibody detection are important for detecting previous disease and defining the epidemiology of Covid-19, rather than being used for diagnostic purposes. Asymptomatic or mildly infected cases can be detected later with serology, but it has been said that serology should not be performed as a single test for diagnostic purposes (19).

In a study conducted in adult inpatients with Covid-19 cases, high lactate dehydrogenase and aminotransferase levels, lymphopenia, and elevated inflammatory parameters such as C-reactive protein were found among basic laboratory tests (20). In a large-scale study of a patient group, enzyme parameters indicating heart, muscle and liver damage and coagulation values were found

to be significantly higher in critical cases, and frequent monitoring of total leukocyte, lymphocyte, platelet, ferritin, and IL-6 levels was recommended. In a publication examining the laboratory parameters in pediatric cases, the leukocyte count was found to be within normal limits, an increase in the leukocyte count was found only in 15.2% of the patients, and low lymphocyte count was observed in two cases (21).

It has been shown that tomography has high sensitivity in the early period in the diagnosis of Covid-19, especially in adults, and it has been reported that in cases with negative PCR test, tomography together with the history of contact and the clinic provides early detection of the patient (22). In all age groups, direct X-ray may not give any symptoms at the beginning of the disease or in cases with mild involvement. In Covid-19, mostly bilateral, rarely unilateral, subpleural ground glass appearance, consolidation areas can be seen on tomography. It should be kept in mind that co-infections that will develop on Covid-19 in patients who are applied for imaging may affect the imaging, and it should not be forgotten that the use of imaging alone in the diagnosis will be insufficient. In a study conducted with one hundred and seventy-one pediatric patients, it was listed radiologically as ground glass in 33%, local patchy involvement in 19%, bilateral patchy involvement in 12%, and interstitial changes in 1% (10). As a result, the necessity of imaging should be decided by considering the radiation that the patient will receive in the imaging method to be used in pediatric cases.

4. Treatment

Effective antiviral drugs are needed for the treatment of Covid-19. But we have a time problem for the development of new drugs, so drugs used for different viral agents have come to the fore. Since the first case was seen in the epidemic, different antiviral agents have been recommended and tried in adults with different characteristics. There is a lack of evidence-based data on the treatment of the disease in the pediatric age group, and antiviral therapy should not be routinely used except for severe and critical patients, and only supportive treatment is recommended for patients with mild symptoms (23).

4.a. Antiviral treatments

Hydroxychloroquine and chloroquine are agents used in the treatment of malaria and in the treatment of autoinflammatory conditions. In in vitro studies, it has been reported that host receptors prevent viral and endosome fusion, and that its

anti-inflammatory effect may also have a positive effect on the clinical course of the cases (24, 25). Since there is not enough information about its use in pediatric cases and it has life-threatening effects such as QT prolongation in cases using it, patients who will use it should be monitored and it should be used in severe cases and children with risk factors. In recent adult studies, discussions about its effect against Covid-19 have increased and it has been removed from treatment guidelines.

Favipiravir is an effective antiviral component by inhibiting RNA polymerase against ebola and influenza viruses. Favipiravir is known to be innocent and limiting in terms of side effects, and it has been shown in studies related to ebola that its effect increases as the dose is increased (26). Although we have insufficient information about its use in children with Covid-19, information about its use against other viruses can be instructive. The fact that the favipiravir tablet can be crushed and given with food provides convenience in use in pediatric cases. However, recent studies have increased the negative opinions about the efficacy of favipiravir and its use has been discontinued by many centers.

In a multicenter study, remdesivir was used in 158 patients with proven Covid-19 diagnosis, and 78 cases were included in the placebo group. In addition, faster clinical improvement was observed in the case group using remdesivir, compared to the groups using lopinavir-ritonavir, interferon, and corticosteroids, but the difference was not statistically significant (27). Oseltamivir is a neurominidase inhibitor used in the treatment of influenza. No in vitro effect has been demonstrated against Covid-19. Oseltamivir was also given to patients, but its effectiveness could not be demonstrated, due to the flu season in China at the time of the Covid-19 cases (28). For antiviral treatment, larger-scale and controlled studies are needed to find antiviral agents with proven efficacy and low side-effect profile for children and adults.

4.b. Other treatments

While the use of corticosteroids to suppress the inflammatory response in severe and critical cases with Covid-19, in the development of acute lung injury and in Mis-C syndrome is a controversial situation, undesirable effects, the development of secondary infections after use, and the possibility of delaying the decline of viral clearance have raised concerns about the use of steroids. It is not recommended to be used routinely in the treatment of Covid-19, except in severe and critical cases (29). “Infectious Diseases Society of America”

recommended the use of ceroids in the Covid-19 treatment guide in the presence of ARDS (30).

Anticytokine and immunomodulatory therapies can be used in severe, critical Covid-19 patients and Mis-C syndrome. It has been stated that proinflammatory cytokines are elevated and cytokine storm developing with increased release of cytokines affects the clinical situation (31). IL-6 plays an important role in this regard. Tocilizumab, which acts through IL-6, is a molecule used in the treatment of rheumatological cases. Large-scale, controlled studies on the use of tocilizumab are needed. It is thought that more research may be useful in cases where plasmas from donors who have recovered from Covid-19 infection are transfused to critically ill patients and show improvement (32). It is emphasized that in order for the immunoglobulin treatment to be effective, the donor group must have had the Covid-19 infection and fully recovered, and the antibody level in the body must be sufficient (33).

Necessary fluid support should be given according to the symptoms, vital signs and clinic of the inpatient. It should not be forgotten that phasic fluid administration may cause pulmonary edema and heart failure, and the fluid balance should be well adjusted and followed. In case of fluid overload, diuretic agents can be used. It should not be forgotten that malnutrition may develop with the duration of hospitalization in patients who are hospitalized in the intensive care unit, and necessary support should be given. In addition to effective cold application to fight fever, paracetamol use should be recommended when necessary. It should be kept in mind that secondary infection may develop, and empirical antibiotic therapy can be started, especially in severe and critical cases and in cases with Mis-C syndrome. Inhaled nitric oxide has been recommended for the treatment of cases with Covid-19 pneumonia. Nitric oxide can correct advanced hypoxia and reduce the duration of respiratory support. It can also be used in pulmonary hypertension and/or right heart failure that may develop. Hypercoagulation can be seen in pediatric cases with Covid-19 infection as well as in adult cases. Antiaggregant and anticoagulant therapy should be considered in patients and should be administered to patients according to their clinical characteristics.

4.c. Respiratory Failure and Oxygen Therapy

In Covid-19 cases with lung involvement, different amounts of oxygen are needed according to the degree of respiratory failure. In a multicenter study, oxygen support was required in 70% of the cases hospitalized in the pediatric

intensive care unit. It was stated that 20% of these cases were treated with noninvasive mechanical ventilation (NIV) and 28.6% of them with invasive mechanical ventilation (IMV). Oxygen mask with reservoir should be preferred for oxygen use. High-flow nasal cannula oxygen therapy (YANKOT) and NIV support should be used in cases with hypoxemia in which the reservoir oxygen mask is insufficient. In cases where noninvasive methods are used, it is important to avoid causing delayed intubation.

YANKOT and NIV can be applied in cases that do not recover with simple oxygen therapy. In cases of viral infection, there are thoughts that YANKOT may increase transmission through droplets. If YANKOT treatment is to be applied, it will be appropriate to apply it in a negative pressure room. In cases where a negative pressure room is not available, the application should be made in an area where appropriate insulation is provided.

In Covid-19 cases requiring endotracheal intubation, the contamination risk of intubation is higher than other intubations. To prevent contamination in endotracheal intubation, the number of personnel in the room should be kept to a minimum and full personal protective equipment should be used at all times. Intubation should be performed in a single attempt by the most experienced staff in the clinic, using a videoryngoscope if possible. One of the most important factors determining the prognosis of patients who underwent IMV due to Covid-19 pneumonia and ARDS is the effective and correctly applied mechanical ventilation strategy. Providing the patient with appropriate oxygenation and protecting the lung from damage due to the ventilator should form the basis of the mechanical ventilation strategy. There is no mechanical ventilation method that has been shown to be superior for Covid-19 cases. Mechanical ventilation to patients can be pressure or volume targeted. Appropriate mode is the mechanical ventilation mode in which the team is experienced. Oxygenation and ventilation goals may differ depending on the severity of the patient's clinic. Mechanical ventilation strategy, in which we provide adequate lung-protective ventilation, can reduce mortality and morbidity.

5. Protectıon and Precautıon

We know that the Covid-19 virus is transmitted through droplets and contact. Especially in the last period, due to the removal of restrictions and the transition of schools to face-to-face education, there has been an increase in child cases. In a study, it was shown that the virus can survive on different surfaces for a long time (34). It should not be forgotten that effective and sufficient hand

washing or providing hand hygiene with alcohol-based disinfectants are of vital importance in terms of society or health service delivery. In terms of protection and prevention, allocating social distance between people, providing appropriate hygiene during the symptoms of the disease, and ensuring the use of masks can be said as protection recommendations (35). Considering the contact with the patient and the service provided in health institutions, necessary and appropriate personal protective equipment should be used in terms of droplet and contact isolation. As a result, Covid-19 infection seems to be mild in the pediatric age group. It should be noted that severe clinical conditions may develop in children with chronic disease, malignancy or immunosuppression. For this, more care should be taken to protect children with risk factors. It should not be forgotten that the disease, which is asymptomatic or has a mild course, plays an important role in the spread of the virus when the necessary isolation measures are not followed, and the necessary protective measures in the community should be taken into consideration.

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CHAPTER XIII

MICROANATOMIC EFFECTS OF COVID-19 ON THE RETINA LAYER

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1. Introduction

1.1. Occurrence of COVID-19 (SARS-CoV-2)

On December 31, 2019, the World Health Organization (WHO) reported cases of pneumonia of unknown origin in Wuhan, China, and research on this issue began as of January 2020. (1) With the help of lung imaging and laboratory investigations, the clinical data revealed that this was a viral pneumonia. (2) On December 30, 2019, SARS-CoV-2 was recovered from the bronchoalveolar lavage (BAL) of three coronavirus COVID-19 patients at Wuhan Jinyintan Hospital. (1)

1.2. Characteristics of Coronaviruses

Coronaviruses belong to one of the two Coronaviridae subfamilies. There are four genera in the coronavirus family: alphaCoV, betaCoV, gammaCoV, and deltaCoV.(3) In humans, alpha and betaCoV cause disease, while gamma and deltaCoV cause disease in animals. There are currently seven coronavirus types in the alpha and beta groups that are known to be human pathogens. (4,5) HCoV-229E and HCoV-NL63 are two alpha coronaviruses. HCoV-HKU1, HCoV-OC43, MERS-CoV, SARS-CoV, and SARS-CoV-2 are beta coronaviruses. SARS-CoV-2 is a member of the Sarbecoronavirus subgenus of beta coronaviruses. (6)

Coronaviruses are the largest enclosed, single-stranded, positive polarity RNA viruses with spike proteins on their surface. Because its appearance in electron microscopy resembles the corona of the sun's rays, it was given the

name coronavirus. (7) Five structural proteins are encoded by Coronavirus RNA.Spike protein (S), membrane protein (M), nucleocapsid protein (N), hemagglutinin-esterase (HE), and envelope proteins (E) are examples of these proteins. (8)

S proteins allow fusion with the host cell membrane and receptor binding. Cytotoxic T cells and key antigen structures that trigger neutralizing antigens are also targets. (9) S glycoproteins form homotrimers, and their protrusions connect with ACE-2 receptors, allowing them to bind to the host cell. (10)

1.3. Serotypes of Coronaviruses

Coronaviruses are mostly found in animals. They cause moderate respiratory infections in people, which manifest as cold symptoms. In the neonatal, pediatric, and elderly populations, however, there are some exceptions. (11)

Coronaviruses are zoonotic viruses found in bats, birds, cats, dogs, pigs, horses, and mice, among other animals. Three coronaviruses caused deadly pneumonia by the turn of the century. These are SARS Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). Bats are the natural hosts of SARS-CoV, MERS-CoV, and SARS-CoV-2, which all cause severe acute respiratory syndrome. It is hypothesized that the novel coronavirus spread from animals to people via an intermediary host. These intermediate hosts could be mammals or birds, according to certain theories. The SARS-CoV-2 genome was shown to be linked to the bat CoV-RaTG13 virus. The new coronavirus 2019 is a virus that infects people and may have originated in bats, reaching humans through intermediate hosts. SARS-CoV and SARS-CoV-2 use ACE-2 as a receptor, whereas MERS-CoV uses dipeptidyl peptidase-4. (12)

1.4. Pathophysiology of COVID-19

1.4.1. Binding of the SARS-CoV-2 Virus

The ACE-2 receptor is used by SARS-CoV and SARS-CoV-2. (12) The ACE-2 receptor can be located on the surface of cells in a variety of organs. It can be present in the lungs, heart, small intestines, and kidneys, among other places. (13) The ACE-2 receptor is SARS-target CoV-2's receptor. This binding is the first stage in the viral infection process. They are SARS-CoV-2 spike proteins that bind to the human ACE-2 receptor (hACE2). ACE-2 is recognized by the receptor-binding site on spike proteins. There is a core and a receptor-binding

motif in this area (RBM). For virus binding, ACE-2 includes two virus binding sites. In comparison to SARS-CoV, the RBM of SARS-CoV-2 generates a larger binding surface with the ACE-2 receptor. Furthermore, when SARS-CoV-2 is compared to SARS-CoV, ACE-2 viral binding sites, SARS-CoV-2 is found to be more powerful. (14)

1.4.2. Humoral Immunity

Antibody synthesis helps to keep the disease at bay and protects against re-infection. Antibodies against SARS-CoV-2 are generated in 12 weeks, while antibodies against immunoglobulin G (IgG) take longer. SARS-CoV-2 also stimulates the development of memory cells (CD4+T and CD8), but the formation of these can take up to four years. (10)

Immune cells gather in the lungs when the immune system is compromised, and a big amount of pro-inflammatory chemical cytokine is released. It harms the lung structure in this scenario. Cytokine storm is the term for uncontrolled and excessive cytokine release in COVID-19. (15) Diffuse alveolar damage, hyaline membrane development, pulmonary edema, and numerous organ damage ensue as a result of the cytokine storm and direct virus damage. (16,17) If the immune system is healthy, virus-specific T-cells travel to the infection site during the initial inflammation and kill virus-infected cells. Macrophages identify apoptotic cells with antibodies produced by the cells, and phagocytosis eliminates them. (18)

1.4.3. The Pathogenesis of COVID-19

SARS-target CoV-2's receptor, ACE-2, is predominantly present in the lungs and small intestines, and is expressed in critical organ endothelial cells and smooth muscle cells. As a result, not only the respiratory system, but also the central nervous system, circulatory system, and gastrointestinal system are involved. (19)

Type 2 pneumocyte involvement is linked to respiratory system involvement. When the lungs are involved, cough, shortness of breath, and fever are common symptoms. On radiology, there are bilateral ground-glass zones and consolidation. (20) In the intra-alveolar areas, histopathology shows interstitial mononuclear infiltrates dominated by lymphocytes and multinucleated and highly enlarged pneumocytes. There may be pulmonary edema, diffuse alveolar injury, and hyaline membrane development. (21)

Although not every patient may experience symptoms such as nausea, vomiting, diarrhea, or abdominal discomfort, gastrointestinal system involvement can produce these symptoms. After consuming an animal infected with SARS-CoV-2, intestinal epithelial cells come in direct touch with the exogenous pathogen and will be the first to be affected. Since SARS-CoV-2 nucleic acids have been found in patient stools, the theory that gastrointestinal transmission is a possible pathway has been strengthened. (19) The virus's attachment to the ACE-2 receptor in cholangiocytes is most likely the cause of liver involvement. COVID-19 patients may acquire elevated liver enzymes as a result of immune-related damage, direct hepatocyte involvement, and therapy medications. (22)

The virus spreads through infected nerve terminals, resulting in central nervous system involvement. The olfactory cavity in the nasal mucosa serves as a conduit for the virus's propagation to the brain. In addition, cytokines generated by glial cells harm the central nervous system. Some patients have headaches and seizures. Respiratory failure may occur if the brain stem is involved. After lung involvement, hypoxia can lead to interstitial edema, congestion, and coma. Except for SARS-CoV-2, which induces myocardial damage with hypoxia and respiratory failure, cardiovascular system involvement has been attributed to myocardial involvement through three separate mechanisms first is the virus's direct myocardial damage, the second is the cytokine storm, and the third is myocardial damage caused by the ACE-2 receptor activating signaling pathways. (20)

1.5. Clinical Manifestations of COVID-19

COVID-19 has a wide range of symptoms, from asymptomatic to acute respiratory distress syndrome (ARDS) and multi-organ failure. Fever, cough, sore throat, headache, weariness, arthralgia, myalgia, and shortness of breath are all common symptoms. In addition to this, conjunctivitis can be seen. As a result, they are difficult to distinguish from other respiratory infections. (23) Other symptoms include loss of smell and taste, sore throat, runny nose, hemoptysis, stomach pain, nausea, vomiting, and diarrhea. (24)

Approximately 80% of COVID-19 patients are asymptomatic or have mild to moderate disease, according to WHO data. In 15% of patients, severe illness and oxygen demand occur, whereas 5% of patients suffer sepsis, septic shock, ARDS, acute renal failure, and multi-organ failure. (25) On average, symptoms appear 5-6 days after exposure to virüs. (26)

1.6. Diagnosis and Laboratory Tests in COVID-19

Other than SARS, laboratory tests are not commonly utilized to diagnose coronavirus infections. The detection of viral RNA in respiratory tract samples using the Real Time Polymerase Chain Reaction (PT-PCR) method is the recommended method for diagnosing coronaviruses, including SARS-CoV. The ELISA method can be used to investigate serum samples serologically. In stool samples, electron microscopy can be utilized to detect coronavirus-like particles. (27)

1.6.1. RT-PCR Test

SARS-CoV-2 is an enclosed virus with single-stranded RNA as its genetic material. The two main types of laboratory diagnostic tests used in COVID-19 infection are nucleic acid hybridization-related techniques, the first of which is based on the detection of SARS-CoV-2 viral RNA by reverse transcriptase polymerase chain reaction (PCR) during the acute infection phase, and serological-immunological techniques based on the detection of IgM and IgG antibodies or antigenic proteins in the subacute recovery period in individuals. The RT-PCR technique, which detects viral nucleic acid, is considered the gold standard for detecting the SARS-CoV-2 virus. It is a molecular technique that involves multiplying extremely small amounts of viral genetic material to detectable levels in a nasopharyngeal swab sample (studies have also used serum, stool, and ocular secretions). The majority of SARS-CoV-2 genomic areas linked with nucleocapsid, spike protein, RNA-dependent RNA polymerase, or envelope proteins are targeted by PCR-based molecular diagnostic procedures. (28) In recent years, breakthroughs in the molecular detection of the viral genome by replicating it have led to the discovery of HMPV, endemic coronaviruses, HBoV, SARS(2003), MERS (2012), and SARS-CoV-2 virus. COVID-19 currently lacks an effective and safe treatment.

1.7. Coronavirus Treatment Approach

There is no proven effective and safe treatment for COVID-19 yet. As a result, supportive and symptomatic therapies are used.

1.7.1. Treatments for Coagulation in COVID-19

In COVID-19, coagulation abnormalities are caused by a variety of causes. (29,30) Endothelial damage caused by attaching directly to the ACE-2 receptor

or indirectly triggering the immune system (31,32), and microthrombus production are examples. (33) Increased cytokines, active platelets, endothelium, and complement system cause significant coagulopathy, which gets more pronounced as the severity of the disease grows. (33)

With ACE-2 receptors expressed in the airway epithelium, SARS-CoV-2 enters the cell. (34,35) Type 2 pneumocytes are triggered in this situation, causing diffuse alveolar injury, hyaline membrane development, and fibrin storage. All of these modifications are ARDS-friendly. Also, intravascular fibrin deposition, angiogenesis, perivascular monocyte infiltration, and microthrombus development can be seen. (36,37) SARS-CoV-2 promotes inflammation in pulmonary endothelial cells either directly or indirectly by stimulating host immunity via ACE-2 receptors on endothelial cells. (31,32) In an autopsy study of patients who died from COVID-19 and H1N1-related respiratory failure, it was discovered that severe endothelial damage, alveolar capillary microthrombi, the amount of new vessel growth, and microvascular changes were more common in COVID-19-related lungs than in H1N1-related lungs. (31) SARS-CoV-2 can cause thrombotic consequences in the kidney, liver, brain, and heart because the ACE-2 receptor is located in all of these organs. (35,38,39) In autopsy series, it is known that venous thromboembolism occurs at a rate of 50%. (36) Furthermore, when pathological abnormalities in autopsy series are evaluated, typical pulmonary embolism and immunothrombosis are found to be present.

1.8. Endothelial Dysfunction and Hemostasis

Endothelial cells border blood arteries and serve as a mechanical barrier between the blood and the basement membrane. It also regulates vascular tone and immunity. (40) Reduced endothelium-dependent vasodilation and endothelial activation occur alongside endothelial dysfunction, resulting in proinflammatory, procoagulant, and proliferative phases. (41) It causes increased vasoconstriction, followed by organ ischemia, tissue edema, and a procoagulant condition. (42)

COVID-19 has a more severe clinical course in patients with endothelial dysfunction, such as hypertension and diabetes. Endothelial dysfunction has two different mechanisms. The first mechanism is SARS-direct CoV-2's invasion of endothelial cells, whereas the second is the indirect formation of an inflammatory process. (18,31) After the SARS-CoV-2 spike protein attaches to the ACE-2 receptor, viral endocytosis and replication occur. After viral release and endothelial damage, an immune response begins, and the endothelium emerges.

2. Eyeball

The bulbus oculi is a spherical structure in the orbit that develops embryonically from the prosencephalon. It is a spherical structure which is roughly 2.5 cm in diameter and weighs 7 grams. From outside to inside, it has three layers: tunica fibrosa bulbi, tunica vasculosa bulbi, and tunica nervosa bulbi (retina). (43-45)

2.1. Fibrous tunic

It is responsible for the bulbus oculi's morphology by forming the tough outer layer. There are two sections to this layer, which is an extension of the dura mater. The cornea is clear in the front 1/6th of the eye, and the sclera is opaque in the back 5/6th.

2.2. Vascular tunic

It is a layer of the eye that is densely packed with blood vessels and pigments. From front to back, it consists of the iris, corpus ciliare, and choroidea. (46,47)

2.3. Nervous tunic (Retina)

It is a thin, translucent layer found in the eye's interior region. The outer pars pigmentosa and the inner pars nervosa make up this structure. The choroidea is in contact with its outer surface, while the membrana vitrea is in contact with its inner surface (hyaloid membrane). (46)

2.3.1. Retinal embryology

The retina is generated via invagination from the neural ectoderm, which is embryologically distinct from the optic vesicle's inner and outer layers. (48,49) It is made up of the optic vesicle's inner layer, the multilayered neurosensory retinal layer, and the RPE layer's outer layer, which is made up of a single row of hexagonal cells. (49,50) In the ora serrata, the neurosensory layer transitions to non-pigmented ciliary body cells, whereas the RPE layer transitions to pigmented ciliary epithelial cells. (50)

2.3.2. Retinal Anatomy

Many anatomists consider the retina to be an extension of the brain because it contains receptors, ganglion cells, glial support cells, and axons. The RNFL is comparable to the gray matter layer in the brain, with changes in thickness

occurring only when axons are damaged. When seen from this perspective, it is widely acknowledged that the retina is a traceable portion of the brain. (51)

The pars optica retina and the pars caeca retina are the two components of the retina. (46) The macula lutea is a yellow pigmented oval area with a diameter of 2-4 mm in the posterior section of the retina where the axis opticus passes, and the depression here is called the fovea centralis. This is where light is best perceived on the retina. The optic nerve is linked to the discus nervi optici, which is located 3 mm on the nasal side of this location. The excavatio disci is a depression in the middle of the discus nervi optici through which the arteria and vena centralis retina travel. This area is termed a blind spot because it lacks light-sensitive cells. The retina, which is sensitive to light, is 0.56 mm thick in the posterior region of the eye and thins to 0.1 mm as it approaches the ora serrata. (43)

2.3.3. Retinal Histology

The retina is bordered on the outside by the retinal pigment epithelium (RPE) and on the inside by the vitreous cortex (50). The retina is divided into ten layers from the choroidea to the corpus vitreum, as observed in histological sections (43-45). The following are the layers:

1. Stratum pigmentosum (Retinal pigment epithelial layer) (RPE): Stratum pigmentosum (Retinal pigment epithelial layer) (RPE) is positioned between the choroidea and neural retina layers. (48) Because of the melanin granules in their structure, they absorb light dispersion. (52)
2. Stratum nervosum (Photoreceptor layer) (Jacob's membrane): It contains light-sensitive cone and bacillus (rod) cells. (43,48) The perception of colorless light in the dark is enabled by around 110-125 million bacillus cells, while the sense of colors in the light is provided by approximately 7 million cone cells. (43)
3. Stratum limitans externum (External limiting membrane): This membrane is made up of cytoplasmic extensions of surrounding photoreceptors and Müller support cells, rather than being a genuine membrane. (48) The photoreceptor cone and bacillus cells travel through this layer. (43)
4. Photoreceptor nuclei make up the stratum nucleare externum (outer nuclear layer). (48) Some of the cells' outer extensions are linked to bacillus cells,

while others are linked to cone cells. Its inner extensions connect to the stratum nucleare internum's outer extensions of cells. (43)

5. External plexiform layer (Stratum plexiforme): In the outer and inner nuclear layers, it has a dense network of cell extensions. (43) It is on this layer that the retina's initial synapse occurs. Photoreceptor synaptic extensions form horizontal and bipolar intercellular synapses. Because the axons of the cone and bacillus cells are longer and oblique in the fovea, the outer plexiform layer of the macula lutea is thicker and more fibrous. (48)
6. The nuclei of bipolar cells, Müller cells, horizontal and amacrine cells are situated in the Stratum Nucleare Internum (Inner Nuclear Layer). (43,48)
7. Stratum plexiforme internum (Inner plexiform layer): This layer contains bipolar and amacrine cell axons as well as ganglion cell connections. (48)
8. The second neurons of the visual pathway are formed by the stratum ganglionicum (Ganglion cell layer), which is made up of the nuclei of ganglion cells. This layer is composed of multipolar cells and its dendrites synapse with bipolar cell axons and amacrine cells. The number of ganglion layers increases from the periphery to the macular lutea, decreases again towards the fovea and completely disappears in the fovea. (53)
9. Stratum neurofibrarum (Retina Nerve fiber layer) (RNFL): This layer, which is formed by axons of ganglion cells, astrocytes, extensions of Müller cells and retinal vessels, is composed of unmyelinated fibers. The thickness of this layer, which is thin in the ora serrata, increases towards the discus nervi optici. It subsequently passes through the sclera's lamina cribrosa and is encased in a myelin sheath before continuing as the optic nerve. (43,54) According to the areas, the nerve fiber layer in the retina is distributed in a specific order. The maculapapillary bundle is formed when fibers extending from the macula lutea enter the discus nervi optici straight. While fibers from the nasal half of the retina reach the discus nervi optici directly, fibers from the temporal half of the retina circulate in an arc around the maculapapillary bundle from above and below. (55-58)
10. Stratum limitans internum (Internal limiting membrane) (ILM): This layer, which is not a true membrane, has a thin and perforated structure consisting of extensions of Müller cells and their adhesion to the basal lamina. It allows the corpus vitreum to separate from the retina. (43,59) (Figure 1).

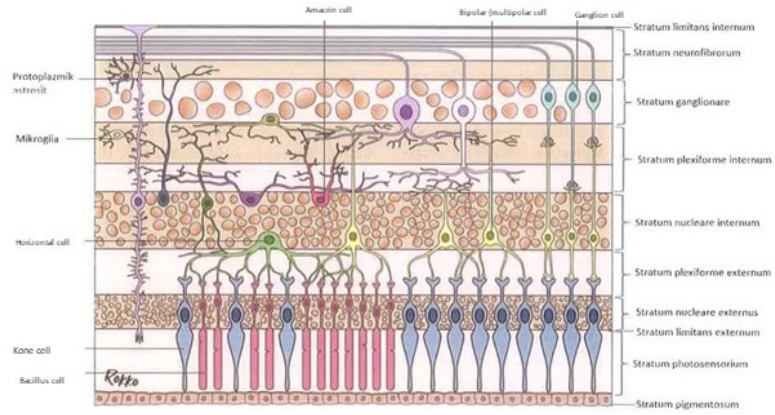

Figure 1. Histological structure of retinal layers (60)

2.3.4. Macula Lutea

The macula lutea is an oval field with an average diameter of 6 mm, consisting of two or more layers of ganglion cells, located between the temporal vessels. (43,61) The macular lutea develops a yellow tint due to the buildup of oxygenated carotenoids, particularly lutein and zeaxanthin. Macula lutea is also known as yellow spot because of this. (61) The fovea centralis is 4 mm posterior to the discus nervi optici, 0.8 mm inferior, and 1.5 mm in the macula lutea's central region. The cone cells that provide color vision in the light are concentrated in this location. (43,61) The foveola is a hollow, avascular structure in the center of the fovea centralis with a diameter of 0.33 mm and a thickness of 0.15 mm, where only cone cells are found. (43) The nicest aspect of the light is the foveola. (43,61) The umbo, which has a diameter of 0.15mm-0.2mm and is located in the center of the foveola, is the portion of the retina that offers the finest vision. The parafovea is the 0.5 mm wide annular area around the fovea, and the perifovea is the 1.5 mm wide annular area surrounding the parafovea. (61)

2.3.5. Optic Disc (Optical Nerve Head) (ONH)

The optic disc, also known as the optic nerve head (ONH), or the optic papilla, was named for the first time by William Briggs. The intraocular surface of the scleral canal via which retinal ganglion cell axons exit the eye is known as the Discus nervi optici. (62) It is in the macula lutea's 3mm nasal section, where the optic nerve attaches. (43) The axons of retinal ganglion cells are gathered in the optic nerve canal to form it. (62) It is also known as the blind spot since there are no photosensitive cells in this area. In the midst of the trench where the retina travels, the arteria and venae centralis is called excavatio disci. (43)

2.3.6. Retinal Veins

Separating from a.carotis interna, a.ophtalmica travels through the outer side of n.opticus in canalis opticus, crosses the optic nerve from above, passes to the inner side, and splits off. The retina is fed by the a.centalis retina branch. The A.centralis retina penetrates the n.opticus 8–15mm behind the bulbus oculi, passes through it, and expands towards the bulbus oculi, as well as passing through the lamina cribrosa and dividing into branches in the retina. (63) The a.centalis retina separates into superior veinferior papillary branches after exiting the optic disc, which subsequently divide into temporal and nasal branches. A.temporalis retina superior, A.temporalis retina inferior, A.nasalis retina superior, A.nasalis retina inferior are the branches of A.centralis retina. (64) The temporal portion of the brain receives more blood than the nasal part. In the retina, there are two distinct circulatory systems. The outer plexiform, outer nuclear layers, photoreceptors, and pigment epithelium of the retina are nourished by the choroid circulation, whereas the inner two-thirds are fed by the arteria centralis retina. (48) Except at the capillary level, the retinal arteries are end-artery without anastomosis. (63) Because it lacks anastomosis, it causes retinal necrosis and permanent vision loss if blood flow is disrupted. (47) Usually, venous drainage of the retina follows artery branching. (64) (Figure 2).

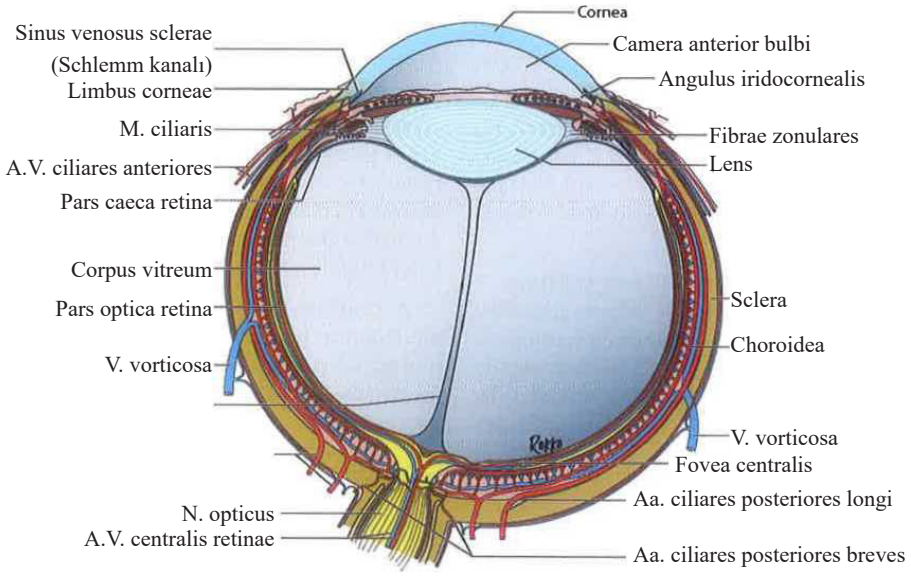

Figure 2. eyeball layers and veins (60)

3. COVID-19 and Retina

SARs CoV-2 is a highly pathogenic human coronavirus that can cause serious life-threatening respiratory diseases such as severe pneumonia,(65) and even multiple organ failure. (15,66) (67,68) Although fever and respiratory symptoms are the most common symptoms in COVID-19 patients, research have revealed that it can influence the cardiovascular, neurological, gastrointestinal, taste, liver, renal, olfaction, hematological, cutaneous, and ophthalmic systems, as well as other organs. (69) Despite growing awareness of COVID-19's deadly implications and diverse clinical signs, reports of ocular manifestations are rare. (67,68) The ocular signs of COVID-19 infection were not fully characterized at the start of the pandemic, and numerous investigations reported ocular surface problems. (70,71) Although the rate of eye involvement in COVID-19 appears to be modest, conjunctivitis is the most common symptom. The most prevalent symptoms are conjunctival hyperemia, chemosis, increased secretions, and blepharitis. (70-74) Furthermore, Insausti-Garcia et al. described a case of papillophlebitis linked to SARS-CoV-2 (75). COVID-19 ocular signs are generally described as anterior segment diseases with conjunctival congestion, while retinal findings have only been seen in a few cases. (70,76)

China, which has the most expertise as the COVID-19 pandemic's genesis, has classified ocular symptoms into five categories. Conjunctivitis is the first of these symptoms in COVID-19, which is comparable to other viral infections. In China's first large COVID-19 epidemiological investigation, 9 instances of conjunctivitis were discovered among 1,099 patients. (2) The prevalence of conjunctival discharge, epiphora, itching, foreign body sensation, and dry eye symptoms ranged from 0.5 percent to 32 percent, according to the same study. (70) Cotton wool spots (CWSs) were found in four patients in a case study, indicating retinal lesions and neurological symptoms by exhibiting microhemorrhages. (77) The second symptom is that the ocular symptoms are abnormal, for the first and only time. (78) Third, SARS-CoV-2 does not transmit from person to person through the eyes. (79) The nasolacrimal system's structure creates a channel for the virus to move through, setting the stage for ocular symptoms. (80) The ocular surface and tears, on the other hand, are possible SARS-CoV-2 colonization sites. SARS-CoV-2 binds to the ACE-2 cellular receptor and interacts with the transmembrane protease serine 2 (TMPRSS2) to gain access to the cornea, retina, and conjunctival epithelium of the human host cell. (34)

Although retinal involvement was uncommon in people who had active COVID-19 infection at the start of the pandemic, minor retinopathy symptoms

have been reported on occasion. (77) Landecho et al. found that 6 of 27 asymptomatic COVID-19 patients had CWSs (81). In research conducted in patients with COVID-19 infection, retinal microangiopathy was later identified as demonstrated by CWSs. (81) Patients hospitalized with severe COVID-19 have immediate vascular lesions such as CWSs, retinal hemorrhages, and sectoral retinal infarction, according to recent investigations. (82) They discovered SARS-CoV-2 virus RNA in the retinas of patients who died from COVID-19 in an autopsy examination. (83) In addition to the retinal damage produced by SARS-direct CoV-2's action, the prothrombotic state documented in critically ill individuals with COVID-19 has revealed that it can cause retinal injury. (38,84) Retinal involvement was observed in a study of mild-to-moderate patients who were later diagnosed with COVID-19, and optical coherence tomography (OCT) indicated hyperreflective lesions at the level of ganglion cells and inner plexiform layers. (77) Marinho et al. looked at the OCT data of 12 COVID-19 patients and found focal hyper-reflective regions in the inner retina in all of them, as well as retinal microhemorrhages and CWSs in four of them. (77) Later, Vavvas et al. pointed out that while the hyper-reflective patches shown on OCT are most likely normal retinal arteries, the presence of CWSs could indicate another disease process or a discrete area of myelinated nerve fibers. (85) Vigo and Mohamed discovered acute macular neuroretinopathy and paracentral acute mild maculopathy in two instances after SARS-CoV-2 infection in their study. (86)

The primary receptor for SARS-CoV-2, ACE-2 (87), is located in type II alveolar cell membranes in the lungs, enterocytes in the small intestine, arterial and venous endothelial cells, and arterial smooth muscle cells in most organs. (32,88) Different types of retinal cells, such as vemullar cells, ganglion cells, retinal vascular endothelial cells, and photoreceptor cells in the choroid, include ACE and ACE 2 receptors. (89) COVID-19 infects the host via binding to the ACE-2 receptor, which is found in many organs, including the retinal endothelial cells. (90) COVID-19 has been found to affect endothelium cells in the lungs, heart, kidney, colon, and brain, and histopathological studies have revealed that direct viral infection of endothelial cells causes endothelial and vasculitis in both arterial and venous circulations. (39,91)

Edema, blockage, and thrombosis in tiny arteries originate from endothelial cell inflammation, which leads to organ ischemia. These data show that COVID-19 is a systemic illness affecting several organs, with direct viral invasions as well as immune-mediated inflammation resulting in tissue ischemia and

microvascular dysfunction. COVID-19 viral RNA was also found in the retinas of patients who were infected. (83) COVID-19 could cause retinal vasculitis and ischemia, according to this report. Intraretinal hyper-reflectivity in OCT has been linked to acute retinal ischemia, while hyper-reflective patches in the inner retina have been linked to superficial capillary ischemia. (92) Although viral infection is a rare cause of retinitis, it has been reported in the past. Occlusive retinal vasculitis is caused by Western Nile virus infection in eight cases and coxsackievirus A4 virus infection in one case, according to research. (93,94) Later investigations used OCT to show focused hyper-reflective areas in the inner retina. The findings suggests that COVID-19 has an effect on the retina. Patients at high risk of retinopathy, such as those with diabetes and hypertension, should be aware of this possibility. Diabetes and hypertension are also included as two of the most significant COVID-19 hazards. For their potential impacts and therapeutic significance, prospective trials in patients with COVID-19 and previously diagnosed retinopathy are particularly important. Given the scope of the present epidemic, as well as the major obstacles in terms of diagnosis and treatment, greater reporting of clinically significant ocular symptoms is critical. It is clear that follow-up testing and retinal examination are required after recovery from COVID-19 to further investigate the possibility of retinal involvement. (95) In a study conducted in patients with COVID-19, it was shown that the superficial and deep retinal capillary plexus vessel density in the foveal and parafoveal regions was significantly lower than in the control group. (96) Savastano et al. observed decreased perfusion density in the radial peripapillary capillary plexus in COVID-19 patients who recovered in OCT angiography. (97) Pathoanatomical anomalies in these ocular tissues are likely due to the presence of ACE-2 receptors in the various layers of the retina and choroid. The necessity of retinal vascular assessment in this disease is highlighted by reports of microvascular injury and thrombosis in patients with severe COVID-19 infection. (98)

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CHAPTER XIV

THE EFFECT OF COVID-19 ON THE REGIO OLFACTORY ANATOMY AND ANOSMIA

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1. Introduction

Epidemics are one of the most important disasters that affect humanity (smallpox, plague, AIDS, bird flu, swine flu, etc.). Humanity has been exposed to two serious coronavirus infections [Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS)] for two centuries. Recently, risky coronaviruses symptoms have started to appear that can cause acute respiratory distress syndrome and potentially lead to reduced lung function or death. (1) The COVID-19 outbreak was first seen in December 2019 in Wuhan, China. The disease was caused by a novel coronavirus of potential bat origin, and the viral genome was rapidly characterised. (2) The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped virus from the Coronaviridae family with a single-stranded RNA genome. (3) SARS-CoV-2 has been recognized as this century's causative agent of the coronavirus (COVID-19) epidemic. The disease quickly spread to Asian and European countries than to African, North, and South American countries. (4) To date (early March 2022), COVID-19 has affected 207 countries. It has infected around 500 billion people (possibly a more significant number considering infected people who did not undergo proper diagnostic testing), and it is the cause of death of more than 6 million people. (5) The World Health Organization declared the disease a global epidemic on March 11, 2020.

A variety of clinical manifestations characterises COVID-19. (6) Many different symptoms (diarrhea, runny nose, nausea/vomiting, nasal congestion, fever, dry cough, dyspnea), confusion, headache, sore throat, chest pain, conjunctival congestion, sputum production, fatigue (weakness), hemoptysis and chills, muscle pain, etc.) can be seen together in COVID-19 patients. (7) It also ranges from mild colds and respiratory failure to severe pneumonia, typically associated with respiratory infections such as cough and fever. Patients often also experience smell and taste disorders. These consist mainly of reduction or loss of smell (hyposmia and anosmia) and taste (hypogeusia and ageusia). (8) Smell disorders are associated with various viral infections. Upper respiratory tract infection can cause acute onset anosmia due to viral damage to the olfactory epithelium. In addition, since the olfactory nerve is close to the central nervous system, it can mediate many viruses from reaching the brain. (9) In this respect, the olfactory pathways' anatomy, physiology, and physiopathology are important.

2. Olfactory anatomy

The sense of smell involves many non-myelinated fibres (fila olfactory). Olfactory nerves form the 1st neuron of the olfactory pathway. The smell is received by olfactory receptors at the ends of the peripheral extensions of bipolar neurons in the mucosa of the regio olfactory in the nasal cavity and first transported to bipolar neurons. The central extensions of bipolar neurons pass through the holes in the lamina cribrosa in the ethmoid bone and form the bulbus olfactorius located on the lower side of the frontal lobe, on both sides of the crista galli, and synapses in the mitral cells here. (10) Mitral cells in the bulbus olfactorius form the second neuron of this pathway. The central extensions of the mitral cells from the tractus olfactorius, located in the sulcus olfactorius, continue posteriorly (Figure 1).

Some fibres are attached to the anterior olfactory nucleus, located in the olfactory tract. The olfactory tract flattens on the back as it approaches the anterior perforated substance and has a triangular expansion called the olfactory trigone. After the olfactory trigone, the olfactory fibres endfibrestwo extensions, namely lateral stria, and medial stria, at the olfactory center, opposite the olfactory nerve and septal area. (11) Fibers coming to the medial stria start from the anterior olfactory nucleus, pass through the anterior commissure, and terminate in the anterior olfactory nucleus in the opposite olfactory tract. Fragrance information is transferred between the two parpartiesand a connection is established.

The lateral striae extend from the lateral portion of the anterior perforated substance and in the uncus, which is the primary olfactory center in the temporal lobe. Brodmann is transported to area number 34, and odour is perceived. Odour information is also evaluated in the Entorhinal region's Brodmann 28 auxiliary olfactory center.

2.1 The olfactory brain rhinencephalon

In humans, the olfactory brain consists of the olfactory bulb, olfactory tract, olfactory trigone, lateral stria, medial stria, intermedia stria, anterior perforated substance, area piriformis, hippocampus formation, para terminal gyrus, and fornix cerebri. The anterior perforated substance is located between the optic tract and the olfactory trigone. Many fibres from the olfactory trigone come to this region. The hippocampus formation in the temporal lobe (hippocampus, dentate gyrus, alveus, and fimbria of hippocampus) is integral to the limbic system. Also, it helps to create mood and temperament with fibres from the olfactory areas. The intake of fragrant food causes secretions from the salivary glands, and the sense of smell becomes active through the autonomous system. (12)

3. Olfactory physiology

The olfactory sense is acquired in the olfactory region, a unique particular the nasal mucosa, located in the upper part of the nasal cavity. The olfactory region contains many olfactory sensory neurons. The total surface area of this region in humans is 5 cm2 (Figure 1).

In the ceiling of the nasal cavity, the olfactory mucosa contains three cell types: olfactory receptor cells (bipolar neurons), supporting cells, and basal cells. The supporting cells secrete mucus lining the nasal passage. The supporting cells are epithelial cells rich in enzymes that oxidise hydrophobic volatile odours. Therefore, these molecules become less soluble in oil, penetrate the membranes less, and can enter the brainless. Basal cells are the guide to new olfactory receptor cells, which are renewed approximately every two months. (13, 14) Olfactory receptor cells that detect odors are located in the olfactory mucosa in the nose, and then their afferent axon goes to the brain.

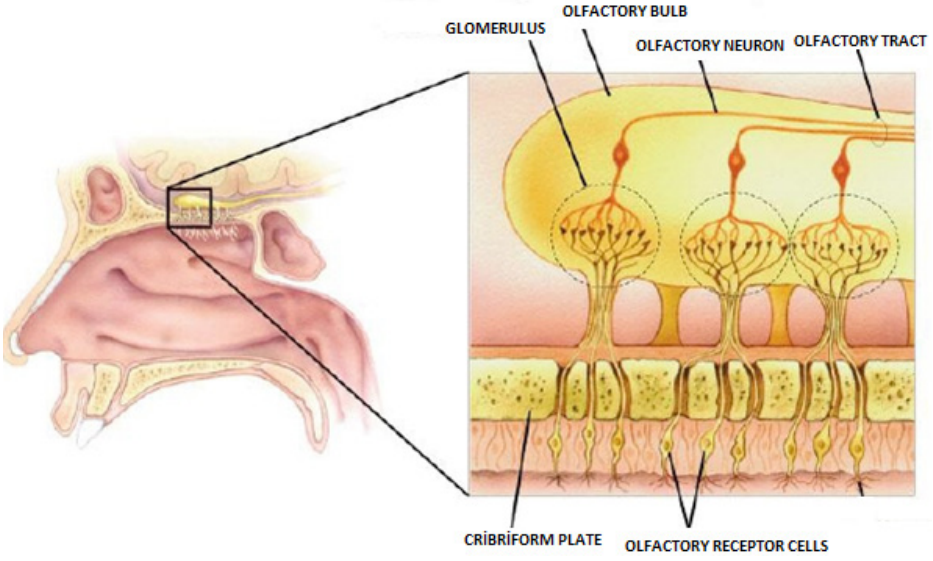

Figure 1. Olfactory anatomy and physiology (15)

The olfactory nerve is formed by the axons of the olfactory receptor cells. These tassel-like cilia contain binding sites for odor molecules. During calm breathing, odors reach the receptors by diffusion, as the olfactory mucosa is above the standard airflow path. The olfactory action amplifies this process by drawing air currents upward within the nasal cavity to allow more aromatic molecules in the air to come into contact with the olfactory mucosa. Fragrances also go to the olfactory mucosa, filtering from the mouth through the pharynx to the nose during meals. To dissolve, a substance must be sufficiently volatile (evaporate easily) to be smelled and adequately water-soluble. (13)

3.1 Olfactory transmission

Olfactory transmission transmits a chemical signal to the central nervous system by converting it into an electrical signal.

The steps in olfactory transmission are as follows:

1- Olfactory molecules bind to olfactory receptor proteins on the cilia.
2- It attaches and activates adenyl cyclase through its g-proteins called golf.
3- In adenyl cyclase, it provides the conversion of ATP.

4- Na+ channels open, and depolarization occurs.
5- The action potential spreads from the axons of the olfactory nerve to the olfactory bulb.

Information from the olfactory bulb goes to the olfactory cortex and other limbic system areas. The only sense that directly connects with the limbic system is the sense of smell. These connections can explain the effects of smell on behavior and emotions. Fragrances can stimulate memories. The olfactory system is the only sensory system that does not have all extensions through the thalamus. (14)

3.1.1 Olfactory perception

The first known rule for forming the olfactory sense and olfactory perception is that when the air enters the nasal cavity during breathing, the olfactory molecules must reach the olfactory area to create the odor stimulus. This is possible in two ways. The first is the (orthonasal) path from the nasal cavity to the regio olfactory with the effect of turbulence of the air entering the nares. Second, air entering the oral cavity passes from the oropharynx to the nasopharynx, reaching the olfactory area retrograde (retronasal) (Figure 2). In the orthonasal pathway, molecules entering the nasal passages are detected by chemical receptors in the nose (like smelling a rose). The retronasal pathway allows us to perceive the aromas in the foods we eat (such as distinguishing the taste of strawberries and bananas). The odor is released into the oropharynx and nasopharynx when chewing food, connecting the throat to the nasal cavity. These chemical molecules reaching the nasal cavity are detected by olfactory receptor cells in the olfactory region. (16) If infectious or tumoral pathologies obstruct the retronasal pathway, the flavors in the food we eat cannot reach the olfactory receptors, and the sense of taste is suppressed. This is why we cannot taste what we eat during sinusitis and other upper respiratory tract infections. Therefore, any factor that causes olfactory disorder also leads to tasting disorder. In COVID-19, many patients report taste disturbance along with smell. Although it is possible for SARS-CoV-2 to target both the olfactory and taste systems, the patient-described taste disturbance is thought to be related more to retronasal olfactory (flavor) deterioration than to taste (sweet, bitter, sour, salty).

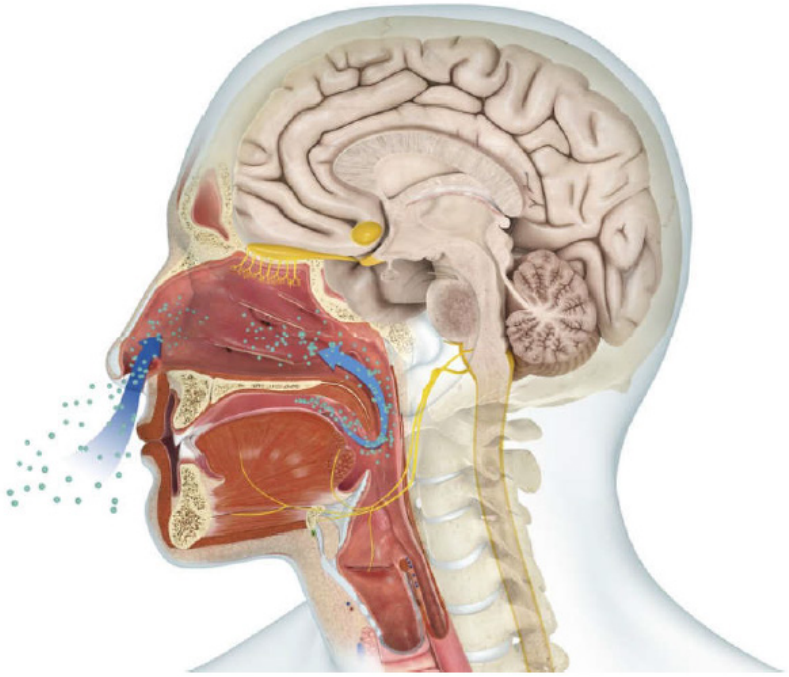

Figure 2. Orthonasal and retronasal olfactory tracts (17)

4. Physiopathology of olfactory loss in COVID-19

Several mechanisms were postulated for the loss of smell due to COVID-19. One is the theory that odor molecules cannot reach the olfactory epithelium due to the development of nasal congestion and rhinorrhea due to the virus. Initially, this theory was thought to cause the loss of smell due to COVID-19. However, many subsequent studies showed that most patients who develop a loss of smell do not have nasal congestion, obstruction, or discharge. (18, 19)

Another mechanism is that the virus infects olfactory sensory neurons and causes damage to these cells. In this scenario, three main inconsistencies are seen. The duration of cellular regeneration does not overlap with the time of clinical recovery, the absence of expression of viral entry proteins in olfactory sensory neuron cells, and the absence of the virus in olfactory neurons. After the olfactory receptor cells die, it takes 8-10 days for new cells to replace them. (20) In addition, the formation of cilia takes five days. (21) However, in many studies, it was observed that the loss of smell usually recovers in less than a week. (22)

Another theory regarding the loss of smell is based on the fact that the virus reaches and then infects the olfactory center in the brain through olfactory cells.

Olfactory neurons, which form a single direct route to the brain by anterograde axonal transport, do not contain entry receptors for the virus to the cell. Animal studies to date have failed to show that olfactory receptor neurons or olfactory bulb neurons are infected with the virus, at least in the first two weeks after infection. (23) In addition, the rapidly developing clinical picture and the fact that symptoms of the central nervous system are observed much less frequently than the symptoms of loss of smell do not comply with this theory.

As of January 2020, angiotensin-converting enzyme 2 (ACE2) is known as the functional receptor of SARS-CoV-2. (24) The fourth and most likely mechanism for olfactory loss is sustentacular cell destruction in the olfactory epithelium. The abundance of ACE2 proteins in sustentacular cells supports this theory. (25) In addition, the fact that these cells' death and regeneration process is much faster than olfactory neurons also supports this theory.

5. Anosmia

Loss of smell in viral upper respiratory tract infections is not new. It emerges in many viral infections due to inflammatory reactions in the nasal mucosa. It may lead to olfactory dysfunction due to rhinorrhea and conchal hypertrophy. The most known agents are rhinovirus, parainfluenza virus, Epstein Barr, and other coronavirus types. (26) However, olfactory dysfunction due to COVID-19 infection differs as it is not associated with rhinorrhea or nasal congestion. After the disease began to spread in Europe, many patients infected with SARS-CoV-2 were observed to experience severe olfactory and taste disturbances without rhinorrhea or nasal congestion. At the beginning of 2019, COVID-19 was not suspected, as some patients did not develop fever, cough, or other systemic symptoms. However, studies found that anosmia was significantly more common among women and younger individuals as time progressed. (9) In addition, organisations such as the American Academy of Otolaryngology-Head and Neck Surgery, the British Society for Otolaryngology and Head and Neck Surgery, and the US Centers for Disease Control and Prevention recommended that sudden onset loss of smell be included in the diagnostic criteria for COVID-19 disease. (27) As a result, the Centers for Disease Control and Prevention added anosmia as one of the six new symptoms of COVID-19 to their advisory pages on April 27, 2020. (28) Although PCR tests are essential for case detection, the presence of loss of smell in asymptomatic and mildly symptomatic individuals is an important factor in detecting cases, directing the patient to PCR testing, and fighting the pandemic.

In early studies, coronavirus 229E was shown to cause hyposmia in humans. (29) It was reported that SARS CoV causes anosmia in the SARS pandemic. (30) However, the loss of smell is seen more frequently in COVID-19 than in SARS-CoV. Anosmia was an initially unknown symptom of SARS-CoV-2 disease. However, it is now accepted by clinicians and society around the world. (3) Yan et al.(31) stated that smell and taste disorders in the United States are seen in COVID-19 patients. Studies conducted in Iran and Italy also reported a similar positive correlation between loss of smell&taste and COVID-19. This led to the argument that loss of smell may be a subclinical marker or a potential early symptom. (32, 33) In the study by Klopfenstein et al.(34), 54 (47%) of 114 COVID-19 patients confirmed by PCR test presented with anosmia. (34) Studies show that patients with anosmia onset may be asymptomatic carriers of SARS-CoV-2 infection. (31, 35) However, more studies are needed as pathological evidence linking COVID-19 infection with anosmia is lacking.

Mukerji and Solomon(36), in their 146 autopsy study examining the olfactory system, found significant acute and chronic inflammation in the olfactory epithelium in 14 cases, microglial activation in 18 points, and red neuron findings in the olfactory bulb in 1 patient. They thought the anosmia in COVID-19 might be related to astrogliosis and microgliosis in the olfactory bulb. Moein et al.(37) presented solid evidence that 59 (98%) of 60 people with COVID-19 exhibited olfactory dysfunction and that this condition was associated with COVID-19 in their study. Beltrán-Corbellini et al.(38) stated that anosmia is more common in patients with COVID-19 than in patients with influenza in a questionnaire survey.

The Mayo Clinic conducted a study to describe and analyse the clinical features of SARS-CoV-2 infection using artificial intelligence with the most advanced in-depth internet database technology available. The study argued that the prevalence of anosmia in COVID-19-positive patients was 28.6 times higher compared to COVID-19-negative patients and that anosmia is one of the earliest manifestations of COVID-19. (39) Google Trends (GT), the most frequently used internet-based search engine worldwide, has been used in medical research in otolaryngology in recent years. (40) During the COVID-19 pandemic, GT associated with olfactory disorders has risen abnormally in many countries. (41) Izquierdo-Dominguez et al.(42) suggested that between 5% and 85% of affected patients lost their sense of smell in international reports about COVID-19.

Menni et al.(43) reported that 59% of COVID-19 cases had anosmia in their study in England. Levinson et al.(44) found anosmia rate was 33% in their

research in Israel. Lechien et al.(45) stated that 79.7% of COVID-19 cases had anosmia in their study of 12 European countries. Kaye et al.(19) analysed 237 patients and found that 73% had anosmia before a diagnosis of COVID-19, and 26.6% had it as the first symptom. They stated that there was some improvement in 27% of the patients in this group, with an average recovery time of 7.2 days. Vaira et al.(46) argued that new information about aspects of viral pathogenesis could be obtained by detecting anosmia in COVID-19 patients.

Galougahi et al.(47) stated that anosmia constitutes 40% of the cases in patients with postviral anosmia in their study. They found that mucosal obstruction, one of the underlying causes, led to the loss of smell. They also stated that in most anosmia cases, the anosmia resolved when the clinical symptoms and occlusion decreased, and permanent anosmia occurred in some patients due to the virus-induced sensory neuronal damage known as postviral olfactory loss. In addition, they noted the mean volume and signal intensity of the olfactory bulb in MR images of patients with isolated sudden-onset anosmia and positive SARS-CoV-2 polymerase chain reaction. (47) Brann et al.(48) suggested that the loss of smell reported by COVID-19 patients was due to infection of the supporting cells, the olfactory epithelium, and the vascular pericytes of the bulb, resulting in altered function of olfactory neurons. They argued that greater involvement of ACE2 receptors might be the basis of long-term olfactory disorders

No approved tests in the literature can evaluate anosmia associated with COVID-19 in children, so it is difficult to assess this finding in children. (49) Parisi et al.(49) showed that approximately 30% of children affected by COVID-19 experience olfactory disorders. Chicco et al.(50) found anosmia in 102 children with COVID-19 at 28.6%. However, the general opinion in studies in the literature is that detecting anosmia in children with COVID-19 is not analytical. (49-51)

Published articles and anecdotal reports suggest that olfactory symptoms resolve in about two weeks. However, the lack of long-term follow-up is unknown to how many patients develop permanent postinfectious loss of smell. The olfactory dysfunction associated with COVID-19 mostly resolves spontaneously, so it does not require specific treatment. However, the medicine may need to be planned if the symptom persists for more than two weeks. While the efficacy of current treatments for COVID-19-related anosmia is unknown, it was thought that therapies targeting postinfectious anosmia could be potentially beneficial for COVID-19.(52)

6. Conclusion

Based on available literature reviews, a high percentage of COVID-19 patients have symptoms of anosmia. (53) But the mechanism of anosmia in COVID-19 cases is unclear, and studies on this continue. (54) With the ACE2 receptor, which is highly expressed in the olfactory epithelium, inflammation in this region may be one of the leading causes of anosmia. Although olfactory neurons do not have ACE2 receptors, inflammation can spread to these cells via supported cells. It can cause anosmia by causing damage to the olfactory bulb and central nervous system. Degeneration of olfactory cilia, olfactory epithelium, odor transmission, and inflammation of the olfactory epithelium, maybe the most important causes of anosmia. (52) In studies, anosmia in COVID-19 cases was mainly seen among women and young individuals. More than 50% of anosmia cases in the literature were associated with dysgeusia and tended to resolve in less than 28 days. (34) Anosmia treatment is only considered if it lasts longer than two weeks. Olfactory exercises, intranasal or oral corticosteroids, and intranasal sodium citrate can treat anosmia. Many new treatment methods, such as tissue engineering and stem cell therapy are under development. (52)

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CHAPTER XV

COVID-19 AND PULMONARY PATHOPHYSIOLOGY

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INTRODUCTION

A new coronavirus (2019-nCoV) from the Coronaviridae family produced an epidemic of pneumonia with unkonown etiologye that first appeared in Wuhan City, China, in December and then spread all across the world. The World Health Organization (WHO) designated the current illness outbreak as coronavirus disease 2019 (COVID-19) in February 2020, and it was classified in March 2020 as a pandemic (1, 2). SARS-CoV-2 is a betacoronavirus that causes COVID-19 affects the lower respiratory tract and appears in people as pneumonia, a condition related to both Middle East respiratory disease (MERS) and severe acute respiratory syndrome (SARS) (3).

Transmission and Clinical Manifestations of COVID-19

Angiotensin converting enzyme 2 (ACE2) receptors, which are primarily expressed by type 2 pneumocytes, allow SARS-CoV-2 to enter human cells (4). The activation of lung-resident dendritic cells, the production of T lymphocytes, and the release of antiviral cytokines into the alveolar septa and interstitial compartments can all occur as a result of SARS-CoV-2 binding to ACE2 receptors, which can also result in acute systemic inflammatory responses (5). COVID-19's clinical manifestation is highly vairable, many individuals with COVID-19 present with modest symptoms, but others go on to have acute respiratory distress syndrome (ARDS) and severe respiratory failure. While there are many other ways in which an infection can manifest, SARS-CoV-2 is mostly spread through aerosolization and frequently manifests as symptoms

like fatigue, malaise, fever, dry cough, dyspnea, headache, and muscle and bone aches. A sore throat, disorientation, nausea, a productive cough, hemoptysis, diarrhea, and chest pain are less frequent symptoms (6). Pneumonia, which is the most common serious clinical manifestation of COVID-19, usually occurs 1-2 weeks after the onset of symptoms, and cough, hypoxemia, fever, dyspnea, and bilateral infiltrates on chest radiographs are evident (7, 8). Reduced oxygen saturation, deteriorating blood gases, multifocal glass floor opacities, or patchy/ segmental consolidation on chest X-ray or computed tomography (CT) are additional indications of pneumonia. Acute renal injury, acute respiratory failure, and multiple organ failure are common in individuals who are getting worse (6, 9, 10). Although many patients have significant arterial hypoxemia, signs of respiratory distress may not be observed. This phenomenon is called 'silent' or 'happy' hypoxemia (11, 12). Although people of all ages and origin are affected, patients with COVID-19 are often adults older than 18 years old and predominantly male, with cases reported worldwide in the pediatric group (13, 14). However, the mortality rate is much higher in the adult group over 65 years of age. Cardiovascular diseases, endocrine diseases, diabetics, respiratory diseases, or immunosuppresed adults are the patient groups most exposed to serious complications of COVID-19 (15). Especially in those with limited lung function reserve, the prognosis is poor.

ACE-2 Receptor and Viral Entry

SARS-CoV-2 is a fairly large enveloped single-stranded RNA virus whose genome encodes approximately 10 proteins (including nucleocapsid/ envelope/ spike proteins/replicase) (16). Four structural proteins make up coronaviruses: nucleocapsid (N), envelope (E), membrane (M), and the spike (S) proteins (17, 18). Spike (S) proteins are the most important part that plays a role in binding and penetration into the host cell through interaction with the functional cellular receptor defined as angiotensin converting enzyme 2 (ACE2) (19). This protein consists of two functional subunits, S1 and S2. S1 is responsible for binding to the host cell receptor. S2 is responsible to fuse the membranes of the host and viral cells (17). The release of viral RNA genome into the cytoplasm; after viral genome replication, genomic RNA creates vesicles that contain virion along with their associated envelope glycoproteins and nucleocapsid proteins. The virus is subsequently released when these vesicles fuse with the plasma membrane (20). The ACE2 receptor on the surface of the host cell is directly contacted by the SARS-CoV-2 spike protein promotes viral entry and reproduction and

downregulating these receptors (21). The entry and attachment processes are then followed by the fusion of the viral membrane and the host cell (22). After fusion occurs, the viral spike protein that binds to ACE-2 undergoes proteolytic cleavage catalyzed by the type II transmembrane serine protease (TMPRSS2) located on the surface of the host cell (23). The spike protein must change its conformation in order for the host and viral membranes to fuse, and TMPRSS2 causes this shift. The internalized virus particle then releases the RNA genome and starts replicating following this spike-mediated fusion process (24).

In general, ACE2 is highly expressed in cardiomyocytes, alveolar vascular endothelial cells, intestinal epithelial cells, epithelial cells, and renal proximal tubular cells (25). ACE2 is also expressed at different levels of the respiratory system, including the bronchi and trachea, the olfactory epithelium, the carotid body, where chemoreceptors sense oxygen (26-28). In humans, type 2 pneumocytes—small, cylindrical alveolar cells that create lung surfactant and serve as stem cells by developing into bigger, flattened type 1 pneumocytes in the event of injury—express the majority of pulmonary ACE2 receptors (26, 29).

Angiotensin 1-7, a physiologically active heptapeptide distinguished by a powerful vasodilator action, is produced by ACE2, and inactivates angiotensin II (AngII) (30). The coronavirus spike protein binds to ACE2, which causes ACE2 to be downregulated and stop producing the vasodilator angiotensin 1-7, while overproduction of the vasoconstrictor AngII. Ang II also acts as a proinflammatory cytokine through angiotensin receptor 1 (AT1R). The Ang II-AT1R axis also activates Nuclear Factor kappa B (NF-κB) and metalloprotease 17 (ADAM17), which stimulate the production of epidermal growth factor receptor (EGFR) ligands and the mature form of tumor necrosis factor-α (TNF-α) (31). In addition, stimulation of ADAM17 also converts the membrane form of interleukin-6 receptor-α (IL-6Rα) to its soluble form (sIL-6Rα), followed by activation of signal transducer and activator of transcription 3 protein (STAT3). Activation of both NF-kB and STAT3 leads to a hyperinflammatory state and increases vascular permeability of the lungs (32).

SARS-CoV-2 has many similarities with the original SARS-CoV. Although SARSCoV-2 and SARS-CoV spike proteins show 76.5% similarity in amino acid sequences, they have a high degree of homology (33, 34). Studies of biochemical interactions and crystal structural analyses revealed that the spike protein of SARS-CoV has a strong affinity for the human ACE2 protein (34). Analysis has revealed that SARS-CoV-2 identifies human ACE2 more well than

SARS-CoV, which boosts SARS- CoV-2's capacity to spread from person to person (35). This resemblance to SARS-CoV is crucial since ACE2 functions as a SARS-CoV receptor both in vitro (36) and in vivo (37). Required for viral replication and host cell invasion.

Pathophysiology of COVID-19

SARS-CoV-2 binding to ACE2, leads to the activation of a number of pathophysiological mechanisms (38). As the virus replicates its own genome, the host's immune system is activated and inflammatory cells are activated with the synthesis of chemokines and cytokines associated with inflammation, as well as dendritic cell maturation (39, 40). But because the viral genome replicates quickly and continuously, the immune system is constantly activated, leading to an out-of-control reaction that kills host cells (41).

Depending on where the infection originated, COVID-19 can be classified into three clinical stages. SARS-CoV-2 that has been ingested by respiratory aerosols become attached to the upper respiratory tract's nasal epithelial cells during the asymptomatic phase. The adult nasal epithelial cells exhibit high expression of ACE-2 receptor, which is the primary host receptor for viral entrance into cells (16, 35). When ciliated cells in conducting airways are infected, the virus reproduces locally and spreads (42, 43). The immune response that is generated during this stage is minimal and lasts for several days. Despite the fact that the viral load is currently low, individuals are highly contagious and nasal swab tests can detect the infection (44). The infection predominantly affects the larger airways' pseudostratified epithelium such as the conducting airways, bronchi, and bronchioles during the mild symptomatic phase. The disease presents with symptoms of fever, dry and cough malaise because the upper respiratory tract is affected. During this phase, a greater immune response occurs, in which CXC motif chemokine ligand 10 (CXCL-10) and interferons (IFN-β and IFN-λ) are released from virus-infected cells (45). Since keratin 5 basal cells are preserved in conductive airways and are progenitor cells of the bronchial epithelium, the epithelium of the conductive airways can easily repair and rescue the infection (46). The deadly third stage occurs in the lung's gas exchange units, where type II alveolar cells that express ACE2 and, to a lesser extent, type I cells are infected. The virus undergoes replication to produce more viral nucleocapsids. Since type II cells are the progenitors of type I cells, their loss causes respiratory failure because it reduces lung surfactant, causes alveolar overflow, and may impair normal repair. Loss of type I and type II cells

also prevents the alveolar fluid from being actively reabsorbable as it should. Following endothelial injury, plasma proteins transude, hyaline membranes develop, and an inflammatory exudate that is indicative of ARDS results (47). At this point, the patient is hypoxic, and radiographic images show dispersed subpleural ground glass densities. Active alveolar fluid resorption involves both cell types (48, 49). The composition and deterioration of the biophysical properties of the surfactant lead to higher surface tension, causing alveolar overflow in the diseased parts of the lung (50-52).

Pathophysiology of COVID-19 Lung Injury

Direct viral injury to the lung as well as a host defense mechanism with thrombotic and inflammatory reactions are all part of the pathogenesis of COVID-19 lung injury (53). In general, viral cytopathic-like alterations with viral particle presence and inflammatory cell infiltration are the main clinical symptoms in lung tissue. Therefore, both direct viral infection and increased immunological activation are thought to be responsible for significant lung injury in COVID-19 individuals. The ACE-2 enzyme, which the virus binds to and then internalizes with the membrane-bound ACE-2 receptor, is expressed by the vascular endothelium and the alveolar epithelium. As a result, cellular damage, interstitial edema, and alveolar fluid accumulation develop. During the disease's latter phases, the formation of hyaline membranes and diffuse alveolar injury, atypical pneumocyte hyperplasia, alveolar and interstitial edema, fibrinous exudates, alveolar hemorrhage, proteinaceous aggregates, infarction, monocytes and macrophages in the alveolar spaces, macrophages and interstitial inflammatory cell mononuclear damage, endothelial inflammatory cell infiltration and micronuclear damage, endothelial cell damage with dilatation, capillary congestion is seen (54-56). In particular, larger vasculopathy problems are common, including macro- and microthrombosis, vascular dilatation, and abnormal angiogenesis (54, 57).

There are two stages of alveolar involvement in COVID-19 (58). Profound hypoxia, normal compliance, and focused alveolar overflow are characteristics of the early phase, and the late phase resembles classic inflammatory ARDS. Early on, compliance is normal since the majority of the lung is healthy and there is no involvement, and the person is breathing near normal functional residual capacity. Damage to the endothelium and epithelium leads to focal alveolar overflow (59). Overflow may result from a combination of factors such as decreased active transport of sodium into the interstitium from the alveolar

space, death of type II cells, high surface tension, serum proteins leak into the alveolar space, fibrin exudates are produced, and surfactant adsorption to the alveolar surface is interfered. Microvascular leakage and increased transmural microcapillary pressure can both be caused by high alveolar surface tension (52). Infected cells spread the virus, leading to the spread of viral particles into adjacent alveoli. This occurs through the apical surface contact of some type II cells with the alveoli or Kohn pores. Cell-to-cell transmission can occur, as infection of type II cells and infecting adjacent type I cells (46). In addition to damage to type I and type II cells, extensive endothelium damage causing leaking of fibrinogen and other plasma proteins into the alveoli. Consequently, these effects may impair the surfactant's ability to absorb onto the surface and lower the surface tension (60). In the following stage, inflammatory cells and fibroblasts move into the alveolar lumen, and some gas units are lost with appositional atelectasis. Loss of type II cells results in loss of type I cell progenitors. Most lung injuries result in type II cell proliferation, the growth of transitional type II cells, and the differentiation of type II cells into type I cells, which restores the alveolar epithelium (61–63). COVID-19 is characterized by disruption of the endothelium barrier in the lungs, defective oxygen delivery through the alveolar-capillary system, and reduced oxygen diffusion capacity (64).

COVID-19-Associated Pneumonia

SARS-CoV-2 replication and viral cell entry can severely harm endothelium and epithelial tissues, increasing the permeability of protein-rich fluids and causing an accumulation of alveolar and interstitial fluid (65). In this early exudative phase, fibrin deposition, surfactant inactivation, (66) hyaline membrane formation and severe tissue inflammation occurs, the cellular homeostasis, including apoptosis and necrosis, is disturbed, often resulting in "extensive alveolar damage." (65, 67). In addition, proliferation is often triggered by an exacerbated increase of fibroblasts and myofibroblasts, which can facilitate the development of pneumonia (67). However, exudation, proliferation, and pulmonary vasculopathy (due to virus-induced endothelitis, thrombosis, and microangiopathy) are additional symptoms (67) and then lung fibrosis may develop with pulmonary structure's irreversible destruction caused by cytokines such as transforming growth factor-β (TGF-β) (68) and IL-1β (69). Immune cell invasion and activation accompany the linked typical pathophysiological phases of ARDS (exudation-proliferation-fibrosis) boosting the release of

cytokines and mediators that are both pro- and anti-inflammatory. Consolidation and atelectasis decrease pulmonary blood flow, which can lead to pulmonary vascular blockage, hypoxia, shunting and/or increased ventilation-perfusion mismatch, as well as decreased decarboxylation (70). Computed tomography (CT) findings for COVID-19 pneumonia include a wide range abnormalities have been reported in different studies (71, 72). However, in the majority of investigations, multifocal, bilateral, ground-glass opacities with peripheral or posterior distribution, particularly in the lower lobes, are the primary CT features of COVID-19 pneumonia in the early stage and pulmonary consolidation in the late stage (71, 73).

Hypoxemia in COVID-19

Hypoxemia is one of the most important and fatal complications of COVID-19 caused by pulmonary disorders (74). In the hypoxemia seen in COVID-19, some people experience dyspnea, defined as respiratory distress, while others experience a type of hypoxemia called 'silent' or 'happy hypoxemia'. This occurs as a deadly but silent presentation of COVID-19 (75). It refers to a paradoxical condition in which patients do not have dyspnea but have dangerously low oxygen levels (oxygen saturation below 90%) and severe hypoxemia (76). Although their lungs are not effectively oxygenated, patients feel well.

Causes of hypoxemia in COVID-19 include hypoventilation, diffusion disorder, shunt, intravascular microthrombus, and ventilation-perfusion disparity (77). The ventilation/perfusion (V/Q) compliance, often known as the balance between capillary blood flow and pulmonary ventilation, is what essentially determines how well gas exchange functions (78). The most important cause of hypoxemia in COVID-19 is ventilation-perfusion mismatch, which originates from areas of the lung that perfuse blood with limited or no ventilation (79). The persistently high pulmonary blood flow to the unventilated lung alveoli suggests that the small intrapulmonary arteries' natural tendency to constrict during SARS-CoV-2 in response to alveolar hypoxia is disrupted (80, 81). Increased pulmonary edema, loss of surfactant, and increased pressure all contribute to alveolar collapse. Additionally, a sizeable percentage of cardiac output is perfused into unventilated lung tissue, resulting in an intrapulmonary shunt (70). During the progression of the disease, tidal volume increases and resulting in an increase in negative inspiratory intrathoracic pressure. As a result of this and increased lung permeability brought on by inflammation, lung injury, alveolar overflow, and progressive oedema eventually develop (82, 83). Alveolar

collapse, dependent atelectasis, and greater lung heaviness will all develop over time as a result of increased edema, which will cause a steadily rising shunt fraction and further reductions in oxygenation that cannot be fully addressed by raising the oxygen fraction (FiO2).

There are three different forms of hypoxemia that may be present in COVID-19 individuals with widespread pulmonary damage. Hypoxic and hypocapnic respiratory failure is the first major kind of hypoxemia in COVID-19 patients, and it is mostly caused by an elevated ventilation-perfusion mismatch and pulmonary shunt fraction in the damaged lung (58, 84). The second kind of hypoxemia, which is less frequent among COVID-19 patients, is hypoxic and hypercapnic respiratory failure. Even when significant hypoxemia sets up with hypercapnia in healthy people, some COVID-19 individuals don't report any dyspnea symptoms (85). Pure hypoventilation is the third form of hypoxemia, and it affects people who have a normal arteriovenous oxygen gradient (86).

When SARS-CoV-2 infects alveolar type II cells, it releases a huge number of viral particles, which are then quickly destroyed by the immune system (a process known as virus-induced pyroptosis) (87). Dead cells, fibrin and complement activation products make up hyaline membranes, cover the basement membrane as a result of the loss of alveolar epithelial cells and the pro-coagulant state (87, 88). Increased activity and a hyperdynamic pulmonary circulation in COVID-19 may not give red blood cells enough time to normalize their oxygen intake in the absence of increased exercise and hypoxic vasoconstriction. As a result, COVID-19 may have a diffusion constraint that results in a arterial hypoxemia brought on by exercise and a significant P(A-a) O2 gradient (89).

The pathophysiology of COVID-19 is increasingly being characterized by endothelial damage, and the cytopathic virus can infect directly ACE2-expressing capillary endothelial cells of lung (90, 91). When there is an imbalance between fibrinolytic activities and procoagulant due to acute inflammation and endothelial injury, intravascular microthrombus is observed (92, 93). Silent hypoxemia in COVID-19 patients is associated with increased thrombus development in the pulmonary vascular structures (94). Thrombus in the pulmonary vascular system can cause severe hypoxemia and dyspnea is observed due to pulmonary vascular obstruction (95).

COVID-19 and ARDS

It has been reported that lung infection caused by SARS-CoV-2 shows a wide variety of clinical features and most seriously worsens arterial hypoxemia and

eventually leads to ARDS requiring emergency mechanical ventilation (8, 96). ARDS is a life-threatening lung disease that prevents adequate oxygen from the lungs to reach the circulation, responsible for most respiratory disorders and mortality from acute lung injury (97). When the disease is not treated, critically ill SARS-CoV-2 patients may proceed quickly to ARDS, coagulation dysfunction, refractory metabolic acidosis, septic shock and multi-organ failure (98). Cytokine storms, a prominent pathophysiological feature during the course of COVID-19, trigger an uncontrolled systemic inflammation and form the basis of the ARDS mechanism (99). Virus-laden pneumocytes releases many different cytokines and inflammatory markers including interleukins (IL-1, IL-6, IL-8, IL-12 and IL-120), TNF-α, IFN-λ and IFN-β, CXCL10, macrophage inflammatory protein-1α (MIP-1α) and monocyte chemoattractant protein-1 (MCP-1). As a chemoattractant, this "cytokine storm" draws neutrophils, CD8 cytotoxic T cells and CD4 helper T cells, which are subsequently trapped in lung tissue. These cells are responsible for fighting the virus, but as a result of their actions, lung damage and inflammation result. New viral particles are released during the host cell's apoptosis, which then similarly infects nearby type 2 alveolar epithelial cells. Extensive alveolar damage develops as a result of the long-lasting harm brought on by both type 1 and type 2 pneumocytes are lost as a result of these inflammatory cells and virus replication, ultimately leading to ARDS (17, 100). Macrophages also release chemokines and other cytokines responsible for increased capillary permeability and consequent activation of neutrophils (101). Excessive neutrophil degranulation destroys the alveolar-capillary barrier, causing permanent damage to pneumocytes and endothelial cells (102, 103). Acute and widespread inflammatory disruption to the alveolar-capillary barrier, reduced compliance and vascular compliance, poor gas exchange, and hypoxemia are all symptoms of ARDS (104). Diffuse alveolar injury, which is characterized histopathologically by irreversible damage to capillary endothelial cells and alveolar epithelial cells, the creation of hyaline membrane as a result, and finally intracapillary thrombosis (105).

COVID-19 and Cytokine Storm

A "cytokine storm," or aggressive inflammatory response accompanied by the release of a lot of proinflammatory cytokines, is a symptom of severe SARS-CoV-2 infection. Cytokine storm is defined as the uncontrolled production of proinflammatory cytokines at both local and systemic levels, with a complex pathogenesis that develops in response to infection and other stimuli. SARS-CoV2 spike protein binds to ACE-2 in human cells to start the cellular infection

(16). Viral replication and cellular infection cause the host cell to become inflamed, which causes the production of proinflammatory cytokines and cell death via pyroptosis. Consequently, it intensifies the inflammatory response (90). One of the processes causing ARDS and multi-organ failure in COVID-19 is exaggerated cytokine release in response to viral infection (90). Abnormal secretion of proinflammatory factors causes disruption of coagulation by damaging the alveolar epithelial cell barrier and microvascular system of the lung, which alters microvascular permeability, inducing vascular leakage, alveolar edema, and shock, and leads to lung endothelial and epithelial cell apoptosis, which causes hypoxia (41, 106).

Excessive proinflammatory cytokine secretion triggers various inflammatory signaling pathways through receptors on immune and tissue cells, causing complex medical symptoms like hypotension, fever, capillary leak syndrome, generalized muscle pain, disseminated intravascular coagulation, ARDS, and multi-organ failure, which in the most extreme cases ultimately results in death (107). Acute sudden increase in circulating levels of proinflammatory cytokines and chemokines such as IFN-λ, interleukin-6 (IL-6), IL-1β, IL-1, IL-8, IL-18, TNF-α, chemokine (CC-motif) ligand-2 (CCL-2), CCL-5, CCL-3 and granulocyte-colony stimulating factor (G-CSF) with reactive oxygen species causes ARDS, pulmonary fibrosis, and death (99, 108-111). This increase in cytokines causes various immune cells, such as neutrophils, macrophages, and T cells, to migrate from the circulation to the site of infection, creating devastating effects that can result in disruption of endothelial cell-to-cell interaction, vascular barrier and capillary damage, extensive alveolar damage, multiple organ failure, and ultimately death (108).

Once SARS-CoV-2 has entered respiratory epithelial cells, it starts to produce inflammatory cytokines and weak interferons response, which set off an immunological response. The proinflammatory immune responses of intermediate CD14+ CD16+ monocytes and pathogenic Th1 cells are mediated by membrane-bound immune receptors and axonal communication channels. Following this, neutrophils and macrophages infiltrate the lung tissue, causing a cytokine storm (112). SARS-CoV-2 in particular has the ability to rapidly activate pathogenic Th1 cells, causing them to release proinflammatory cytokines such as granulocyte-marophage colony stimulating factor (GM-CSF) and IL-6. Additionally, CD14+CD16+ inflammatory monocytes are stimulated by GM-CSF to release significant levels of IL-6, TNF-, and other cytokines (113). Among other lymphocytic alterations, IL-6 starts an amplification

cascade that directly causes the differentiation of T helper 17 (Th17) cells (114). Endothelial cells are indirectly activated by circulating IL-6 and soluble IL-6 receptor complexes, triggering systemic cytokine production cascade that causes hypotension and ARDS (114). Leukotrienes and reactive oxygen species are released by activated neutrophils, which locally damage pneumocytes and endothelial cells and directly result in acute lung injury (115). To create neutrophil extracellular traps (NETs), which can both capture pathogens and help thrombi develop, inflammatory mediators encourage neutrophil release of nuclear deoxyribonucleic acid (DNA) (107). The correlations between thrombin and inflammatory activation and cytokine production serve as an example of this process, which is also known as immuno-thrombosis (116). Circulating cytokines and other immune mediators are exposed to vascular endothelial cells, which leads to cytokine storms that induce coagulation diseases like diffuse intravascular coagulation, capillary leak syndrome, and thrombus development (107, 117).

High quantities of circulating inflammatory cytokines can cause tissue damage and cell death, while promoting macrophage activation can cause anemia and erythrophagocytosis (107, 117). Multi-organ failure may develop as a result of severe lung injury, unexpected changes in vascular hemostasis, and tissue damage caused by cytokines (107, 117). Cytokine storms also result in high levels of fibrinogen and D-dimer, a byproduct of fibrin breakdown, which increases vascular permeability and triggers the coagulation cascade on the endothelial surfaces of small blood vessels (118).

CONCLUSION

The COVID-19 outbreak, which was deemed a pandemic, has caused a significant public health crisis on a global scale due to the virus's widespread infectivity and substantial medical effects, which have an influence on the economy. Although the pandemic's virus is identified, the precise pathogenesis of the outbreak is still not entirely understood. With an emphasis on its pathophysiology, this section describes the current state of COVID-19. A coronavirus called SARS-CoV-2 spreads through close contact and respiratory droplets. It is highly virulent and contagious. Infection of the lower respiratory tract contributes to severe ARDS, which triggers a "cytokine storm" with the release of various cytokines, leading to pneumonia and respiratory failure. The severity of COVID-19 is correlated with cytokine storm, which is also a prominent factor in COVID-19-related fatalities. Therefore, in order to develop efficient therapeutics and

preventive measures against COVID-19 with fatal clinical conditions, a greater understanding of the nature of the initiation and progression of this systemic inflammatory process as well as an accurate and precise understanding of its physiopathology are absolutely necessary.

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CHAPTER XVI

CANCER AND COVID-19 PANDEMIC

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1. Introduction

Cancer is one of the major problems that threaten health all over the world, and its incidence is increasing every passing day (1-3). Cancer has killed an estimated 10 million people in 2020 (4). That is, cancer is the cause of one in six deaths, and is the second leading cause of death worldwide (2). Its incidence is quite high in both developed and developing countries. However, due to disruptions in early diagnosis and access to appropriate treatment, its mortality is even higher in underdeveloped countries (5).

COVID-19 has become prominent on December 31st, 2019, with the reports of unspecified cases of pneumonia in Wuhan, China, and was declared a pandemic by the World Health Organization (WHO) in March 2020 (6). Since its emergence, COVID-19 has affected almost the entire world and caused the deaths of more than 6 million people (7). In addition to its mortal course, COVID-19 has increased the number of patients in need of medical treatment, leading to the rapid depletion of both medical resources, and the personnel workforce. The pandemic, which affected large masses in a short time and brought socioeconomic problems, became a global crisis (6).

Although COVID-19 usually causes mild or moderate respiratory conditions, leading to a population of patients who recover without medical intervention, its course is more severe in individuals with chronic diseases (8,9,10). Cancer is one of the chronic diseases that are highly susceptible to COVID-19 infection (11). The biological properties of cancer cells, treatment standards, and the presence of another comorbidity cause suppression of the

immune system, making the body vulnerable to many infectious agents such as bacteria or viruses (12). It has been found that older individuals whose immune system is suppressed are more likely to get COVID-19 infection and that their course is more severe (13,14). Due to the increased risk of cancer and suppression of the immune system in line with the increased age, cancer patients are more susceptible to COVID-19 infection (11). Many complications develop in cancer patients during the pandemic, the prognosis of the disease worsens, and the risk of mortality increases (11,15).

Patients with cancer and their families are at greater risk of COVID-19 exposure than the general population due to their frequent hospital visits, and the high number of hospitalizations. The development of significant complications such as COVID-19 pneumonia leads to delays in treatments and increased severity of symptoms (16-18). On the other hand, there is a group of patients who are worried about staying away from health institutions due to the infection risk during the pandemic. This, in turn, resulted in a decrease in hospital admissions and delayed treatment of patients with cancer who have received treatment (19).

According to studies, it was found that the patients with lung cancer are the majority among the patients with cancer who got COVID-19, and they were found to experience more symptoms, have increased rates of hospitalization in intensive care units, have higher mortality risk and mechanical ventilator need compared to other types of cancer (20,21). Symptoms such as anxiety, fatigue, insomnia, nausea, vomiting, pain, and dyspnea, which are common in cancer, are accompanied by acute respiratory distress syndrome (ARDS) and pneumonia, especially during the pandemic. This, in turn, makes COVID-19 diagnosis difficult for patients with cancer. It was found that approximately 50% of patients hospitalized with ARDS and pneumonia died of SARS-CoV2, not cancer (22,23).

The care of cancer patients during the pandemic is more important than ever due to the fact that they are one of the patient groups most affected by the pandemic, the severity of possible complications of cancer increased, and the onset of these complications shortened due to COVID-19 infection.

2. Patients with Cancer during the COVID-19

The COVID-19 pandemic is a process that negatively affects almost all patient groups. The most frequently affected group is undoubtedly patients with cancer especially due to increased symptom load, prolonged symptom duration,

postponement or cancellation of cancer treatments, development of severe complications, and greater mortality (12,24-27). Therefore, patients with cancer should continue their treatment, despite the risk of infection. Otherwise, delayed treatments cause a worsening prognosis of metastatic patients with cancer and the loss of chance of treatment (28). In addition, the fear of infection in patients causes patients to stay away from even mandatory health services and delay diagnosis, as seen in the rapidly decreasing number of cancer screenings (29,30). In this process, digital technologies that are rapidly being used to control the spread of the virus also cause inequality in health practices, reduce the examination findings of clinicians, and reduce the quality of care (27, 31,32).

The severity of COVID-19 may vary depending on the suppression of the immune systems of patients with cancer. Due to the biological structure of cancer, treatment standards, and the presence of SARS-CoV-2, immunologically suppressed patients with cancer are more at risk. It is seen that T, B, and natural killer (NK) cells that provide immunity, lymphocyte, and leukocyte counts decrease, and CD-6, CD-6, IL-8, CRP, PCT, D-Dimer, and LDH values increase in patients with cancer infected with SARS-CoV-2. These increased inflammatory indexes are important determinants of the cytokine crisis in infected patients (33,34). Irregularities in the production of cytokines and imbalances in the immune system also cause the progression of the disease (35). It can be stated that inflammatory cytokine response increases in advanced COVID-19 infection (36). With the massive release of cytokines, atherosclerotic and thromboembolic events are triggered. Due to the developing hypoxia, the oxygen requirement of the tissues cannot be met, and multi-organ failure develops due to decreased blood flow in the body, especially in the lung and heart (37,38). The need for follow-up in the intensive care unit, being over 40 years of age, the presence of widespread involvement in thoracic computed tomography imaging, the presence of chronic diseases, elevation in troponin value, thrombocytopenia, and lymphopenia increase the need for immunosuppressive treatment. However, it was found that the mortality rate in this group of patients who underwent this treatment regime was high (39). Therefore, patients with cancer, whose immune system has already been suppressed, have become more susceptible to the disease.

Symptoms such as a change in bowel habits, unexplained weight loss, difficulty swallowing, constant hoarseness, cough, loss of taste and smell, headache, hemoptysis (38,40), nausea, vomiting, pain, insomnia, loss of appetite, decrease in social-cognitive functions (41), as well as severe problems such as

liver damage, ARDS, sepsis, myocardial-pericardial involvement, pericardial effusion are also seen in patients with cancer during the pandemic (20,38). In addition, their quality of life decreases in line with the financial difficulties experienced (41).

In addition to many routine treatments such as chemotherapy, radiotherapy, surgical treatment, and targeted treatments in patients with cancer, regulated treatment standards due to COVID-19 infection also affect mortality and morbidity. Patients with cancer who have undergone chemotherapy or surgical procedure in the month just before COVID-19 diagnosis are more likely to develop severe complications (42). It was determined that severe symptoms such as ARDS were more common in patients with cancer receiving immunotherapy and surgical treatment, and duration of hospital stay and mortality rates were also higher than in other treatment groups. In addition, patients with cancer who got COVID-19 need medical treatment (antibiotics, antiviral, systemic glucocorticoids, oxygen therapy) more than those in other groups (21).

The pandemic also affects cancer survivors, as well as patients with cancer. The severity of the symptoms experienced by cancer survivors is less than in patients with cancer but more than in non-cancer patients (42). For this reason, it is important to protect and follow up cancer survivors during the pandemic as much as the patients with cancer who are still receiving treatment.

3. Conclusion

COVID-19 is one of the pandemics that affects the whole world and increases morbidity and mortality, especially for individuals with chronic diseases. One of the groups that is undoubtedly most affected in this process is the patients with cancer. Patients with cancer stay away from health institutions due to the fear of infection and lose their chances of recovery by not receiving their treatment in a timely manner.

In patients with cancer, the suppression of the immune system has become more difficult to manage during the pandemic due to both the biological characteristics of cancer and the standards of treatment. The severity of the symptoms increases and conditions that require urgent intervention emerge. For this reason, diagnosis of COVID-19 becomes difficult in patients with cancer. The protection and follow-up of patients with cancer who have finished or continued treatment are especially important during the pandemic.

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CHAPTER XVII

COVID-19 AND PULMONARY REHABILITATION

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1. Introduction

Coronaviruses have spherical shape and rod-like extensions on their surface. For this reason, it was named crown virus in Latin. (1) It includes alpha, beta, delta and gamma groups belong to Coronaviridae family in the Orthocoronavirinae subfamily, of the Nidovirales orders. Among these groups, alpha and beta are human coronaviruses. The viruses that started in the People's Republic of China in 2003 Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in Saudi Arabia in 2012 and spread to the world are descendants of Betacoronavirus. (2, 3)

2. Covid-19

With the increase in pneumonia cases in the city of Wuhan, People's Republic of China, Coronavirus Disease (Covid-19), descended from Betacoronavirus, was detected in 2019 and was declared the outbreak a pandemic by the World Health Organization (WHO) on March 11, 2020. (4)

2.1. Epidemiology

According to the data released by WHO, it has been reported that as of October 2021, Covid-19 has infected 240 260 449 people, caused the death of 4 890 424 people, and vaccinated 6 544 787 495 people all over the World. (5)

Covid-19 can affect all age groups, but it has been reported that the prognosis is poor in people with advanced age and additional diseases (such as hypertension, diabetes, obesity, cardiovascular diseases and chronic obstructive pulmonary disease . Symptoms are less severe in children. It has been reported that the incidence of men and women is similar. (6, 7)

2.2. Contamination and Protection from Contagion

The first transmission of Covid-19 was infected from animal to animal case in Wuhan. (8) In later cases, it is known to be transmitted directly from person to person through the respiratory system, and indirectly through contaminated objects or surfaces. (9) It has been reported that a positive case can be transmitted by speaking, sneezing and coughing at a distance of less than 1.8 m with a healthy person, and by contact of the secretion with the mouth, nose and eyes. These secretion saliva, respiratory secretions or secretion droplets. (10) In addition, since virus particles are shown in faeces, it has been shown that Covid-19 can also be transmitted by oral fecal route.

Studies have shown that the virus hangs in the air for more than 3 hours (11). High amount of virus exposure in a closed area is important in terms of transmission. It has been observed that the risk of transmission decreases with airing of the area and an effective disinfection. (12) For this reason, personal protective measures consisting of the trio of mask, distance and cleaning form the basis of protection from contamination. (13)

It has been observed that the risk of transmission is higher when symptoms are seen and the viral load is high in the early stages of the disease. The median incubation period was estimated to be 3-5 days. The risk of being contagious may last more than 10 days in mild cases and longer than 1 month in severe cases. (14, 15)

2.3. Clinical features

WHO has classified Covid-19 as clinically mild illness, mild pneumonia, severe pneumonia, and acute respiratory distress syndrome /sepsis/ septic shock. While approximately 80% of the patients have mild or no complications,

15% receive hospitalization and oxygen support and 5% receive intensive care support. (16)

The most common findings in the disease are fever, cough, headache, sore throat, muscle pain, fatigue, and dyspnea. In addition to these findings, nausea, vomiting, diarrhea, abdominal pain, gastrointestinal symptoms, rash, altered taste sensation and ageusia, conjunctivitis, confusion can also be seen. The most common complication of Covid-19 has been recorded as acute respiratory distress syndrome (ARDS), acute kidney damage, anemia, heart failure and secondary infection. The most common cause of death from the disease is ARDS, respiratory failure and multi-organ failure due to cardiac arrest. (17)

Cardiovascular disease, Diabetes mellitus, Hypertension, Chronic lung disease, Cancer, Chronic kidney disease, Immune system weakness, Obesity and Smoking are comorbid conditions that exacerbate the disease and are associated with mortality. (18)

2.4. Imaging Findings

Chest radiography and Computed Tomography (CT) are most commonly used in the diagnosis and follow-up of the disease. Radiography is not very effective in detecting involvement in the early stages of the disease, but it can show bilateral multifocal alveolar opacity and pleural effusion in advanced stages. CT finding consist of multifocal bilateral ground-glass in the peripheral/subpleural area, mostly in the inferior and posterior lobes. In addition, consolidations, air bronchograms, and interlobular septal thickening are among the CT findings. (8, 19)

2.5. Laboratory Findings

Laboratory findings in predicting intensive care need and death of Covid-19 patients. Understanding the common laboratory features of Covid-19 lymphocytopenia, high C-reactive protein level and high erythrocyte sedimentation rate. Thus, in the most severe cases, the prognosis can be markedly worsened by increasing in blood levels ferritin, procalcitonin, interleukin IL-6, IL-7, IL-8, IL-9, IL-10, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, tumor necrotizing factor alpha, VEGF-A. (20, 21)

2.6. Pulmonary manifestation

It has become apparent that although Covid-19 many organ systems can affect, predominantly affects the respiratory system. Manifestation can be asymptomatic or can be seen with fever, cough and shortness of breath. Pneumonia can be found in one out of every four cases. 12-24% of these cases required invasive mechanical ventilation. The mortality rate of patients dependent on mechanical ventilation is 65-88%. Respiratory failure and ARDS have been reported as complications of pulmonary manifestation. (22-25)

2.7. Extrapulmonary Manifestation

Emerging literature suggest that in many systems, including cardiac, gastrointestinal, hepatic, neurological, dermatological, hematological, endocrinological and renal can be affected. These manifestations can be seen in isolation or together with pulmonary manifestations. (26)

The clinical cardiovascular manifestations of Covid-19 include heart failure, acute cardiac injury, arrhythmia, myocarditis, and cardiogenic shock. (27)

Gastrointestinal symptoms such as loss of appetite, diarrhea, nausea, vomiting, and abdominal pain were encountered. Morever, Covid-19 can cause hepatic manifestation up to liver failure with abnormal liver function tests, increased alanine aminotransferase (ALT) and aspartate aminotansferase (AST) levels. (27)

Peripheral system findings such as neuralgia, musculoskeletal damage, loss of sense of taste and smell can be seen in neurological symptoms. In addition, central nervous system findings such as headache, dizziness, seizures, encephalopathy, impaired consciousness, Cerebrovascular accident and Guillian barre syndrome may also be seen. (28)

Skin manifestations of Covid-19 has been demonstrated with and urticarial rash. Hematological manifestation characterized by laboratory findings such as lymphopenia and thrombocytopenia has been reported, and these findings have been associated with a poor prognosis. (26) In addition, increased activated partial thromboplastin time (aPTT), prothrombin time (PT) and D-dimer levels were observed, which was associated with a poor prognosis. (29)

Endocrinological manifestations of Covid-19 presents with disorders in glucose homeostasis and cortisol Dynamics. (30) In addition, the presence of Diabetus Mellitus and obesity has been associated with poor prognosis. (26)

During severe clinical course in Covid-19, proteinuria, hematuria, acute kidney injury (AKI), electrolyte abnormalities, metabolic acidosis and kidney involvement were recorded. (31) AKI is associated with a poor prognosis and, kidney failure or kidney transplant recipients have been associated with a high mortality rate. (26)

2.8. Diagnosis and Treatment

The clinical diagnosis of Covid-19 is nucleic acid detection in nose and throat swab sampling or other respiratory tract sampling by real-time Polymerase Chain Reaction (PCR). In addition, clinical, laboratory and radiological symptoms occur depending on which system it affects. (32)

There is no specific drug or vaccine treatment for Covid-19. However, there are many pharmacological potential approaches to combat Covid-19, such as small molecule drugs, interferon therapies, vaccines, oligonucleotides, peptides and monoclonal antibodies. Various drugs, especially lopinavir/ritonavir, remdesivir, favipravir, emtricitabine, hydroxychloroquine and azithromycin, which can be effective against RNA viruses, have been widely used. Symptomatic treatment has been used in mild Covid-19, and oxygen therapy has been used in severe Covid-19. Mechanical ventilation is required for patients with respiratory failure, and hemodynamic support for patients with septic shock. In addition, Pfizer/Biontech, CanSino, Sputnik V, Vector Institute, Sinopharm-Beijing, Sinopharm-Wuhan, Sinovac vaccines, which are in Phase 3, have been decided to be used urgently from different countries. (33-35)

3. Pulmonary Rehabilitation

The benefit of pulmonary rehabilitation (PR) shown by the joint study American College of Chest Physicians (ACCP) and American Association of Cardiovascular and Pulmonary Rehabilitation (AACVPR) in 1997. Since then, pulmonary rehabilitation (PR) studies have been carried out and it has been proven to reduce the cost and mortality of the disease. (36) PR is one of the clinically standardized programs in the treatment of chronic respiratory diseases. (37)

PR programs are used in immobility, musculoskeletal system problems, neurological diseases, cardiovascular diseases and post-operative periods that will affect the lung. The program starts with the evaluation of the patient and includes interventions that regulate the physical and psychological state such as

exercise, patient education, behavioral therapy, smoking cessation, occupational therapy, nutrition and psychosocial support planned according to the evaluation. To put it briefly, it is a set of approaches integrated with the lifelong care and management of the patient with a chronic respiratory disease. (38)

PR is a multidisciplinary approach. There is also a dynamic cooperation and communication between healthcare professionals, patients and family members. Rehabilitation team consists of pulmonologists, physiotherapists, nurses, occupational therapists, speech therapists, psychologists, social workers and dietitians with experience in chronic respiratory diseases. Depending on the patient's needs, the efficacy of the individuals in the team may vary in the treatment. (39)

PR includes respiratory strategies such as postural drainage, percussion, vibration, active breathing techniques cycle, breathing exercises, coughing exercises, expansion exercises, triflow, incentive spirometry, intermittent positive pressure (IPPB), and continuous positive pressure (CPAP). (37, 40)

PR can be applied in cases of dyspnea, hypoxemia, hypercapnia, decrease in exercise tolerance or level of performing activities of daily living, deterioration in health status, increase in the duration and frequency of hospitalization, decrease in performance in work life, and nutritional deficiency. (39, 41) Contraindications of PR are lack of motivation, incompatibility, lack of financial support, severe cognitive dysfunction or psychiatric disease, concomitant unstable disease, severe exercise hypoxemia that cannot be corrected despite oxygen support, and malignancies with bone instability. (42)

Purpose of PR;

- Reducing the symptoms of the disease,
- Keeping the airways open and preventing the accumulation of secretions that interfere with normal breathing,
- Increasing the effectiveness of cough,
- Reducing energy consumption during breathing with lung training,
- Optimizing the functional and emotional state,
- Provide relaxation,
- Making it easier to cope with the disease,
- İncreasing participation in daily life and quality of life,
- Reducing health-related expenditures and mortality by reversing or stabilizing the systemic effects of the disease,
- İncreasing physician-patient-family cooperation,

- Associated with health to bring about behavioral change,
- Reducing healthcare burdens. (43-46)

3.1. PR in Covid-19

WHO states that in critical cases of Covid-19, patient suffer from conditions such as pneumonia, acute respiratory distress syndrome, sepsis and septic shock and therefore the respiratory system is affected. The long-term sequelae of the disease are still unclear. For this reason, after the detailed evaluation of the patient, PR practices are recommended to keep the patient's airway open, normalize the functioning of the diaphragm and other auxiliary respiratory muscles in the proper position, regulate the respiratory rate, regulate the respiratory workload, and provide chest mobility and postural smoothness with personalized exercises. (47)

It is recommended that all healthcare personnel involved in PR practices in Covid-19 undergo infection control training and examination. PR is patient-specific and includes close contact programs, so the use of personal protective equipment (PPE) is essential. In addition, single session therapy, such as images or video visual elements, home program and teletip applications are also important in patient treatment according to the hospital infrastructure and personnel status. (48)

According to the guideline published by WHO, healthcare workers who will come into contact with a possible/definite Covid-19 case should use a surgical mask, gown, gloves, goggles or face shieldas PPE in terms of droplet and contact transmission. In addition, a particle-retaining mask (N95) should be used, especially for people who take respiratory samples, who are in close-range examinations and treatments, due to aerosol contamination. The use of N95 is important in applications such as assisted coughing technique, breathing exercises, postural drainage and percussion. The order of putting on and taking off the PPE is significant. (49)

3.1.1. PR for mild cases of Covid-19

Mild cases of Covid-19 is defined as mild symptoms without signs of pneumonia on imaging. These patients should remain in isolation for the risk of transmission. Rehabilitation for mild illness can be managed using teletip in an outpatient setting. patients in isolation may experience decreased muscle strength due to immobilization, exercise intolerance, difficulty in expelling mucus, increased risk of deep vein thrombosis, depression and anxiety. (47, 50)

Peripheral muscle dysfunction develops as a result of loss of muscle strength, and the most appropriate treatment for this dysfunction is exercise training. Exercise training is one of the most important components of the PR program and provides improvement. Exercise capacity increases with exercise and it is ensured to return to daily life activities more easily. Exercises should be planned individually according to the patient. Physical activities or exercises such as breathing exercise, tai chi, yoga, step and dance are recommended to be done at home for 30-45 minutes twice a day. It is important to inform patients about the course of the disease. Patients should also be guided on adequate sleep, hydration, smoking cessation, weight control and proper nutrition. Professional help should be sought when necessary in the management of anxiety. (47, 51)

3.1.2. PR for case with pneumonia of Covid-19

In cases with Covid-19 pneumonia, the oxygen requirement should be determined at rest and during exertion. Heart rate, oxygen saturation and blood pressure should be monitored. (51)

PR is not performed in cases with pneumonia if fever ≥38.0 °C, dyspnea, blood oxygen saturation ≤ 95, resting blood pressure <90/60 mmHg or > 140/90 mmHg. During PR, the treatment is stopped when headache, dizziness, blurred vision, palpitations, excessive sweating, balance disorder and dyspnea score above 3 on the borg scale. (48)

In cases with Covid-19 stable pneumonia, the first purpose is to provide airway patency by expelling mucus during deep breathing exercise. For this, pursed-lip breathing and diaphragmatic breathing should be exercised with respiratory control to the patient. In pursed lip breathing, inhale through the nose for 3 seconds, exhale through the mouth in 7 seconds by contracting the lips (Figure 1). This exercise relieves dyspnea and is effective in relaxation. (42) In diaphragmatic breathing, the main muscle of respiration is the activation of the diaphragma, with the diaphragm descending during inspiration and rising during expiration. In this respiration, the air taken from the nose is filled into the abdomen, after waiting for 3 seconds, the air in the abdomen is taken out by blowing through the mouth. (52) Since the diaphragm muscle is used instead of the auxiliary respiratory muscles in this respiration, the respiratory load decreases, the level of ventilation of the lungs increases and respiration improves. (53)

Figure 1. A: Pursed-lip solunum, B: Diaphragmatic breathing (52)

If there is presence of dyspnea while doing the exercise or in activities of daily living, it is recommended that the patient sit upright in a chair with supporting arms normally and leaning forward from the waist, arms resting on table or on the kness. In this position, breathing control is achieved by teaching the person to breathe through the nose and exhale through the mouth. (Figure 2)

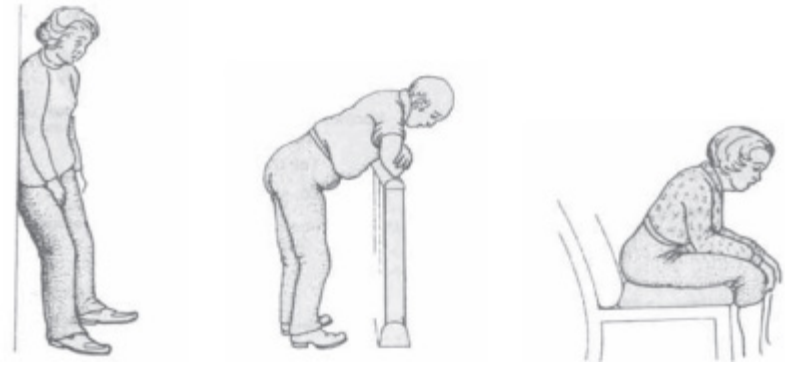

Figure 2. Positions to relieve dyspnea (52)

In cases with stable pneumonia, in-bed exercises, upper and lower extremity range of motion exercises, balance in sitting, standing up and standing ambulation, exercises for 15-45 minutes 2 times a day can be planned to suit the patient. (Figure 3) (49, 54)

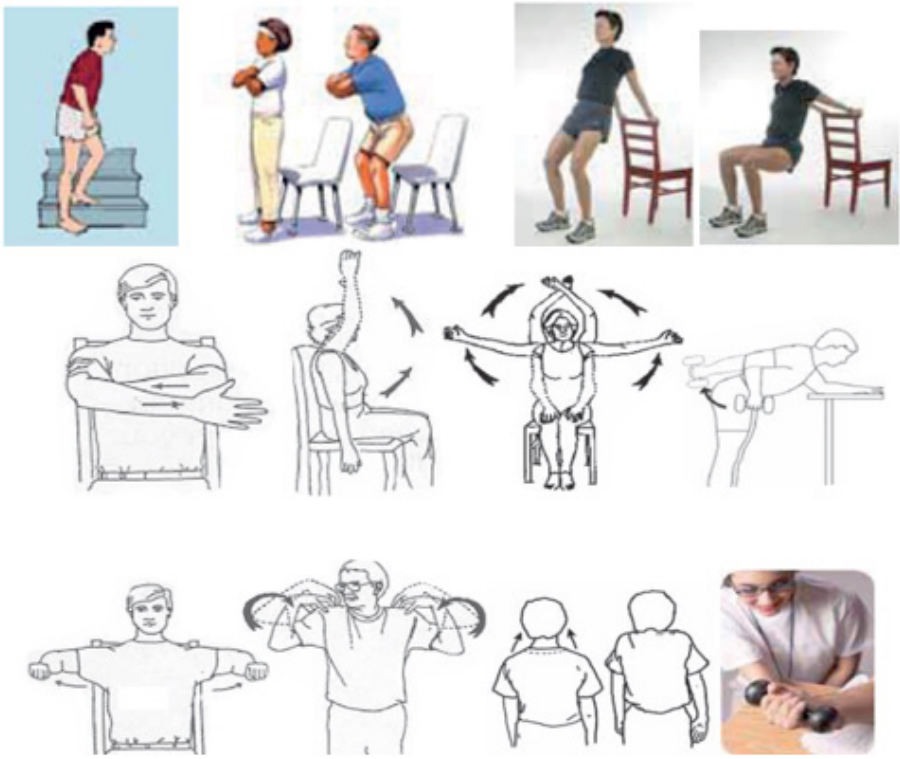

Figure 3. Exemplary exercises in cases of covid-19 stable pneumonia (52)

In addition, this patient group should be educated about the course of the disease, the importance of proper posture, the use of accessory respiratory muscles, nutrition, and they should be directed to specialist support for anxiety management when necessary. (51)

3.1.3. PR for severe cases of Covid-19

In severe cases of Covid-19 can be complicated by the severe infection, ARDS, septic shock, sepsis and multi-organ failure. In critical cases, the patient's cognitive status, respiratory, cardiac and musculoskeletal functions should be evaluated before rehabilitation. If the general condition of the patient is suitable for rehabilitation and the viral load has decreased, PR is started. If the patient is in ARDS, postural drainage, percussion, vibration, shaking and passive range of motion exercises can be applied, which are among the secretion management techniques, can be applied together with position management. (47)

In the position management, when the physiological condition of the patient allows, the head of the bed with the anti-gravity posture is gradually increased up to 60°. Position management is done in 30-minute sessions and 3 sessions are held every day. In COVID-19 patients with respiratory distress who have not yet been intubated but are at high risk for intubation, the prone position has been shown to increase oxygen saturation and decrease respiratory rate within 1 hour. For this reason, it is recommended to perform prone ventilation for 12 hours or more in ARDS patients. (51)

Postural drainage positions from these application are the process of removing secretions with the help of gravity. Tracheobronchial tracts anatomy is important in positioning. Postural drainage can be applied to each segment of the lung. While the middle and lower lobe bronchi drain more effectively in the upside down position, the upper lobe bronchus drains more effectively in the head-up position. (Figure 4) Postural drainage should be performed in the trendelenburg position in individuals undergoing cardiac surgery. (55)

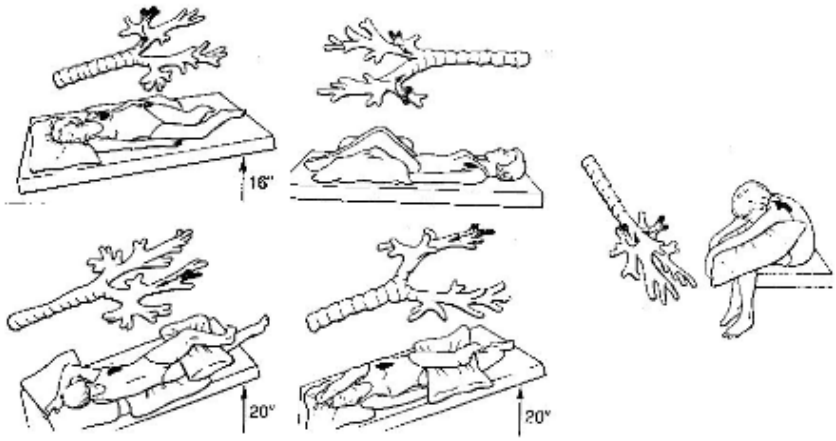

Figure 4. Examples of postural drainage positions (42)

Special techniques such as percussion and vibration are also used in postural drainage. These techniques help clear the lungs of secretions. Of these techniques, percussion provides mobilization of the adhered secretions in the lungs. In percussion, the hand is shaped into a dome and tapped on the segment to be drained. It causes the secretions that are loosened by the coarse vibrations to be shaken. In another application of vibration, the patient takes a deep breath to move secretions to a wider pulmonary pathway and vibration is applied

during expiration. In vibration, two hands are placed over the chest wall. It is applied by vibrating the chest wall with gentle compression and quick shaking. The secretions move with the very fine vibrations that occur during this time. (42) (Figure 5)

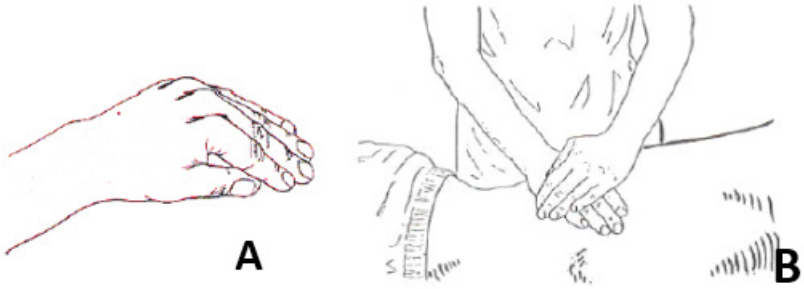

Figure 5. A: Hand position in percussion,
B: Hand position and application in vibration (42)

3.2. PR the Post-Covid 19

Physical, cognitive and psychosocial evaluation of patients after Covid 19 is important. It is necessary to increase exercise capacity and muscle strength in mild cases after discharge. For this purpose, progressive aerobic exercises are recommended so that the patient can regain his physical condition before Covid-19. (47, 48)

PR is recommended for severe patients with respiratory and musculoskeletal problems after discharge. In PR applications, the presence of comorbidities such as pulmonary hypertension, myocarditis, congestive heart failure, deep vein thrombosis should be considered. (47, 48)

4. Conclusion

Covid-19 is a global epidemic disease affecting the upper respiratory tract. This disease is personal symptoms and the disease varies according to the patient's history in degree and time. After the active phase of the disease, it is not clear how much damage or sequelae will be left in patients. With the evaluations to be made in this context, pulmonary rehabilitation in the appropriate patient at the appropriate time attempts will be required. In the months and years following this pandemic, the burden of disease can be large and is crucial in the rehabilitation of patients with PR related disabilities.

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CHAPTER XVIII

TELEREHABILITATINON: INTERFACE BETWEEN PHYSIOTHERAPIST AND PATIENT

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1. INTRODUCTION

With the developing technology all over the world, we continue to experience a transformation stage both in our daily lives and in the field of health. Everyday, a new application related to health is installed on mobile phones, while treatment tools are getting their share of technology.

Although the history of studies on the application of telerehabilitation dates back to the 90s, its use and the number of studies on this application have increased, especially in order to meet the health needs of people in the covid 19 pandemic. Interruption of social distancing and physical therapy activities can have enormous negative effects on the health of thousands of patients.(1) Therapeutic strategies implemented by physiotherapists can be adapted to minimize physical contact and disseminated using new digital strategies.

Randomized controlled trial of rehabilitation have shown that rapid management of an illness is critical to achieving good outcomes in terms of increasing patient self-efficacy. Therefore, a rehabilitation program should

start as soon as possible, be as intense as possible, be long-term and continue during the recovery period. For this reason, the physiotherapy and rehabilitation practices started in the hospital have gained continuity with telerehabilitation. However, since physiotherapy and rehabilitation applications include different applications in different disease groups, it may not be possible for each patient to participate in treatment with telerehabilitation application. Although haptic feedback term 'telepresence' was introduced, the use of manual therapy techniques was not possible in telerehabilitation applications, so the application was limited to certain disease groups.

In this section, our aim is to examine the application of telerehabilitation, which has become popular in ensuring continuity in treatment, in all details, and to reveal the limitations of the application that will shed light on future studies.

2. HİSTORY

Although the term telerehabilitation has come into our lives in recent years, telemedicine applications date back to the 1880s, when some doctors tried telecommunication technologies after the invention of the telephone in 1876. The history of the telerehabilitation application, which acts as a bridge between the patient and the physiotherapist, who are far from each other with video communication, gained awareness in 1998 with the article written by Burns et al. (2) However, image-based technologies described in the telerehabilitation literature have a deeper history than telerehabilitation and have been used in telerehabilitation research since the early 1990s. (3)

In sensor-based telerehabilitation, which is used to sample and measure three-dimensional motion in space, the method of interpretation of biosignals is used clinically. While substantial progress has been made with this technique of three-dimensional mapping of movement, there has been little attempt to integrate this information with telecommunications technologies for telemetry and rehabilitation of patients. (4)

3. TELEREHABILITATION APPLICATIONS

It includes the use of video conferencing via the internet, phone calls and virtual reality systems, where remote interaction with patients can be recorded in real time or in advance. (5)

3.1. Why Do We Need Telerehabilitation Application?

- Reducing hospital stays and costs for patients and healthcare professionals.

  It has shown that prompt management of the disease is critical to achieving successful outcomes in terms of increasing patient self-efficacy. Therefore, a rehabilitation program should start as soon as possible, be as intense as possible, be long-term and continue during the recovery period. For this reason, the physiotherapy and rehabilitation practices started in the hospital have gained continuity with telerehabilitation. In addition, long-term exercise follow-up after early intervention can shorten the hospital stay of the patient and healthcare professional with this application.

  Telerehabilitation is a form of telemedicine that utilizes telecommunications technologies to deliver rehabilitation services to remote patients synchronously or asynchronously to minimize distance, time and cost barriers. (6) In particularly, the rules of living in isolation or with less contact brought by the covid 19 pandemic can be placed in physiotherapy applications with telerehabilitation applications. Shorter hospital stay can result in a reduction in hospital costs. This means reducing the burden of insurance expenditures and costs.

- As an alternative to the conservative face-to-face approaches within the scope of patient-rehabilitation service

  Due to the pandemic, the rules of isolated life came to the fore in various fields of life such as art, sports, travel, education, and caused many different applications to come to the fore in the field of health. In particular, the reduced face-to-face hospital visits, examination and treatment times of patients brought along different problems. Precousations such as “isolation” strategies to limit the spread of this virus have created many challenges in the healthcare system and home care services, including servis disruption or reducing outpatient. Because of this situation physiotherapy and rehabilitation applications have become more difficult. In these days living in the age of technology, technological applications that are used more frequently in the field of entertainment have been modified and adapted to the field of education and health. Although these applications were used to make life easier before, they are trying to be used to support isolated life with the pandemic. Even if limited, telerehabilitation applications have been able to respond to the health needs (such as exercise follow-up,

exercise change, functional level evaluation, questionnaire application etc.) of people who have contracted the life-threatening covid 19 disease after they are discharged from the hospital.

The medical and rehabilitation needs of non-COVID-19 patients have also been imperiled due to the focus of healthcare systems has shifted to the needs of patients with COVID-19 in worldwide since 2019. (7) This situation has created inequality or weakness in access to health services for people with various disabilities. This means that many people with disabilities who do not have COVID-19 continue to need face-to-face rehabilitation services that are now inaccessible due to community quarantine as well as individuals with complications related to COVID-19. Adult or pediatric patients with chronic diseases experienced disruptions in their access to rehabilitation services due to the pandemic. Telerehabilitation applications tried to help eliminate these disruptions. However, in the rehabilitation services offered in telerehabilitation applications only the exercises that the patient could do by himself or with the help of the patient's relatives could be applied. When viewed from this aspect, the continuity of rehabilitation can be maintained with telerehabilitation applications after discharge, as an alternative to the conservative face-to-face approach for a patient with early intervention.

In addition, patients can receive group telerehabilitation services, physiotherapists reach more patients, enables patients to benefit from social network to strengthen their achievement of functional goals. (8)

- Where patients' access to rehabilitation infrastructures is complex

Telerehabilitation applications, using as an alternative to face-to-face rehabilitation services in the pandemic it were used before the pandemic, especially in cases where it was complicated for patients to reach convansiyonel rehabilitation infrastructures far from where they live. (9) Be in question in telerehabilitation applications, there is not only the distance of the patients from the institutions providing rehabilitation services, but also the fact that the physiotherapist is far away. In more rural and difficult to reach areas, there may be people who have difficulty in accessing rehabilitation services because of the physiotherapist is less employed or does not prefer these regions. (10) After a limited number of patient-physiotherapist therapeutic meetings, the continuity of the treatment can be

maintained with the telerehabilitation service. This situation brings with it the autonomy to receive rehabilitation services from the desired institution (domestic or foreign) regardless of physical location. By staying in their own social life, patients will contribute positively to the treatment process by receiving the desired rehabilitation service without experiencing transportation problems and without disturbing their comfort zone. (11) In addition, physiotherapists specializing in a certain field in their profession will also be able to access to patients requiring with telerehabilitation applications. Telerehabilitation is encourage hope for both patients and physiotherapists in terms of eliminating travel barriers, lack of time or financial constraints, and problems in accessing treatment.

3.2. Usage Fields Of Telerehabilitation Applications

Telerehabilitation applications, historing background is not as old as telemedicine, but using has increased with the pandemic, are used to provide rehabilitation services in areas such as patient follow-up, intervention, supervision, training and counseling. (12)

3.2.1. Follow-up

Patients starting a physiotherapy and rehabilitation program are re-evaluated and the data are analyzed at regular intervals by the physiotherapist in order to measure the progression of the disease, the effects, the gains, the level of benefits of the treatment. Not only the progression of the disease, but also the control (application and principles) of the exercises given to the patients are also done by physiotherapists. In telerehabilitation applications, methods such as 'virtual check-in' or remote evaluation of recorded videos can be used to evaluate and follow-up the exercises performed or the functional capacity level of the patient. (9)

Unlike the face-to-face follow-up process, telerehabilitation applications may experience disruptions in patient follow-up. The most important issue is that the chosen objective or subjective tests to evaluate the patient can be applied correctly by the patient. Every evaluation method cannot being applied correctly by patients will return to physiotherapists as incomplete data about their patients or the program. This situation shows us two ways: (1) every evaluation method to be used in the follow-up of patients should be a method can being easily done by the patients either alone or with the help of the patient's relatives, being

understandable and can giving the right result in a short time.(2) Physiotherapists should reorganize the evaluation methods they use to a level that can be used in telerehabilitation applications.

3.2.2. İntervention

In the telerehabilitation applications offering treatment program, therapeutic applications are given that the patient can do either by himself or with the help of the patient's relatives. However, in this regard, the patient's correct understanding of the given exercise and its correct performance are the determinants of the effectiveness of the treatment program. Therefore, patients may being included in the telerehabilitation program can be allocated to certain functional levels in advance. For example, many different classifications can be made, such as individual participation in the program or not, complications requiring emergency intervention may develop or not. According to this classification, the status of being included in the program can be reviewed. n addition, parameters should be established to evaluate the effectiveness of the applied program (development of complications, connection problems (internet), frequent rest breaks during the session, late participation of the physiotherapist, etc.). Unlike face-to-face rehabilitation applications, long-short-term periods in rehabilitation for some diseases should be reconstituted for telerehabilitation.

Physiotherapy program of children with neuromotor or muscle impairment can interactive teleplay, including therapeutic toys. Post-traumatic and post-surgical intervention typically includes only a few days as an inpatient. Most receive intervention as outpatients and/or through community/home programs, which include aggressive use of exercise rehabilitation, medication, behavior modification (e.g., diet), and management of secondary complications.

3.2.3. Supervision

Among physiotherapists or other health professionals working in a health institution or in a specific area of profession, studies can be done under the guidance and support of a supervisor to address issues such as exchanging clinical information about the patient and discussing different applications.

Examining the patient during telerehabilitation practices or with other physiotherapists after being recorded may be beneficial in re-evaluating the treatment program and eliminating deficiencies, if any. For physiotherapists are experting in the field of supervision in telerehabilitation applications, gaining

a different perspective may lead to the development of innovative treatment approaches and increase professional experience.

Sharing the patient's clinical consultation with the other healthcare team supports multidisciplinary work. Physiotherapy and rehabilitation applications require a multidisciplinary approach, as patients often have accompanying comorbidities. Monitoring the patient by other health professionals (such as physician, psychologist, dietitian) during telerehabilitation practices may provide benefits for the patient's treatment effectiveness. Precautions can be taken for necessary situations.

3.2.4. Training and consultancy:

In the rehabilitation of people with chronic diseases, it is important to emphasize self-management and motivation to patients. (13,14) The focus of patients in rehabilitation is not on recovery but on the individual achieving and maintaining a well-functioning daily life with the greatest possible independence and quality of life. (15) Effective patient education has been shown to improve patient self-efficacy (16,17) and support patient self-treatment. (16,18) Face-to-face patient training in physiotherapy and rehabilitation programs can also be done with telerehabilitation applications. In some studies, positive developments have been revealed that physiotherapists are more involved in the treatment process through face-to-face home visits (19) or video conference communication. (20) However, despite various limitations such as flexibility and resource management, videoconferencing-based programs can be considered as a radical alternative solution to the traditional rehabilitation program for patients. (21)

In telerehabilitation programs, subjects such as informing about their diseases, when to apply to the hospital, emergencies, ways of protection, special issues to be considered can be explained under the title of education and counseling of patients.

3.3. The Benefits of Telerehabilitation

The telerehabilitation applications, which the physiotherapist uses as a bridge in providing treatment services to the patients, enable the patient to take responsibility in the treatment with his active participation in the patient's self-care. The patient is placed at the center of this process and it is up to the patient to authorize the use of such tools. This situation made it clearer that the patient gave consent to the treatment. The creation of sessions for patients to participate in convantional physiotherapy and rehabilitation practices may be

limited by some factors. However, with telerehabilitation applications, patients can arrange their session times more convenient for them. In addition to this situation, transportation problems (financial, emotional) to the hospital/clinic can be reduced. In emergencies, it can be ensured that healthcare professionals reach them more quickly. From the point of view of health tourism, a less costly communication network can be established with health professionals living in a different province/country.

3.4. Lacks of Telerehabilitation

Telerehabilitation applications, are using within the scope of patient follow-up and treatment, provide convenience to both physiotherapists and patients in certain subjects. However, limitations may be encountered in practice due to some deficiencies in its content. From the point of view of physiotherapists, the absence of 'physical contact-touch' in telerehabilitation applications, unlike face-to-face applications, brings some limitations in the intervention phase. Many physical therapists recognize touch as an integral part of the definition of physiotherapy practice and one of the critical distinguishing skills of the profession. (22) Physiotherapists assist in the effectiveness of tactile assessment (such as palpation), intervention (manual therapy), and practices. (23) Therefore, the success of telerehabilitation can be limited as the touch component is not provided. The term "telepresence" was coined to overcome this limitation. The term telepresence has been defined in order to enhance haptic technology in the sense of maximizing the feeling of being a part of the virtual environment and to allow physical interaction with real or virtual environments. (24) However, there is no published report on telerehabilitation on synchronization via telepresence. It has also been said that telerehabilitation is primarily not a substitute for future face-to-face rehabilitation and is not easily a viable option for all categories of patients. (25)

It has not yet been clarified whether patients with known functional capacity or disease activity can be included in the treatment. There is a need for detailed comparative studies on which criteria should be met by patients who can be included in telerehabilitation. For this purpose, various scales or questionnaires can be developed. Thus, the levels are determined at which people can participate in the telerehabilitation application. In fact, thanks to these evaluation systems, patients can be differentiated for which telerehabilitation application can be better, and the appropriate method is selected. For example: (1) the patient can only participate in telerehabilitation with a synchronized or asynchronous method,

(2) the patient has the capacity to receive services only in the fields of training and consultancy or supervision from the telerehabilitation application areas, (3) the patient can be included in the telerehabilitation applications but needs help. Scales or questionnaires used in face-to-face physiotherapy applications and even functional capacity assessment methods should be reorganized according to telerehabilitation applications.

For this, factors such as the patient's internet provider not working properly during the session, the patient's cognitive level, and the ability to use the computer may be patient-related problems that we can encounter. In addition, there can be problems with confidentiality of data, risks for patient safety, resistance to change or compliance with treatment with this method.

Even though there are some problems for the physiotherapist and the patient, problems such as not being able to invoice the practice, not being covered by insurance, not being covered by insurance, problems of pricing because it is not a standard practice, not providing sufficient financial support to both the practitioner and the patient, and being out of scope in occupational accidents can be reflections on the state.

The fact that a certain ethical framework of the practice has not yet been drawn may cause confusion for both the practitioner and the patients. More detailed studies are needed to address questions about the feasibility, safety and effectiveness of the modalities used in telerehabilitation. For example, which modalities and how should be applied in people with high risk of falling, level of weakness or vital problems such as saturation?

4. CONCLUSIONS

In physiotherapy and rehabilitation services touching is the basic need with non-touch telerehabilitation applications, both evaluating and intervening in patients make physiotherapists question the effectiveness of the treatment and the success of patient follow-up. In addition, there is a need for comparative studies within the framework of occupational issues and types of disability in the selection of appropriate methods for the populations where the applications will be made. In this sense, the application should not be used only for financial gain in health. The main goal should be focused on the benefit that patients can see.

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CHAPTER XIX

COVID-19 AND PALLIATIVE CARE

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1. Introduction

COVID-19 infection caused by the novel type of coronavirus (SARS-CoV-2) first appeared in the city of Wuhan, China, in December 2019. The virus, which is highly contagious from human to human, spread around the world in a very short time and was declared a pandemic by the World Health Organization in March 2020. (1, 2) Since the first reported case, there have been almost 500 thousand positive cases and more than 6 million deaths to date. The COVID-19 virus particularly affects the lower respiratory tract and causes severe respiratory distress in patients. In addition to the hospitalization of a significant number of infected patients, some patient groups also needed ventilator support and hospitalization in the intensive care unit. (3) (ICU)

The COVID-19 pandemic and its changes in social life have affected individuals with chronic diseases or patients who receive long-term care in particular. Elderly people and individuals with comorbid diseases are among the groups susceptible to COVID-19 complications and constitute a group with high mortality rates. The increase in the number of patients with COVID-19 and the associated need for medical treatment worldwide has led to an increase in the number of patients in the health system, especially in ICU beds and mechanical ventilator-dependent patients. Moreover, patients whose treatment continues in ICUs and who receive end-of-life care by palliative care teams have been sharing health services and limited resources and facing the risk of transmission in care settings after the COVID-19 pandemic. (4)

2. Palliative Care

Palliative care is defined as an interdisciplinary care practice aimed at achieving a high quality of life in individuals with terminal illnesses, with the aim of controlling or relieving the symptoms that may arise, (5) It is not only the care given in the last stages of life but also a form of treatment that should be offered in a curative manner to improve quality-of-life care along with medical care, regardless of the disease and progression of the disease. (6) In its first definition in 1986, the World Health Organization (WHO) considered palliative care in two different dimensions, therapeutic care, and palliative care, and emphasized that one begins where the other ends. In line with the reflection of technological advances in medical science, many new definitions have been made for the term palliative care. (7) In the latest recent definition by WHO, palliative care is stated as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. (7) With this new definition, the WHO has effectively emphasized the importance of starting palliative care at an early stage of the disease. WHO states that palliative care is accepted and respected as a normal process that life brings.

The purpose of palliative care is to support the patient and patient relatives in terms of physical and emotional problems that may arise during the patient's life and during the grieving process after death. It is neither to prolong the life nor to accelerate the inevitable death. On the contrary, it is to accept death in its normal course and improve the quality of life until the last breath. In other words, the focus of palliative care is on eliminating the symptoms that cause distress rather than disease and improving the quality of life. (8)

Palliative care is based on improving the quality of life of both groups according to the needs not only of the patient but also of the patient's relatives. Palliative care requires physicians, nurses, patient care personnel, social workers, and hospital management to work in a coordinated manner within a multidisciplinary framework. (9)

3. Palliative Care During The COVID-19 Pandemic

Although the COVID-19 pandemic is a process that affects all of humanity, it is obvious that the pandemic has a more devastating effect on some disadvantaged

groups. In order to minimize this devastating effect of the pandemic, countries have had to make new regulations in the provision and implementation of health care services as part of the fight against the COVID-19 pandemic. (10) Along with these new regulations, like many other health care services, palliative care, which includes health care for individuals with life-threatening diseases and their relatives, has also been limited. Therefore, patients receiving palliative care services, their relatives, and health care providers have started to have numerous difficulties in accessing palliative care. During this period, palliative care patients experienced problems such as inability to access medicines, fear/anxiety about lack of treatment, inadequate health care, inability to access health care equipment (such as dressing material, diapers), concerns about family members contracting the virus, inability to fulfil their last wishes, lack of social support, fear of being alone, and fear of dying alone. Patient relatives have experienced problems such as helplessness and guilt caused by not being able to properly care for their patients, lack of knowledge, physical health problems, frustrations, and sadness related to an undesired way of last rites (funeral procedures, not being able to say goodbye as desired).

Another group most affected by the COVID-19 pandemic has been middle-aged and older individuals with weak immune systems. (11) It is of great importance that patients in this group are protected and supported from infection during the pandemic. Especially elderly patients with cancer and dementia who need palliative care are among the most at risk for COVID-19 disease. Therefore, during the COVID-19 pandemic, special attention should be paid to elderly individuals and their feelings, thoughts, and concerns should be listened to carefully. (12)

During the palliative care process, bedridden patients and caregivers should pay particular attention to the use of protective equipment. Patients with cancer, the elderly, and bedridden patients in need of palliative care should be considered the most vulnerable group during the pandemic. In addition, this group of patients is the most difficult group in terms of the application of preventive measures. Bedridden patients, caregivers, and team members working in nursing homes and palliative care centres should carefully use their personal protective equipment, and pay special attention to hand hygiene and the use of disinfectants. (12)

Considering the palliative care services in pandemics, it is very difficult to provide palliative care services during a pandemic. This is because, in the event of a pandemic, deaths occur that exceed the capacity of palliative team members.

During a pandemic, palliative care programs should be accelerated in such a way as to protect the health of personnel. For this purpose, it is important that the team members who provide symptom control and are effective in providing communication skills in palliative care take the lead in training. Another difficulty during the pandemic is isolation methods and social distancing, which will negatively affect the effective provision of holistic interdisciplinary palliative care. (13) This is especially difficult during the COVID-19 pandemic when medical personnel are trying to protect their personal protective equipment and therefore the number of personnel who can enter the patient room is limited. There is evidence and recommendations for the implementation of telemedicine practices in the provision and continuation of palliative care. Telemedicine is a technological method used to provide medical care to patients while trying to reduce COVID-19 transmission among patients, families, and care providers. (14) However, the need for adequate preparation and technical expertise to effectively implement in an acute care setting, some technological challenges, and changes in the technology literacy of patients are among the factors that health care practitioners should consider. Palliative care teams need specialists who have the necessary knowledge and equipment to determine and implement the most appropriate platform to provide services to patients and families. (4, 14)

4. CONCLUSION

The COVID-19 pandemic is the most important health care problem in Turkey as well as in the whole world. In particular, individuals over the age of 60, patients with cancer, diabetes, heart, hypertension, chronic liver and kidney diseases, patients with obesity disease, patients with Parkinson's and MS patients, patients with chronic lung diseases such as COPD, bronchitis, or asthma, those receiving immune system suppressive therapy and individuals with immunodeficiency are in the risk group.

In addition, in parallel with the COVID-19 pandemic exceeding the capacity of the health care system, the integration of palliative care is needed in pandemic planning. Current and local guidelines are needed for the training of health care providers on how to triage patients in accordance with palliative care principles and resources. Alternative methods such as technological methods, telemedicine, and tele-counselling can be used to provide palliative care, and online grieving support groups can be formed in this regard.

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CHAPTER XX

EVALUATION OF THE EFFECTIVENESS OF TESTS, CONTACT TRACING, AND ISOLATION MEASURES IN COVID-19 CASES IN TURKEY IN COMPARISON WITH ITALY AND SOUTH KOREA

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1. Introductıon

Coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, and has since spread globally. By 21 April 2020, more than 2,400,000 confirmed cases of COVID-19 have emerged worldwide (1). On January 2, 2020, after the first report of the disease from China, the Ministry of Health (MoH) in Turkey with a population of approximately 83 million developed a local case definition. The MoH advised all healthcare professionals to be careful and take necessary precautions for suspected COVID-19 patients (2). SARS-CoV-2 detection by reverse transcription-polymerase chain reaction (RT-PCR) for a confirmed case or using a positive antibody test for the virus that causes COVID-19 (3). RT-PCR test is performed on samples taken with at least two nasopharyngeal swabs collected

24 hours apart from patients suspected of having COVID-19 in hospitals, and chest radiographs are examined Physicians are responsible for registering and reporting all suspected and confirmed COVID-19 patients through a centralized disease reporting system. In Turkey, clinicians have been authorized to make a diagnosis in medical consultations, to perform the contact tracing of patients with a laboratory-confirmed COVID-19, and to identify possible infectious diseases from different patient groups, primary care patients with an influenza-like disease, and COVID-19. Various measures have been taken, including isolation and quarantine of the patients, active tracing of the contacts, border controls, and community education and measures, to minimize the spread of the disease. This study aimed to compare the COVID-19 data of Turkey with those of Italy and South Korea and to discuss how the precautions and measures taken by the Turkish Government affected the spread of the pandemic in Turkey.

2. Materıals And Methods

The data for this report has been provided by the reports shared by the Ministry of Health of the Republic of Turkey and sent to the relevant centers. The case definition has been updated over time according to the global course of the epidemic. The ministry of health has carried out contact tracing in the immediate vicinity of confirmed cases to identify people who are or may be infected. Suspects with elevated febrile conditions or respiratory symptoms were referred directly to hospital for further evaluation and testing. Close contacts were defined as close (1 meter) and prolonged (generally ≥30 minutes) contact with a person positive for COVID-19, low-risk contacts, and shorter contact with a person positive for COVID-19. Asymptomatic close contacts were placed under mandatory quarantine for 14 days and low-risk contacts were actively monitored (1). In order to determine whether the person had fever or respiratory symptoms, individuals exposed to close contact were called by public health officials three to five times a day during the quarantine or monitoring period whereas lower-risk contacts were called once a day. The contacts that became symptomatic were transferred to the hospital and the number of tests applied to some groups for COVID-19 increased in early March 2020. These groups were as follows: 1) all patients with pneumonia, who were hospitalized, 2) intensive care unit (ICU) patients with possible infectious causes identified by the doctor, 3) patients in a primary care clinic with a history of abroad, influenza-like illness and involved in routine influenza surveillance, and 4) deaths due to the presence of possible infectious causes.

The effectiveness of the epidemic surveillance and control efforts of Turkey was evaluated by calculating the moving average from the onset of the

outbreak until 8 April to the isolation in the hospital or under quarantine. This measure provides an indication of the time spent within the community when a person with COVID-19 is potentially infectious.

2.1. Statistical Analysis

Shapiro–Wilk test was used to determine whether the variables followed a normal distribution. For the variables not following a normal distribution, the difference between countries was examined using the Kruskal-Wallis H test. Dunn-Sidak test, one of the post-hoc tests, was used for multiple comparisons. A p value of <0.05 was considered statistically significant. Statistical parameters were expressed as median (min-max). Statistical analysis was performed using SPSS version 22.0 software (IBM SPSS for Windows version 22, IBM Corporation, Armonk, New York, United States).

3. Results

In Turkey, 42,282 patients diagnosed with COVID-19, for whom contact tracing was performed, were reported. All cases seen until the eighth day were reported to be imported. A total of four patients died until the ninth day. Patients who died and had severe conditions were known to be >60 years old or have comorbidities. Rapid identification and isolation of cases, placing the close contacts under quarantine, and actively tracing of other contacts were effective in suppressing the spread of the epidemic and made inferences for other countries exposed to the epidemic.

In the evaluation of 30-day official data on confirmed COVID-19 cases in Turkey, Italy, and South Korea, the total number of cases was calculated to be 42,282 in Turkey, 41,035 in Italy, and 8,413 in South Korea; total mortality was 908 in Turkey, 3,405 in Italy, and 84 in South Korea; the total number of tests performed was 276,338 in Turkey, 182,777 in Italy, and 295,647 in South Korea; and mean number of tests performed daily was 9,211 in Turkey, 6,093 in Italy, and 9,854 in South Korea (Table 1). Both the ratio of positive cases per day to the number of daily tests and the ratio of the total number of positive cases to the total number of tests were seen to be higher in Turkey and Italy compared to South Korea. In light of this finding, the perception that more cases could be identified by performing more tests was seen to be wrong. The ratio of the number of daily deaths to the number of positive cases per day and the ratio of total mortality to the total number of cases were found to be higher in Italy compared to Turkey and South Korea. This rate was significantly lower in Turkey than in Italy. There was no statistically significant difference between Turkey and South Korea in terms of this rate; which was almost equal to each other (Figure 1).

Table 1: General data of countries on 30-day COVID-19

30-day general data of countries				
Country	Case	Mortality	Test number	Average number of tests per day
Turkey	42282	908	276338	9211
Italy	41035	3405	182777	6093
South Korea	8413	84	295647	9854

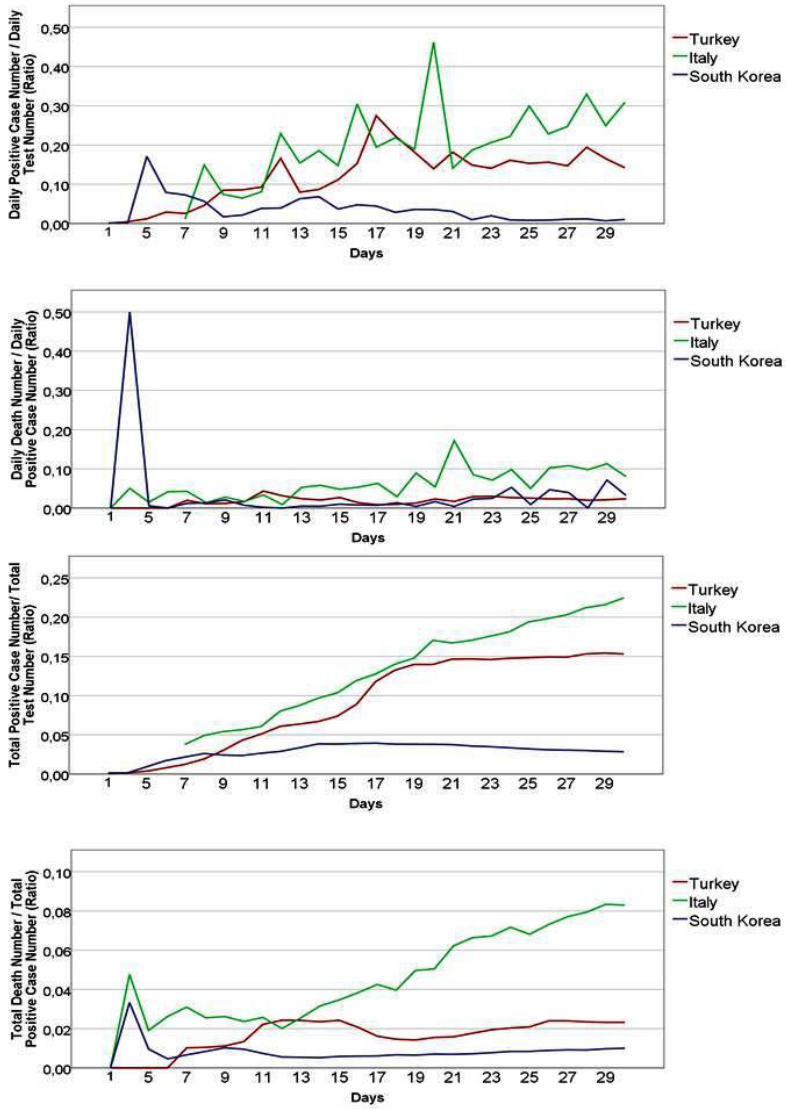

Figure 1: Demonstrating countries' monthly COVID-19 testing, cases and mortality rates

There was a significant difference between all countries in terms of the number of positive cases per day and the number of daily mortalities (p<0.004). The number of daily deaths was found to be significantly higher in Italy compared to Turkey and South Korea (p<0.001). The number of daily tests was significantly higher in South Korea compared to Italy and Turkey (p<0.05). There was a statistically significant difference between all countries in terms of the number of positive cases to the number of tests (p<0.001). The ratio of the number of deaths to the number of positive cases was found to be higher in Italy than in Turkey and South Korea (p<0.001)(Table 2).

Table 2: Comparison of countries' 30-day COVID-19 test, case and mortality rates

	Countries			
	Turkey	**Italy**	**South Korea**	
	Med(Min-Max)	Med(Min-Max)	Med(Min-Max)	p
Daily Positive Case Number	1403,00 (1,00-4117,00)[c]	773,50 (1,00-5322,00)[c]	232,00 (2,00-1062,00)[a,b]	**0,004***
Daily Death Number	16,00 (0,00-96,00)[c]	38,50 (0,00-475,00)[c]	3,00 (0,00-7,00[a,b]	**p<0,001***
Daily Tested Number	7587,00 (1000,00-28570,00)	6319,00 (987,00-17236,00)	12231,50 (1047,00-19621,00)	0,225
Positive Case Number/test Number (Ratio)	00,14 (0,00-0,27)[b,c]	0,20 (0,01-0,46)[a,c]	0,03 (0,00-0,17)[a,b]	**p<0,001***
Death Number/ Positive Case Number (Ratio)	0,02 (0,00-0,04)[b]	0,05 (0,00-0,17)[a,c]	0,01 (0,00-0,50)[b]	**p<0,001***

Kruskal Wallis H test; Post-Hoc: Dunn-Sidak Test; α: 0,05; * The difference between countries is statistically significant; [a] statistically significant difference with Turkey; [b] The difference with Italy is statistically significant; [c] Differences with South Korea are statistically significant

When the total bed capacities of the countries were compared, South Korea stood out as the most advantageous country in this regard. Considering the bed capacity in ICUs, one of the most important parameters in the fight against COVID-19 infection, it was striking that these opportunities were significantly more in Turkey than in South Korea and Italy (Figure 2).

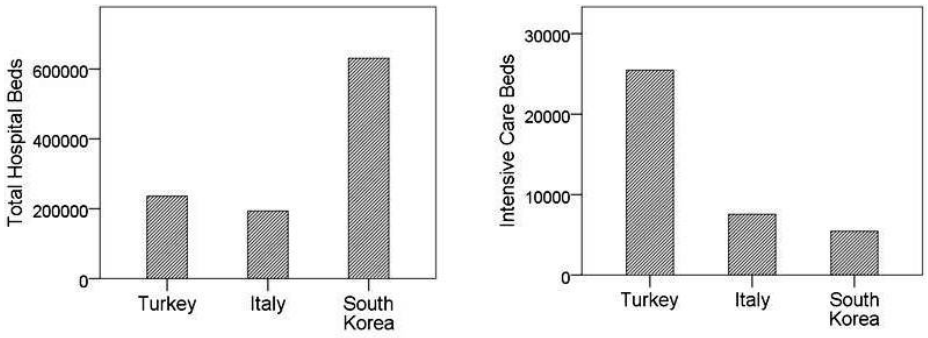

Figure 2: Demonstrating of countries the intensive care and total hospital bed capacities

4. Dıscussıon

The emergence of COVID-19 evokes the outbreaks of SARS and Middle East respiratory syndrome (MERS). The increase in the number of cases and the widening of the geographical areas brought along problems with the future management of the infection. Therefore, WHO has declared COVID-19 outbreak a global pandemic on 11 March 2020 (5). Public health and infection control measures are urgently needed to reduce the damage associated with COVID-19 and to limit its global spread (6). Overseas travel history has been emphasized to be of great importance in terms of early identification and isolation of COVID-19 cases. Interruption of human-to-human transmission is important to reduce close contact and secondary infections among healthcare professionals and to prevent further spread of the pandemic (7). One of the objectives of the present study is to evaluate the measures taken to identify COVID-19 patients in Turkey and to determine the spread of the disease in the early stage of the outbreak and to compare Turkey with South Korea, which is now in the best position in the fight against the COVID-19, and Italy, which is, unfortunately, a bad example, based on the data shared by Republic of Turkey MoH.

Improved surveillance measures of SARS-CoV-2 testing of COVID-19 patients and clinician testing demand, surveillance of ICU patients with severe illness, and potentially deaths from COVID-19 are important in identifying patients initially disconnected for further investigation (8). Turkey's surveillance methods are complementary to identify infected individuals and establish a security network with overlapping components. Case identification is important for clinicians to use and has been useful in detecting active cases and early

identification of new patients for isolation by tracing the contacts of COVID-19 patients.

The adoption of multiple surveillance mechanisms provides a wide screening area since any missed cases can lead to contact or transmission chains, which can later be difficult to trace and identify. In Singapore, the number of newly identified cases has been reported to decrease 45 days after the onset of symptoms after the first increase in locally transmitted cases. This decrease has been reported to be the result of early and strict implementation of surveillance and identification measures, however, the small number of patients and the possibility of restriction at the individual level prevented the rapid transmission due to the larger number of cases (9). Clear and distinct measures covering the transmission of local COVID-19 has been implemented in Turkey. The number of cases has increased, but the uncontrolled spread of the pandemic was prevented thanks to correct isolation, performing the tests as necessary, contact tracing and isolation of positive cases, and strict local isolation. A correct contact tracing approach was adopted depending on whether the cases were due to contact with another COVID-19-positive patient or imported from any country where the infection was present.

The number of infected cases is the main parameter mostly emphasized by the authorities and the media. Critically, the number of tests performed on humans is important to identify the infected cases, which means a limited number according to the population. In a study reported from Italy, it has been stated that the testing procedure varies by region and that the number of cases is not statistically homogeneous due to inconsistency and not suitable for interpreting the true evolution of the infection. In the same study, the case fatality rate (CFR), which is defined by dividing the number of deaths by the total number of infections, has been reported to be significantly high (11%) in Italy (10). In another study, CFR rates have been shown to be 0.4% in Australia and Israel and 2–3% in Germany, Austria, and Ireland (11). In the present study, CFR is significantly lower in Turkey than in Italy and is almost at the same level as South Korea reporting almost the lowest number of cases. Therefore, obtaining reasonable estimates of CFR and infection fatality rate (IFR) during the spread of the outbreak is important to understand the real danger of the disease and to determine the actual number of infected people.

It is believed that there are several reasons for the high mortality rate in Italy. Firstly, the number of tests carried out in Italy covers a very small proportion of the total population and the number of asymptomatic and pseudo-

symptomatic cases should not be taken into consideration. Public transportation used for business or mobility in Italy causes a large number of potential daily infections (12). In a study conducted in Italy, it is stated that significantly high mortality rates may be caused by high air pollution in the region around the Po valley, where most of the cases are seen, and that the high antibiotic resistance seen in the people of this region may also be effective. It has been further stated that the high mean age and the number of smokers have a limited effect on mortality (10). The annual number of deaths directly or indirectly related to seasonal flu has been reported to be is 8,000 in Italy and 25,000 in Germany (13). In the present study, most of the deaths reported from Turkey have been in Istanbul, where industry, business, and education life are very active and the population is very high, similar to Italy. However, CFR and IFR rates of Turkey show that the situation is more positive and controlled in Turkey compared to Italy considering the lethality of the pandemic although its general population is higher than Italy. We attribute this to the fact that identification, isolation, and contact tracing processes have been carried out in a good, careful, and quality manner.

The saturation of public hospitals and particularly the limited number of ICUs may have contributed significantly to the increase in IFR. Pre-pandemic data show that the ICU beds per person are 8.4 in Italy. Furthermore, some mistakes made by public hospitals in managing the first days of infection have caused a significant increase in the spread of infection. Moreover, abnormal behaviors in the region, in which the cases are identified, have increased deaths and infected cases throughout Italy (14). Italian researchers believe that the results based on the trend of mortality rates are statistically depending on nonhomogeneous sampling in Italy, that these results are not related to the actual evolution of the outbreak, and that the increase or decrease of new infections depends on the number of tests. In the same study, it has been further reported that if more tests are performed, more cases would be recorded (10). The present study has shown that ICU bed capacity in Turkey is quite high compared to both Italy and South Korea, that the occupancy and intensity rates of hospitals are very low compared to other countries in the pandemic since the ICU capacity of the hospitals are used efficiently in Turkey thanks to the adoption of correct approaches, and that IFR and CFR rates are low despite the high number of cases. The fact that the ratio of the number of cases to the number of tests and the IFR rates in Turkey and South Korea are very low compared to Italy although the number of tests in South Korea is quite high compared to Italy and Turkey shows that Italian researchers were wrong.

In this study, the COVID-19 pandemic, which is the greatest and fatal public health problem that has occurred in the last century, has been analyzed. Positive or negative actions taken by Italy, where the mortality rate is higher than other countries, South Korea, where is shown as the most successful example, and Turkey within the scope of the fight against the pandemic have been discussed. In a comprehensive study, it has been reported that the old average age of the Italian population, high antibiotic resistance, or even smoking is not related to the spread of the pandemic and high mortality rates. In the same study, the strongest reason for the spread of the infection has been reported to be the underestimation of the virus. The authors have emphasized that air pollution, which they think may facilitate the transmission of the virus, is more effective. Healthcare system being unprepared, underestimating the number of infections, nonhomogeneous sampling, and inadequate testing have been further reported to contribute to the spread of the pandemic (10). The results obtained from the present research have shown that measures taken by the Turkish government since the day before the first appearance of the outbreak and contact tracing, isolation, and social distance implementations have been effective in keeping the pandemic under control and preventing its impact from being destructive.

Turkey, Italy, and South Korea samples were utilized and despite the differences in isolation policies between countries, contact tracing, social distance, and other actions taken to limit the spread of the outbreak were compared. In its reports, WHO strongly underlines that the most important criterion in the evaluation of the data of the COVID-19 pandemic is the testing policy. We believe that the low mortality rates are compatible with accurate testing and contact tracing policy. In the COVID-19 pandemic, we are facing the dramatic consequences of a disease that we are not immune to, and as a global problem, there are many deaths throughout the world. In conclusion, realistic approaches should be adopted, governments should conduct many comprehensive tests as far as possible, an appropriate contact tracing should be performed, and social distance and isolation should be ensured for the required time. Thus, we can make time for clinical trials on drugs and vaccines that are definitive solutions. Furthermore, the use of purely economic criteria in the economy and primary healthcare environments thanks to the right policies and methods will enable the health system, possibilities and capabilities of which are invaluable, to be further improved and prepared against greater potential problems in the future.

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