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Special Issue
for CONCOVID Conference (12-14 June 2020, www.concovid.org)

"Health Care and Health Management in Pre and Post Pandemic Period"

The aim of this special issue is to compile the qualified research articles on the medicine and other related areas with the interdisciplinary perspective during and after the COVID-19 pandemic period.

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From the Editors

SARS-CoV-2 disease, which emerged in Wuhan, China in December 2019 and was declared a pandemic in March due to its fast-spreading nature, has had serious consequences in almost every field besides health all over the world. After the first case was detected in Turkey on March 11, 2020, the case curve started to decrease at the end of May, but with the autumn, it started to rise again, particularly in the metropolises. Although almost a year has passed since the emergence of the pandemic, no reliable data have yet been available to show when it will end or how its impact will be reduced by vaccination or similar practices.

The SARS-CoV-2 pandemic, which will take its place on a new page in the history of medicine and humanity, revealed the need to question themselves for societies and systems, and develop new perspectives on several issues. Instead of the traditional practices, new approaches and alternatives have begun to be developed in all areas from health to education, and from economics to social life. Therefore, not only the need to think, discuss, and develop ideas on the ways how to fight with the pandemic, but also to put forth policy recommendations for the post-pandemic period in the fields of health sciences, social sciences, and engineering sciences has made the scientific events essential to discuss and evaluate these issues.

In order to share the latest improvements on the pandemic, which has shown its effects in areas such as health, social psychology, economics, international relations, and politics on a global scale, FOR THE FIRST TIME IN THE WORLD, the ***Online International COVID-19 Conference (CONCOVID***, www.concovid.org) was organized with the participation of 10 universities, including Düzce University as one of the chief organizers, various NGOs, and public institutions. CONCOVID was broadcast live on 12-14 June 2020 on three channels and simultaneously on the YouTube channel. The CONCOVID Conference started with the reading of the letter of our esteemed President Recep Tayyip ERDOĞAN in which he conveyed his appreciation and continued with the speech of Mr. Şuayip BIRINCI, Deputy Minister of Health, about the course of the pandemic and the policies implemented in Turkey to fight with it. The conference then continued with the paper presentations, panel discussions and keynote presentations both from Turkey and all over the world. In their presentations, the participants from different fields of science discussed the current developments on the COVID-19 and suggested alternative policy recommendations to combat with the pandemic.

Editörlerden

Aralık 2019'da Çin'in Wuhan kentinde ortaya çıkan ve hızlı yayılım özelliği nedeni ile Mart ayında pandemi olarak kabul edilen SARS-CoV-2 hastalığı, tüm dünyada sağlık dışında da hemen her alanda ciddi sonuçlar doğurmuştur. Ülkemizde ilk vakanın 11 Mart 2020 tarihinde tespit edilmesinin ardından Mayıs sonunda vaka eğrisi düşüşe geçmiş, ancak sonbaharın gelmesi ile birlikte, başta büyük kentlerde olmak üzere yeniden artışa geçtiği gözlenmiştir. Pandeminin ortaya çıkmasının üzerinden neredeyse bir yıl geçmiş olmasına karşın henüz ne zaman sonlanacağı, ya da aşı ve benzeri uygulamalarla etkisinin nasıl azaltılabileceği hususunda sağlam veriler oluşmamıştır.

Tıp ve insanlık tarihinde farklı bir sayfa olarak yer alacak olan SARS-CoV-2 pandemisi, insanlığın ve sistemlerin birçok konuda kendilerini sorgulamaları ve yeni bakış açıları geliştirmeleri gereksinimini ortaya koymuştur. Sağlıktan eğitime, ekonomiden sosyal hayata kadar akla gelebilecek bütün alanlarda geleneksel uygulamalar bir kenara bırakılarak, yeni yaklaşımlar ve alternatifler geliştirilmeye başlanmıştır. Bu nedenle pandemi ile mücadele konusunda sağlık bilimleri başta olmak üzere, tüm sosyal bilimler ve mühendislik bilimlerini ilgilendiren alanlarda, pandemi ile mücadele ve pandemi sonrasına yönelik politika önerileri üzerinde düşünmek, tartışmak ve fikir geliştirmek ihtiyacı, bu konuların tartışılacağı ve değerlendirileceği toplantıları elzem hale getirmiştir.

Sürecin başladığı ilk günlerden itibaren küresel ölçekte sağlık, toplumsal psikoloji, ekonomi, uluslararası ilişkiler ve siyaset gibi birbirinden çok ayrık gibi görünen alanlarda etkilerini gösteren pandemi konusunda en yeni bilimsel bilgilerin paylaşımını, pandemi sürecinin tüm bilim dallarında küresel ölçekte seyrinin en doğru şekilde tanımlanmasını ve takibini gerçekleştirmek üzere DÜNYADA İLK DEFA Düzce Üniversitesi'nin baş düzenleyicileri arasında olduğu 10 üniversitemizin, çeşitli STK'ların ve kamu kurumlarımızın katkı ve katılımları ile ***Online International COVID-19 Conference (CONCOVID***, www.concovid.org) organize edilmiştir. CONCOVID, 12-14 Haziran 2020 tarihleri arasında canlı olarak üç kanaldan ve eş zamanlı olarak Youtube kanalından yayınlanmıştır. Sayın Cumhurbaşkanımız Recep Tayyip ERDOĞAN'ın takdirlerini ve tebriklerini ilettiği mektubunun okunmasıyla başlayan CONCOVID kongresi, Sayın Sağlık Bakan Yardımcımız Dr. Şuayip BİRİNCİ Beyefendi'nin pandeminin ülkemizdeki seyri ve uygulanan sağlık politikaları ile ilgili açıklamaları ile devam etmiştir. Kongre, Türkiye'den ve dünyanın farklı ülkelerinden bilim insanlarının pandemi konusunda güncel gelişmeler ve hastalıkla mücadeleye yönelik alternatif politika önerileri çerçevesinde hazırladıkları bilimsel tebliğ, panel ve konuşmaları ile devam etmiştir.

Düzce Medical Journal, one of the scientific partners of the CONCOVID Conference and the most reputable scientific journals in the field of medicine in Turkey, has made a very valuable contribution to CONCOVID by publishing the ***"CONCOVID Special Issue"***. A great significant contribution by Düzce Medical Journal has been made to the literature with the publication of the high-quality papers selected among the valuable papers presented at the conference after the peer-reviewing process. As a result of the blind reviewing, 15 quality papers had the opportunity to be published in the special issue. We hope that the papers published in the CONCOVID Special Issue of Düzce Medical Journal will not only contribute to the relevant field but also shed light on future studies.

The CONCOVID Special Issue has been brought to the literature with the outstanding support and efforts of precious academicians. We kindly express our gratitude to Prof. Dr. Nigar DEMIRCAN ÇAKAR, the Rector of Düzce University and the Vice-Rector Prof. Dr. Mehmet Akif ÖNCÜ, for their valuable contributions in organizing the world's first online conference on COVID-19, CONCOVID Conference, and for their opening speeches. We would also like to express our special thanks to Prof. Dr. İdris ŞAHIN, the Vice-Rector of Düzce University and the Dean of the Faculty of Medicine of Düzce University, for his contributions to the publication of this special issue, and Assist. Prof. Mehmet Ali SUNGUR, the editor-in-chief of the journal for his extraordinary hard work for the publication of this work, and to the team of the journal for their valuable contributions. In addition to all these names, we would also like to express our sincere thanks to Prof. Dr. Seyfettin ERDOĞAN and Assoc. Prof. Dr. Ayfer GEDIKLI, the chief organizers of the CONCOVID Conference, who had never lost their enthusiasm of academic performance during the pandemic period and made extraordinary efforts to organize the first conference on the COVID-19 in the world.

In addition to these precious scientists, we would like to express our thanks to the authors whose studies, including research papers and clinical observations from different fields, were published in the CONCOVID Special Issue of Düzce Medical Journal, for their unique contribution to the relevant literature as well as their efforts in the sharing of knowledge.

We bow respectfully to all those special people who work on the frontline to combat with the COVID-19 and who lost their lives during this fight. We kindly dedicate this precious special issue to their cherished memories.

CONCOVID Kongresi'nin bilimsel paydaşlarından olan ve ülkemizin tıp alanında en itibarlı bilimsel dergileri arasında yer alan ***Düzce Tıp Fakültesi Dergisi*** de bu kıymetli bilimsel çalışmaya ***"CONCOVID Özel Sayısı"*** çıkararak çok değerli katkı sağlamıştır. Kongrede sunulan kıymetli tebliğler arasında seçili ve kör hakem değerlendirmesinden geçen kaliteli ve öncü bilimsel çalışmaların Düzce Tıp Fakültesi Dergisi'nde yayınlanması ile literatüre önemli katkı sağlanmıştır. Bilimsel değerlendirmeler neticesinde tıp ve sosyal bilimlerin konu ile ilgili olan çalışmalarından oluşan 15 adet bilimsel eser, özel sayıda yayınlanma imkanı bulmuştur. Düzce Tıp Fakültesi Dergisi CONCOVID Özel Sayısında çıkan makalelerin, ilgili alana önemli katkılar sağlaması yanında gelecek çalışmalara ışık tutmasını umuyoruz.

CONCOVID Özel Sayısı çok değerli bilim insanlarının üstün destek ve çabaları ile literatüre kazandırılmıştır. Dünyada ilk olan CONCOVID Kongresi'nin kusursuz şekilde gerçekleşerek başta Sayın Cumhurbaşkanımız ve devlet büyüklerimizin iltifatına mazhar olmasına yönelik kıymetli katkılarından ve açılış konuşmalarından dolayı Düzce Üniversitesi Rektörü Prof. Dr. Nigar DEMİRCAN ÇAKAR hocamıza ve Rektör Yardımcısı Prof. Dr. Mehmet Akif ÖNCÜ hocamıza şükranlarımızı arz etmek isteriz. Eserin yayınlanmasında gösterdiği katkılarından dolayı Rektör Yardımcısı ve Düzce Üniversitesi Tıp Fakültesi Dekanı Prof. Dr. İdris ŞAHİN hocamıza, eserin yayınlanmasında olağanüstü çabalarından dolayı dergi baş editörü Dr. Öğr. Üyesi Mehmet Ali SUNGUR hocamıza ve eserin yayınlanma sürecinde emeği geçen ve adını sayamadığımız tüm dergi ekibine teşekkürlerimizi sunuyoruz. Tüm bu değerli isimler yanında, pandemi karantinası nedeniyle tüm dünyanın evine kapandığı dönemde, bilimsel çalışma şevkini asla kaybetmeyen ve insanlığı tehdit eden bu virüs ile baş etme konusunda dünyada ilk kongrenin ülkemizde gerçekleştirilmesi için olağanüstü emek sarf eden CONCOVID Kongresi Düzenleme Kurulu'ndan Prof. Dr. Seyfettin ERDOĞAN ve Doç. Dr. Ayfer GEDİKLİ hocalarımıza teşekkürlerimizi borç biliriz.

Bu değerli bilim insanları yanında, Düzce Tıp Fakültesi Dergisi CONCOVID Özel Sayısı'nda yayınlanan farklı alanlardan araştırma makalesi, klinik gözlem ve araştırmalardan oluşan kıymetli eserlerin yazarlarına, ilgili literatüre yaptıkları eşsiz katkılarının yanında, bilginin üretilmesi ve paylaşılması yolundaki tüm çabaları ve emeklerinden dolayı şükranlarımızı sunuyoruz.

Ülkemizde COVID-19 salgını ile mücadelede ön cephede yer alan özel insanlar ve bu mücadele sırasında hayatını kaybeden değerli meslektaşlarımız önünde saygıyla eğiliyor ve bu kıymetli eseri onların aziz hatıralarına saygılarımızla ithaf ediyoruz.

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The Diagnostic and Prognostic Importance of Neurological Findings on SARS-CoV-2 Infection

SARS-CoV-2 Enfeksiyonunda Nörolojik Bulguların Tanısal ve Prognostik Önemi

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ABSTRACT

The coronavirus invades the nervous system with the spread we call neuroinvasion, and "cytokine storm" becomes an important factor affecting the course of the disease. Serious damage occurs in the brain and other organs as a result of cytokine storm. Evidence is accumulating that the coronavirus, which infects millions of people all over the world, affects both the central and peripheral nervous system and muscles as well as the respiratory tract. Increasing evidence has revealed neurological involvement in 36-54% of the patients, which corresponds to almost one in every 2 or 3 patients. In severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) patients, we frequently encounter neurological symptoms such as smell and taste disturbances, fatigue and muscle pain, headache, nausea, vomiting, impaired consciousness, numbness in hands and feet. To a lesser extent, we encounter neurological handicaps such as dizziness, inflammation of the meninges, loss of myelin in nerve tissue, muscle inflammation, and severe rhabdomyolysis. Some of the nervous system diseases accompanying SARS-CoV-2 disease recover with complete or partial sequelae. Observation of permanent dysfunction in patients with neurological findings draws attention to the importance of a detailed neurological evaluation in the examination of these cases.
Keywords: SARS-CoV-2; neurological involvement; dysfunction.

ÖZ

Koronavirüsü, nöroinvazyon adını verdiğimiz yayılımla sinir sistemini tutmakta, ‘sitokin fırtınası’ hastalığın gidişatını etkileyen önemli bir faktör olmaktadır. Sitokin fırtınası sonucunda beyin ve diğer organlarda ciddi hasarlar ortaya çıkmaktadır. Tüm dünyada milyonlarca kişiyi enfekte eden koronavirüsün solunum yollarının yanı sıra hem merkezi hem de periferik sinirleri ve kas sistemini etkilediğini gösteren kanıtlar gün geçtikçe birikmektedir. Artan kanıtlar, hastaların %36-54’ünde yani neredeyse her 2 veya 3 hastanın birinde nörolojik tutulumu ortaya koymuştur. Şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) hastalarında koku ve tat bozuklukları, yorgunluk ve kas ağrısı, baş ağrısı, bulantı, kusma, bilinç bozukluğu, el ve ayaklarda uyuşma gibi nörolojik belirtilerle sıkça karşılaşıyoruz. Daha az olarak ise baş dönmesi, beyin zarı iltihapları, sinir dokusunda miyelin kaybı, kas iltihabı, ağır kas yıkımı gibi nörolojik handikaplara rastlıyoruz. SARS-CoV-2 hastalığına eşlik eden sinir sistemi hastalıklarının bir kısmı tam ya da kısmi sekel ile iyileşmektedir. Nörolojik bulgu gösteren hastalarda kalıcı fonksiyon kaybının gözlenmesi, bu olguların değerlendirilmesinde ayrıntılı nörolojik değerlendirmenin önemine dikkati çekmektedir.
Anahtar kelimeler: SARS-CoV-2; nörolojik tutulum; fonksiyon kaybı.

INTRODUCTION

It has been understood with our increasing knowledge and experience that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is not limited only to the respiratory tract and that it could also damage the nervous system causing neurological diseases and these damages may sometimes be permanent. Having information on neurological findings of SARS-CoV-2 disease has a guiding importance in terms of early diagnosis and treatment of neurological diseases and public health. In light of scientific research, it could be stated that neurological findings are observed more on coronavirus cases. SARS-CoV-2 could enter the nervous system through retrograde neuronal or hematogenous pathway. As the severity and course of the disease increase, the frequency of encountering nervous system-related findings has increased. Evaluating findings related to the nervous system in SARS-CoV-2 cases and the early detection and treatment of involvement are of utmost importance in terms of containing the constraint and death caused by the disease (1-3).

CYTOKINE STORM

The coronavirus attaches itself to the nervous system with a dissemination that we call neuroinvasion while 'cytokine storm' is an important factor affecting the course of the disease. As a result of the cytokine storm, serious damage could be observed in brain and other organs (4). In action mechanisms in the nervous system, direct invasion, hematogenous and neuronal dissemination, hypoxic and immune damage have been found responsible (2).

While coronavirus disease 2019 (COVID-19) moves to a severe stage in some of the infected individuals, most people recover within an average of 14 days. Although we cannot fully explain what determines this clinical course with our current knowledge, there is some evidence indicating a relationship between disease severity and proinflammatory cytokine levels. Recovery from COVID-19 is only possible with the generation of an effective immune response. In fact, it has even been suggested that the main cause of the existing tissue damage may be related to immune dysregulation and increased release of proinflammatory cytokines during the formation of protective antibodies against the disease (4,5). This theory also explains the radiological finding of increased lung involvement in the recovery phase (6,7).

The limitation of virus spread in COVID-19 is possible through the production of proinflammatory cytokines and the immune response that enables the activation of T cells. When tissue damage caused by the virus affecting the endothelium results in over-activation of macrophages and granulocytes, and induces excessive production of proinflammatory cytokines, a clinical picture resulting in severe tissue damage termed "Cytokine Storm" occurs (8-10).

In COVID-19, various cytokines and chemokines play a role in the course of the disease. IL-2, IL-6, IL-8, IL-10 and TNF-α plasma levels are significantly higher in cases with poor clinical prognosis compared to patients with good clinical prognosis (11). A close relationship has been found between IL-6 level, which has significant proinflammatory characteristics, and lymphocyte subgroups in peripheral blood. In laboratory tests, lymphocyte levels are normal or decreased in many patients. With both T and B cell immunity playing a role in immunity formation against COVID-19, it is thought that this disease intersects with some autoimmune neurological diseases such as multiple sclerosis (MS) in some common pathophysiological mechanisms.

Corticosteroid Administration in Autoimmune Neurological Diseases

Corticosteroids are frequently used orally or intravenously (IV) in neurology practice. Corticosteroids are commonly used in acute phase and maintenance treatment in patients with MS, myasthenia graves, chronic inflammatory neuropathy and myopathy. There is no consensus yet on steroid applications during the pandemic. Determining whether the person is in the asymptomatic period for COVID-19 and, if so, reaching a diagnosis to reduce the risk of the adverse reactions of high-dose corticosteroids do not seem easy with the current capabilities. For example, although there is variability between centers in patients with MS, there are also emerging trends such as waiting for mild attacks to pass without treatment or recommending short-term intravenous methylprednisolone (IVMP) without resorting to neuroimaging.

During the COVID-19 pandemic, both patients and physicians feel anxiety regarding the increased risk of contamination during admission to the hospital, commuting by public transport, frequent use of public bathrooms, closure of day treatment centers, and contamination due to the environment during intravenous treatment. Although it is theoretically possible that corticosteroid treatments may increase the spread of viral infection in the early period in case of COVID-19 transmission, limited case reports so far report no such issue (12,13). If the physician decides to use corticosteroids according to the severity of the disease, use of nonsteroidal drugs in the last three weeks should be questioned. If fever and pulse are required, cardiac beat monitoring, complete blood count (CBC), liver function tests (LFT), creatine kinase (CK), C-reactive protein (CRP), ferritin, D-Dimer, lactate dehydrogenase (LDH), and fibrinogen values should be checked (14,15). During this process, IV treatments may be planned for shorter periods, preferably for an average of 5-7 days (12).

Which Neurological Diseases and Findings did the COVID-19 Pandemic Affect?

Evidence demonstrating that the SARS-CoV-2 virus, infecting millions of people all over the world and affecting both central and peripheral nervous system and muscles in addition to the respiratory tract has been on the increase. We could categorize neurological findings that we see on SARS-CoV-2 infection as findings related to central and peripheral nervous system and musculoskeletal findings. It is sometimes possible to encounter some of these findings in a single patient at the same time. Increasing evidence has demonstrated neurological involvement in 36% of patients, which corresponds to almost one-third of all patients. Among common neurological symptoms of SARS-CoV-2 infection are smell and taste disorders, lethargy and myalgia, headache,

nausea, vomiting, impaired consciousness, and numbness in hand and feet. Less common neurological cases are vertigo, encephalitis, central and peripheral demyelination, myositis, and rhabdomyolysis (2,3,16).

One of the most common symptoms of SARS-CoV-2 infection is sudden loss of smell and taste. In coronavirus patients with loss of smell and taste, one in every four cases is asymptomatic, one in every four cases is at the early stage, and one in every four cases has severe findings. The disease could even progress without any other symptoms but loss of smell and taste. Since early diagnosis is important for this disease, having information on early signs such as loss of smell and/or taste could be greatly beneficial for diagnosis and patient isolation. The sudden loss of smell and taste, observed at the earliest stage of SARS-CoV-2 infection, is caused by the virus entering nose and reaching the olfactory neuron neighboring the cribriform plate. Although the disease is treated, the loss of smell could last for weeks in some cases (17-20).

Headache could sometimes be the alarm symptom in the SARS-CoV-2 disease. Unprecedented severe headaches could be guiding for SARS-CoV-2 diagnosis during the pandemic. We predict that the virus, through the unipolar receptors perceiving smell in the nose or a direct effect on the trigeminal nerve, enters the brain and could cause headache. Our literature information corresponds to 12-19%, which means that almost one in every five patients has headache as the primary sign or an accompanying sign (21,22).

Scientific data and patient observations suggesting lethargy, myalgia, and increasing serum CK are increasing. This could be explained by the damage of high cytokines on skeletal muscles. Neurological symptoms accompanying SARS-CoV-2 infection such as myositis, critical illness neuropathy and/or myopathy, rhabdomyolysis, and inflammatory neuropathy such as Guillain-Barre syndrome have been treated with partial or total sequelae while they may cause permanent dysfunction in some cases (23,24).

In order to prevent deaths related to the virus in our country, meticulous and assiduous studies are conducted. We observe that cerebrovascular diseases are a common mortality cause in all age groups, especially more in chronic patients, in the SARS-CoV-2 disease. Complications such as thrombosis and stroke determine the progression of infection and one of the most important indicators is thought to be D-dimer levels. Compared to deaths related to ischemic stroke and stroke, which have been more common in China and Europe, we strongly believe that D-dimer follow-up, mentioned in the guidelines formed by the Ministry of Health in Turkey, as well as the antiaggregant administration have remarkably contributed to the current good state and the low levels of mortality rate in our country (25,26).

When Exactly is the COVID-19 Pandemia Normalization Happening?

One of the two most important factors determining normalization in a pandemic is natural immunity, in other words, recovering from the infection, and the other is vaccination. COVID-19 IgG positivity is an indicator that a person is immune to the disease, but it is not yet clear with the available data whether it will be sufficient to return to normal social life. The quality of the antibodies produced after the disease seems to be more important than antibody positivity.

SARS-CoV-2 Immunity and Vaccines

When COVID-19 vaccines become available, it is thought that the effect will probably be low, especially in those receiving immunosuppressive therapy, and it will be even less effective in individuals with suppressed B cells. If the vaccine becomes available in daily practice, lymphocyte subgroups and immunoglobulins can be checked to give an idea before vaccination in autoimmune neurological diseases.

It is obvious that when the vaccine is developed, vaccination before initiating treatment in individuals with suspected risk of autoimmune disease and determining that vaccine produces sufficient antibody titer will be included in treatment algorithms for people receiving immunosuppressive therapy. For example, inactivated vaccines are considered safe for people with MS. It is generally accepted that vaccines administered during treatment with interferons, glatiramer acetate, dimethylfumarate, teriflunomide and natalizumab maintain their efficacy to a large extent and vaccines administered during treatment with fingolimod maintain their efficacy partially (27-29).

Live vaccines such as measles, polio, smallpox, chickenpox, and BCG should be avoided in patients receiving immunosuppressive therapy and taking corticosteroids for a long time. Tetanus vaccine is recommended during pregnancy and when necessary, even during an attack period. Necessary vaccines are recommended to be completed especially in the period before immunosuppressive treatments are initiated (28,29).

If the COVID-19 vaccine enters daily clinical practice, it seems that when and under what conditions we will vaccinate our patients, and in particular how effective the vaccine is in patients receiving immunosuppressive treatment and whether there is an increase in the frequency of attacks after vaccination will form the outline of our discussions in the near future (30).

CONCLUSION

It has been understood with our increasing knowledge and experience that SARS-CoV-2 infection is not limited only to the respiratory tract and that it could also damage the nervous system causing neurological diseases and these damages may sometimes be permanent. Having information on neurological findings of SARS-CoV-2 disease has a guiding importance in terms of the early diagnosis and treatment of neurological diseases and public health. Neurological findings and follow-up approaches in this article reflect the current status. We believe that these should be reviewed once ample evidence-based information is accumulated.

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Laboratory Tests in the Diagnosis of COVID-19

COVID-19 Tanısında Laboratuvar Testleri

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ABSTRACT

The gold standard for routine microbiological diagnosis of coronavirus disease 2019 (COVID-19) is quantitation of viral RNA in respiratory specimens by reverse-transcription polymerase chain reaction (RT-PCR). Detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific IgM and IgG antibodies in patient sera are additional diagnostic tests. It has been known that virus release begins a few days before clinical signs appear, and therefore, beginning from 2-3 days before the manifestation of clinical symptoms, virus RNA can be detected in the respiratory tract during the symptomatic period of the disease. Since the viral load is higher in lower respiratory tract samples such as bronchoalveolar lavage and tracheal aspirate, PCR positivity rate might be found higher compared to nasopharyngeal samples. Confirmatory PCR tests require specific equipment and trained personnel, and they are also time-consuming and costly. Antibody assays are simple, faster tests, do not require much equipment and applicable in any laboratory. They can even be performed with 2-3 drops of blood collected from the finger tip of patients using relatively inexpensive chromatographic-rapid tests. These tests can be used in the later period of the disease since specific antibodies appear on the 7-10th day of clinical signs in patients with COVID-19. Rapid antibody card tests have an average specificity and sensitivity, while antibody tests using microELISA have higher sensitivity and specificity.
Keywords: COVID-19; PCR; antibody; serology.

ÖZ

Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) için rutin mikrobiyolojik tanıda altın standart, solunum yolu örneklerinde viral RNA'nın gerçek zamanlı revers-transkriptaz polimeraz zincir reaksiyonu (RT-PCR) ile gösterilmesidir. Hasta serumunda şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)'ye spesifik olan IgG ve IgM antikorların gösterilmesi de ek tanısal testlerdir. Virüs atılımının klinik bulgulardan birkaç gün öncesinden başladığı ve bu yüzden semptomların başlamasından 2-3 gün öncesinden itibaren klinik dönem boyunca virus RNA'sının solunum yollarında tespit edilebileceği bilinmektedir. Bronkoalveolar lavaj ve trakeal aspirat gibi alt solunum yolu örneklerinde viral yük daha fazla olduğundan PCR pozitiflik oranı nazofaringeal örneklere kıyasla daha yüksektir. Zaman alıcı ve pahalı olan doğrulayıcı PCR testleri, özel ekipman ve deneyimli personel gerektirir. Antikor testleri ise basit, hızlı sonuç verebilen, ciddi ekipman gerektirmeyen ve hemen her laboratuvarda yapılabilen testlerdir. Nispeten ucuz olan kramotografik hızlı kart testlerle parmak ucundan alınan 2-3 damla kanla, hasta başında bile yapılabilir. COVID-19 geçiren kişilerde hastalığın 7-10. gününden itibaren oluşan antikorlar sebebiyle, bu testler daha geç bir zamanda kullanılabilir. Hızlı antikor kart testleri ortalama bir özgüllük ve duyarlılığa sahipken, mikroELISA ile çalışılan antikor testlerinin duyarlılık ve spesivitesi ise daha yüksektir.
Anahtar kelimeler: COVID-19; PCR; antikor; seroloji.

INTRODUCTION

The emerging coronavirus disease 2019 (COVID-19) is caused by a novel coronavirus which is in the same group of severe acute respiratory syndrome coronavirus (SARS-CoV) of 2003; therefore, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 led to a serious global pandemic affecting the whole world. The clinical spectrum of the disease ranges between asymptomatic infection and multiorgan failure. In fact, the essential clinical picture involves pneumonia and acute respiratory distress syndrome (ARDS) that develop in the lung tissue and thromboembolic events that emerge in the organs such as heart and brain. The gold standard of routine microbiological diagnosis for COVID-19 is the identification of viral RNA by real time reverse transcriptase polymerase chain reaction (RT-PCR) assay in the appropriate clinical samples obtained primarily from the respiratory tract. Besides the identification of the antigen in the clinical samples, the detection of the IgG and IgM type specific antibodies against SARS-CoV-2 is also critical for diagnosis.

In the present review, it was aimed to analyze the available laboratory tests and diagnostic stages that should be followed in the process of global COVID-19 pandemic affecting the whole world.

GENERAL INFORMATION

SARS-CoV-2 is a member of the *Coronavirus* family from the zoonotic RNA viruses. Coronaviruses (CoV), enveloped RNA viruses, have relatively large genomic structures with a single-strand, positive polarity, and a length of 27-32 kb. Infectious genomic RNA and N phosphoprotein constitute helical nucleocapsid. The lipoprotein envelope surrounding the virus consists of transmembrane matrix (M) glycoprotein and envelope (E) protein. Two types of spike-shaped protrusions are present on the CoV virion. The long (20 nm) and short protrusions comprise spike (S) and hemagglutinin-esterase (HE) glycoproteins, respectively (1,2). Because of the crown-like appearance of these protrusions, these viruses have been named coronaviruses, meaning "crowned virus" and originating from the word "corona" which means "crown" in Latin. The SARS-CoV-2 genome contains at least six open reading frames (ORF). Two-third of its genome is composed of ORFs encoding non-structural proteins, while ORFs in the remaining one-third of the genome encode at least four (S, M, E, and N) structural proteins (3, Figure 1). The first described human pathogenic coronaviruses (CoVs) were HCoV-229E and HCoV-C43, identified in the mid-1960s. CoVs have four main genera -alpha, beta, gamma, and delta- that are further divided into subgenera. CoVs can cause diseases in mammals (bats, cats, dogs, and pigs, and various poultries as well as humans). SARS-CoV was identified in 2003, leading to a global pandemic, and has been shown to be 88% genetically identical with SARS-CoV-2, the agent responsible for the ongoing 2019 pandemic (4,5). SARS-CoV-2 is also a typical CoV and belongs to the *betacoronavirus 2b* family, like SARS-CoV and Middle East respiratory syndrome coronaviruses (MERS-CoV).

Human CoVs can cause a wide range of diseases, varying from a simple cold to serious respiratory and multiorgan failures as in SARS, MERS, and COVID-19. The mortality rate of COVID-19 has been reported to be between 0.1% and 21% (mean 3.5%), which is lower than the rates for SARS-CoV (9.6%) and MERS-CoV (34.4%) (6-8). COVID-19 was first identified in pneumonia cases with unknown etiology in Wuhan City, China in December 2019, and subsequently shown to be caused by a novel virus. Being highly contagious, by September 2020, SARS-CoV-2 had caused 25 million cases of COVID-19.

MICROBIOLOGICAL DIAGNOSIS OF COVID-19

The incubation period of COVID-19 is 2-14 days (average, 5.2 days), and virus excretion is considered to begin a few days before the manifestation of clinical symptoms. Viral RNA can be detected in the respiratory tracts as long as the symptoms continue, beginning from 2-3 days before the emergence of the clinical symptoms. Since samples obtained from the lower respiratory tract, such as bronchoalveolar lavage and tracheal aspirate, have a higher viral load, a higher PCR positivity rate might be detected in those samples than nasopharyngeal samples. PCR positivity rates in the samples from the lower respiratory tract such as lavage and aspirate were 93% and 69%, respectively (9,10).

It has been demonstrated that the virus is replicated in the gastrointestinal system, and that alive virus is excreted in the stool. Nevertheless, transmission via the fecal-oral route remains unclear (11). PCR assays used for confirmation of the diagnosis have several disadvantages, such as the need for appropriate equipment and experienced personnel, its time-consuming nature (5-6 h even for the fastest laboratories) and high testing costs (10).

The detection of the IgG and IgM type-specific antibodies that form against SARS-CoV-2 in the blood serum of the patient is also critical in diagnosis as well as in the identification of SARS-CoV-2-specific antigens in the clinical samples (12,13, Figure 2). The tests based on the detection of the antigens in the clinical samples are not recommended since they have low specificity and sensitivity levels. However, antibody testing is useful in cases that cannot be confirmed by PCR despite the presence of clinical symptoms. The guiding impact of antibody testing is incontrovertible in surveillance studies due to contact isolation, rapid detection and early treatment of infected subjects and prevention of disease progression towards advanced stages. These tests also have an important supportive effect in early and accurate diagnosis of COVID-19, while treatment modalities are controversial and given the lack of vaccination. The transmission of the virus to the sensitive subject groups can be prevented by early diagnosis in asymptomatic or mild cases. Antibody testing is an easily applicable and rapid test that can be performed in almost all laboratories without the requirement of advanced equipment, even at the bedside for rapid tests by collecting 2-3 drops of finger-prick blood samples. The only disadvantage of these tests is their applicability after later periods in the subjects who had COVID-19 since the antibodies emerge after the seventh to tenth day of the disease.

IgG and IgM type-specific antibodies that emerge in the serum of the patient can be detected by high sensitivity and specificity using the devices found in a typical microbiology laboratory or manually from human blood serum using the microELISA method for the detection of

antibodies. On the other hand, the qualitative rapid card-based tests commonly used during the pandemic period for chromatographic detection of antibodies have an average specificity and sensitivity comparable with PCR and microELISA tests (12). The easily applicable antibody card-based tests without the requirement of experience and equipment also have other advantages such as rapid results and low-cost.

Although SARS-CoV-2 causes temporary viremia in the blood, there is no evidence of viral transmission via transfusion of blood products (9).

As a consequence, the essential samples that can be used for the diagnosis of COVID-19 are the specimens from the respiratory tracts and patient sera. Besides this, the following should be kept in mind as critical facts: the samples obtained from the lower respiratory tracts likely contain a higher level of viral load compared with the upper respiratory tracts; viral detection rate can be elevated in the samples obtained from the upper respiratory tract by concurrent nasopharyngeal and oro-pharyngeal swab sampling and transferring to an identical viral transport media, if possible; and performing nasopharyngeal sampling very deeply (inducing lacrimation and gagging) is ideal. Polyester or Dacron swabs should be used to avoid an adverse impact on PCR reaction, and those antibody tests might be significant and helpful only after the tenth day of the clinical process in the patients with COVID-19.

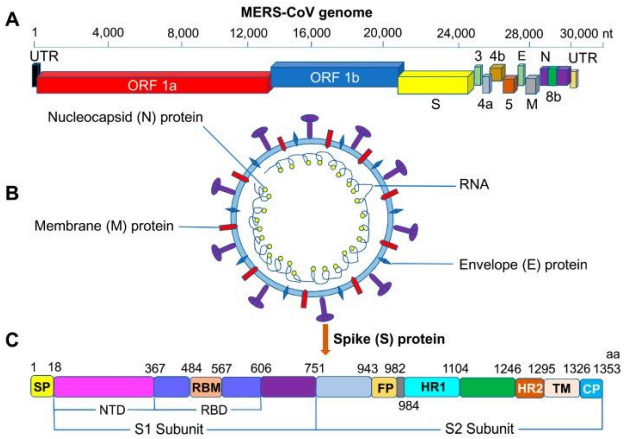

Figure 1. The genomic structure of SARS-CoV-2 and MERS-CoV (3)

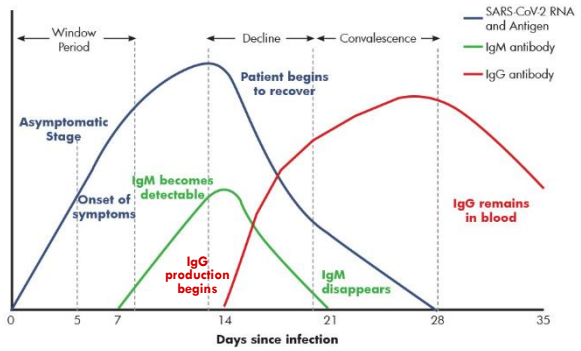

Figure 2. The clinical correlation of the COVID-19-specific PCR and serological tests (13)

PCR Tests

The gold standard of routine microbiological diagnosis for COVID-19 is the identification of SARS-CoV-2 RNA by PCR (RT-PCR) in respiratory tract samples. RNA extraction from the appropriate clinical samples and PCR procedures should be carried out in molecular microbiology laboratories that have experience and adequate technical infrastructure in this field. Biosafety level 2 (BSL 2) precautions should be followed, beginning with the acceptance of the samples by the laboratory, and it should be assured that authorized laboratory staff trained in this field must work in BSL 2 cabinet using personal protective equipment.

Viral RNA might be detected in the respiratory tracts by PCR as long as the symptoms continue, beginning from 2-3 days before the emergence of the clinical symptoms. Since the samples obtained from the lower respiratory tract (bronchoalveolar lavage, tracheal aspirate, and sputum) have a higher viral load, the PCR positivity rate of those samples is higher than that of nasopharyngeal samples (10). Viral clearance can be achieved in the first ten days, whereas this period can prolong to six weeks in serious cases. Even though pharyngeal samples become negative, viral excretion in sputum or stool might last longer. Viral RNA can be identified in 30-60% of the COVID-19 patients by PCR tests (14).

The virus detection rate of PCR tests varies with various factors such as the releasing time of SARS-CoV-2 from the respiratory tract, sampling techniques, storage or transfer conditions during pre-analytical processes, or PCR experience of the working laboratory (Table 1). Therefore, PCR tests should be repeated within 24-48 h in COVID-19 suspected patients. Even if the RT-PCR tests used today are tests validated for the respiratory tract, various studies have shown that SARS-CoV-2 RNA can be isolated in cerebrospinal fluid and tear samples. In contrast, SARS-CoV-2 RNA is not detected in breast milk, amniotic fluid, and genital samples (15,16). It has been reported that in COVID-19 cases the virus load (which is normally only high in the early period) is high in all periods and prolonged especially in the elderly and those with severe diseases. High and prolonged viral load is known as an important prognostic factor for COVID-19 (17,18).

The target gene regions used in RT-PCR tests are on the RdRp, E, N, and S genes, and it is known that the best results are obtained with the E and RdRp genes (9,19). Nucleic acid sequence analysis can also be used when necessary. The local PCR kit (that was produced in Turkey and distributed free of charge to authorized COVID-19 diagnostic laboratories by the Turkish Ministry of Health) also targets the RdRp and N gene region and has a sensitivity of 99.4% and a specificity of 99% (9).

Table 1. Factors contributing to the false-negative PCR (18)

- Poor quality sample with very little patient material
- A sampling at a very early or late period of COVID-19 infection
- A sample not properly processed and/or sent to the laboratory under unsuitable conditions
- Taking samples with cotton-tipped or wooden-shaft swabs
- Technical reasons inherent in the test such as PCR inhibition or virus mutation
- Wavy scattering of the SARS-CoV-2 virus into the respiratory tract in symptomatic and asymptomatic cases

Antibody Tests

The long time needed to get PCR test results, high cost, and requirement of experienced medical staff for implementation and interpretation have driven efforts to identify easier and more rapidly applicable tests for diagnosis of SARS-CoV-2. Despite the rapidly increased number of serological tests worldwide to detect SARS-CoV-2 antibodies thanks to supporting the attitude of the FDA on the regulation of the serological diagnostic tests at the beginning of the pandemic, these tests were used only in limited sampling groups (20,21).

Even though different results that have been obtained in the various tests used to assess the presence of the antibodies clear the usage field of serology, no consensus on this issue could be established because of the contradictory results (22). Infectious Diseases Society of America (IDSA) has recommended the use of serological studies in the selection of plasma donors, vaccination evaluation, and epidemiological studies in the patients with clinical symptoms despite negative results for SARS-CoV-2 RNA (23).

At the beginning of the pandemic, both IDSA and the World Health Organization (WHO) suggested that the presence of positive antibodies should be interpreted in favor of immunization; nevertheless, no study has yet determined whether immunization can be achieved in humans. The WHO is still examining the evidence on the antibody responses against the SARS-CoV-2 infection (24).

Since immune plasma obtained from the subjects who had recovered from COVID-19 contributed to recovery, the antibodies formed in these procedures were thought to be protective against SARS-CoV-2 (25-27). However, uncertainties remain because the specificity and titration of the epitope have not been determined. Of the 12 commercially available and approved antibody kits, only five could assess IgG solely, and three could assess both IgG and IgM. Subsequent studies have reported conflicting findings on titrations (28,29). An important antigenic similarity is present between SARS-CoV-2 and other seasonal coronaviruses, and this point indicates the importance of antigen selection for serological tests for high specificity. Even the sensitivity levels of those serological tests based on the antibodies that are formed against the N or S proteins of the virus and approved by the reference centers such as FDA and EUA were low. This is because cross-reactions with other coronaviruses could not be prevented (20,30).

Although serological tests intended for use against a rapidly spreading pandemic should have a high positive predictive value and high specificity, the antibody tests used for SARS-CoV-2 do not meet these requirements (20,31). Another study that evaluated the adequacy of serological tests reported that the four most well-known antibody tests with adequate specificity and sensitivity became positive on the tenth day of the disease, at the earliest; therefore, this outcome narrowed the usable window of serological tests in the diagnosis of COVID-19 (32).

Circumstances that affect the formation of antibodies should be kept in mind. For example, cancer patients have significantly lower seroconversion rates than healthcare professionals (33).

As a consequence, because of inadequate quality and low sensitivity levels, serological diagnostic kits used to assess SARS-CoV-2 IgM and IgG should not yet be used for general screening of the SARS-CoV-2 pandemic (34).

CONCLUSION

The gold standard for routine microbiological diagnosis of COVID-19 is quantitation of viral RNA in respiratory specimens by PCR. Detection of specific IgM and IgG antibodies for SARS-CoV-2 in patients' sera might be helpful tests in COVID-19 diagnosis. Virus detection rate of PCR tests vary on various factors such as the releasing time of SARS-CoV-2 from the respiratory tract, sampling techniques, storage or transfer conditions during pre-analytical processes, or PCR experience of the working laboratory. Specific IgM and IgG antibodies for SARS-CoV-2 in patients' sera might be useful after the 10^{th} day of clinical signs. Negativity of PCR tests and antibody tests cannot exclude COVID-19. Therefore, patients should be evaluated together with clinical, laboratory and radiological findings.

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Management of Neurorehabilitation During the COVID-19 Pandemic

COVID-19 Pandemisi Sürecinde Nörorehabilitasyonun Yönetimi

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ABSTRACT

Neurorehabilitation originates from the concept of neuroplasticity and it has an important role -both physical and cognitive- in the restoration of a damaged nervous system. Interruption in neurorehabilitation negatively affects a patient's prognosis. Unfortunately, after the World Health Organization declared coronavirus disease 2019 (COVID-19) a pandemic, there were some disruptions in neurorehabilitation practices. Therefore, according to the principles of infection prevention and protection, the issue of developing new neurorehabilitation management strategies was raised. Providing appropriate physical distancing in shared rehabilitation areas and strict training of the rehabilitation team with regard to hygiene rules are important issues in terms of preventing contamination. In new treatment schemes, options such as discharging patients from hospital at the earliest possible time, home-based treatments and telerehabilitation have become standard. Online patient-physician consultation can provide the continuity of neurorehabilitation and reduce anxiety and the feeling of social isolation felt by many patients and their families. In addition, the pandemic period can be turned into an opportunity for caregivers to learn physical and cognitive exercises and apply them to their patients. The current article focuses on the new neurorehabilitation approaches in the neurological diseases sample which includes stroke, multiple sclerosis, dementia, Parkinson's disease and neuromuscular diseases within the context of the COVID-19 pandemic.
Keywords: COVID-19; neurorehabilitation; home-based treatment; telerehabilitation.

ÖZ

Nörorehabilitasyon nöroplastisite kavramından köken alır ve hasarlanmış sinir sisteminin restorasyonunda hem fiziksel hem de bilişsel açıdan önemli bir role sahiptir. Nörorehabilitasyonda kesinti yaşanması hastanın prognozunu negatif yönde etkiler. Ne yazık ki, Dünya Sağlık Örgütü'nün koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'u pandemi olarak ilan etmesinden sonra, nörorehabilitasyon uygulamalarında aksamalar olmuştur. Bu nedenle, enfeksiyon önleme ve koruma kurallarına göre yeni nörorehabilitasyon stratejileri geliştirme konusu gündeme gelmiştir. Ortak rehabilitasyon alanlarında uygun fiziksel mesafenin sağlanması ve rehabilitasyon ekibinin hijyen kuralları açısından sıkı eğitimi, bulaşmayı önleme açısından önemli konulardır. Yeni tedavi şemalarında, hastaların mümkün olan en kısa zamanda hastaneden taburcu edilmesi, evde yapılan tedaviler ve telerehabilitasyon gibi seçenekler ön plana çıkmaktadır. Çevrimiçi hasta-uzman görüşmesi, nörorehabilitasyonun devamlılığını sağlayacağı gibi hasta ve yakınlarının, anksiyetesini ve sosyal izolasyon duygusunu azaltabilir. Ayrıca pandemi dönemi, bakım verenlerin, fiziksel ve bilişsel egzersizleri öğrenerek hastalarına uygulamaları açısından bir fırsata da dönüştürülebilir. Bu makalede, COVID-19 pandemisi bağlamında; inme, multipl skleroz, demans, Parkinson hastalığı ve nöromusküler hastalıkları içeren nörolojik hastalıklar örnekleminde, yeni nörorehabilitasyon yaklaşımlarına odaklanılmıştır.
Anahtar kelimeler: COVID-19; nörorehabilitasyon; evde tedavi; telerehabilitasyon.

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INTRODUCTION

Neurorehabilitation is a branch of neurology that includes multidisciplinary approaches such as motor skills improvement, psychosocial support, cognitive rehabilitation, nutritional and nursing care recommendations implemented in the wake of nervous system damage and focused on the patient's well-being (1). Neurorehabilitation supports recovery by using diverse treatment methods such as physical therapy (electrical stimulation, walking splints, manual and robotic exercises, virtual reality, etc.), cognitive training, language therapy, informative activities for patients and their relatives and reorganization of the patient's environment (2).

Neurorehabilitation is based on the concept of providing neural reorganization by triggering neuroplasticity, and it aims to enhance the functioning of intact neural circuits. Neurodegeneration and neuroregeneration run parallel to each other during both acute and chronic neurological diseases (3). Therefore, any delay in neurorehabilitation may negatively affect the prognosis of the diseases. Unfortunately, the disruptions which occurred in the neurorehabilitation of neurological disease cases especially in the coronavirus disease 2019 (COVID-19) lockdown period and the subsequent "controlled life period" included strict infection prevention rules (4).

Telerehabilitation and home-based treatment options seem a promising solution to overcoming the restrictions brought about by the COVID-19 pandemic (5). This article aims to review the new neurorehabilitation management strategies developed during the COVID-19 pandemic through examining examples of neurological diseases, including stroke, multiple sclerosis (MS), dementia, Parkinson's disease (PD) and neuromuscular diseases (NMDs).

Stroke and Neurorehabilitation

Due to the COVID-19 pandemic, the stroke care component in medical services has been reported to have decreased on average by 40%. The reasons for this situation have been ascribed to the fact that a large part of hospital bed capacities are now reserved for COVID-19 patients and other patients' fear to attend emergency units lest they catch the virus (6).

In the case of acute stroke, if the patient's vital signs are stable, a speedy hospital discharge and short neurorehabilitation programs are recommended (7). Common rehabilitation areas should not be used if sufficient physical distancing is not possible. Instead, rehabilitation could take place in the patient's own room under suitable isolation conditions. In order to ensure safe contact (8), physiotherapists must be informed about the infection control procedures and the use of appropriate personal protective equipment (PPE).

If the patient's body temperature is above 38 °C, rehabilitation should be postponed until the results of the COVID-19 test have been received. If the COVID-19 test is positive, the patient should be transferred immediately from the neurology service to the isolation ward. The general approach to patients showing no COVID-19 risks is for the rehabilitation specialist to instruct caregivers in basic exercises which can be done at home. In addition, patients should be encouraged to join the telerehabilitation follow-up programme, if available (9).

Telerehabilitation means using communication programs with electronic tools (mobile phone, computer) to provide internet-based rehabilitation services. The patient or caregiver can watch videos to improve motor, language and cognitive functions. However, telerehabilitation programs that can facilitate online meetings of physicians and physiotherapists with their patients at certain specified times are much more effective (10). In addition, this doctor-patient meeting using electronic media can reduce both patient anxiety and the isolation caused by stroke during the COVID-19 pandemic (5).

Home-based rehabilitation programs may be useful in stroke cases with mild neurological deficit (11). Therefore, patients with mild deficit and their caregivers should be encouraged to continue neurorehabilitation at home. It should be explained to them that the risk of COVID-19 will increase parallel to any prolonged hospitalization.

Nowadays, the importance of the 'specialized stroke centers' which have been established to provide high-quality stroke care has been highlighted once again (12). In these centers, rules of hygiene must be strictly followed, and stroke cases suspected of being COVID-19 positive should be isolated immediately.

Multiple Sclerosis and Neurorehabilitation

Continuity of neurorehabilitation is a basic need in MS cases, especially for those having symptoms such as spasticity and fatigue (13). In the early lockdown period, in some countries (14), in patients with MS, it was reported that neurorehabilitation was fully discontinued and instead in the following weeks evolved into teleassessment and telerehabilitation by an individual or group video meeting. Similar delays in neurorehabilitation were experienced in our country at the beginning of the COVID-19 pandemic. Subsequently, however, under the leadership of the Turkish Neurological Society (TNS), Study Groups for Multiple Sclerosis, Neurorehabilitation and TNS COVID-19 have started to share informative images and videos with patients via social media. In our country, the development of the electronic basis required for telemedicine and telerehabilitation is already sufficient. These treatment and follow-up options will become widespread after medico-legal provisions are instituted.

Depression affects approximately 50% of patients with MS. The social isolation caused by quarantine may have increased depression. In MS, in combating spasticity, as well as depression and chronic fatigue, regular exercise is important. For the duration of the COVID-19 pandemic, patients should be encouraged to alternately perform cardiovascular and stretching exercises three times a week for 30 minutes (or every day, 10 minutes) at home (15). In addition, patients should be encouraged to learn effective exercises such as pilates for walking, balance, and posture from web based platforms.

In order to avoid Uhthoff's syndrome, patients should be informed about the importance of an adequate fluid intake and they must stop if there is an excessive increase in body temperature during exercise (9,13). If the patients' disability status is high, a daily routine exercise programme should be maintained by rolling in the bed, frequent change of position, and the contraction of abdominal, gluteal and thigh muscles. For deformed joints and spastic muscles, caregivers should be informed about the range of motion and passive stretching exercises to be done twice every day (13).

Dementia and Neurorehabilitation

Due to the nature of the disease, cases of dementia have limited access to accurate information about the COVID-19 pandemic. They may forget mask wearing procedures or be agitated by them. This can expose them to a higher risk of infection (16). In our country, a quarantine for people aged 65 and over was imposed in the first 3 months of the pandemic and some facilities were provided for them to access their medications. Later, restrictions were gradually relaxed and it was announced by the media that dementia patients should act together with their caregivers. As a part of this process, it was permitted for the caregivers of certain dementia patients to intervene by telephone in the case of patients who had developed neuro-psychiatric problems. Afterwards, the caregivers were informed about cognitive and physical exercises that can be done at home, during routine hospital examinations, and via social media. In a study that compared the cognitive status of dementia cases in which a system called TV-AssistDem (TeleVision-based Assistive Integrated Service to support European adults living with mild DEMentia or mild cognitive impairment) was used during the lockdown period of COVID-19, researchers reported that there was a better cognitive status in the group using this system (17). This result indicates that telemedicine methods should be more widely used in the future.

Mild cases should be encouraged to do stretching, flexion-extension, sit-to-stand and walking exercises in their home, at least twice a day under the observation of a caregiver. In addition, occupational activities such as knitting, painting, cleaning, and cooking should be suggested after safe conditions have been provided (18).

Cognitive stimulation therapy (CST) is a well-known cognitive training method that can be individualized and can be applied under home conditions. It reduces the rate of cognitive decline -especially in mild cases. CST includes certain therapeutic techniques such as reality orientation (talking about time, place and person) and reminiscence therapy (talking about past activities and experiences using prompts such as photographs or objects) (19). For the duration of the COVID-19 pandemic, we could inform caregivers about such simple techniques and suggest that they use them with their patients. In immobile dementia cases, active assisted or passive flexion-extension movements and frequent positioning may prevent contractures, pressure ulcers and pain. To avoid aspiration pneumonia, caregivers should be taught to feed the patient while he/she is in an upright position (20).

Unfortunately, at the onset of the COVID-19 pandemic, there was a large loss of life among dementia patients staying in nursing homes. This was a wake-up call for the restructuring of nursing homes (21). Strict supervisory mechanisms have to be established by the authorities. Neurorehabilitation should be recommenced only after a reorganization of personal and common areas according to the rules of infection prevention has been established.

Parkinson's Disease and Neurorehabilitation

There is extensive scientific evidence to support the belief that exercise and daily physical activity are important elements in managing symptoms and potentially modifying disease progression in patients with PD (22).

Performing walking, balance and posture exercises provides improvement in their quality of life and enables them to remain mobile for a long time. Home exercises should be carried out not only during this pandemic period, they must also be routinely continued lifelong. Doing exercises together with caregivers will increase the sense of socialization that is lacking in our patients and also reduce undesirable consequences such as falling (9).

In a study conducted in the early period of the pandemic it was shown that patients can be directed to exercise regularly with positive results obtained by using a telehealth-based coaching system called 'Engage-PD' for early-middle stage PD patients. However, in that study, only 52% of the targeted patients remained in the study. The authors explained this situation by claiming that some of the patients might have been limited in their ability both to access and to adapt to the telehealth system (22). In our country, this kind of system -which provides access remotely and allows follow-up and monitoring of exercise- should be developed immediately for patients with PD.

Neuromuscular Diseases and Neurorehabilitation

Due to their nature, NMDs (neuromuscular junction diseases, motor neuron diseases, hereditary and acquired muscle diseases, etc.) can be more severe when affected by other neurological diseases, especially respiratory complications caused by COVID-19. Providing and implementing remote neurorehabilitation training programmes for these patients is particularly important.

Neurorehabilitation of NMDs includes a wide spectrum of treatment techniques from physical therapy approaches that increase joint flexibility, muscle strength and endurance to methods for coping with aphasia and dysphagia (23). After COVID-19 was declared a pandemic, neurorehabilitation for almost all NMDs was suspended for the first two or three months at the recommendation of the disease and occupation associations in so many country like ours. Various websites in our country provide counseling exercises -and also promote a variety of support systems for self-rehabilitation.

The French Rare Health Care for Neuromuscular Diseases Network (FILNEMUS) has reported that patients were informed through their web sites. By sharing the contact information of the departments during the lockdown period (23), they also tried to provide patients with the opportunity for teleconsultation with experts.

In an Italian study, persons with NMD and healthy controls were compared regarding the effects of physical inactivity during the COVID-19 quarantine period. The International Physical Activity Questionnaire Short-Form (IPAQ-SF) and Short-Form Health Survey (SF-12) were used as the evaluating tools in this study. The results of the study suggested that physical inactivity was positively correlated with the presence of NMD, impaired gait, male gender and high body mass index. It was natural that physical inactivity was found to be associated with the NMD because it is well-known that the muscles of NMD patients are more prone to atrophy due to impaired oxygen and glucose metabolism (24). However, this study has certain limitations, one of which is its inclusion of a short quarantine period. Also, interviews with the participants about the ‘pre’ and ‘during’ quarantine days were done in the same session in this study. This might be a second limitation because of certain psychological effects quarantine has on a person’s memory. Long-term studies including more data are needed.

CONCLUSION

In conclusion, discontinuation of neurorehabilitation could be negatively affecting the prognosis of neurological diseases in the COVID-19 pandemic. Aside from the negative effects of the disease itself, social isolation and fear of death made our patients more depressed. There is a need for a new system with less physical but more informational contact between the patient and the doctor. The general population and the medical community both should be conscious of this issue. Among the newly developed neurorehabilitation management strategies, telemedicine-supported home-based approaches seem to be promising for the future.

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COVID-19 and Rheumatic Diseases

COVID-19 ve Romatizmal Hastalıklar

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infectious agent affecting respiratory system the most and spreads rapidly due to large number of ACE2 receptors in the lung. Arthralgia and myalgia are the most common rheumatologic findings, but arthritis is rare. Hyperinflammatory condition called cytokine storm causes acute respiratory distress syndrome (ARDS) leading to death. Although coronavirus disease 2019 (COVID-19) is mild or asymptomatic in most cases, it may progress to pneumonia and ARDS, especially in elderly patients who have comorbidities. Drugs such as tocilizumab which suppress inflammatory response and reduce cytokine storm may be effective on treating COVID-19 pneumonia. Cytokine storm, the cause of which is not fully understood and in which many structures of immune system interact with each other, is quite complex and has different mechanisms contributing to it. Although antimalarial drugs such as hydroxychloroquine are used in the treatment, there is no definite evidence that they are effective. It has been shown that the prevalence and course of COVID-19 in rheumatic diseases is similar to the general population, and that increasing age and additional comorbid conditions increase the risk of mortality. It is recommended that anti-rheumatic drugs used in the treatment of rheumatic diseases should not be stopped unless the patient is infected with COVID-19.
Keywords: COVID-19; rheumatic diseases; cytokine storm; anti-rheumatic drugs.

ÖZ

Şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) solunum sistemini en çok etkileyen ve akciğerdeki çok sayıda ACE2 reseptörü nedeniyle hızla yayılan bulaşıcı bir ajandır. Artralji ve miyalji en sık görülen romatolojik bulgulardır, ancak artrit nadirdir. Sitokin fırtınası adı verilen hiperinflamatuar durum, akut solunum sıkıntısı sendromu (acute respiratory distress syndrome, ARDS)'na neden olarak ölüme neden olur. Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) çoğu durumda hafif veya asemptomatik olmasına rağmen, özellikle ileri yaş ve komorbiditeleri olan hastalarda pnömoni ve ARDS'ye ilerleyebilir. Enflamatuar yanıtı baskılayan ve sitokin fırtınasını azaltan tosiluzumab gibi ilaçlar, COVID-19 pnömonisinin tedavisinde etkili olabilir. Nedeni tam olarak anlaşılamayan ve bağışıklık sistemindeki birçok yapının birbiriyle etkileşime girdiği sitokin fırtınası oldukça karmaşıktır ve buna katkıda bulunan farklı mekanizmalara sahiptir. Tedavide hidroksiklorokin gibi antimalaryal ilaçlar kullanılsa da etkili olduklarına dair kesin bir kanıt yoktur. Romatizmal hastalıklarda COVID-19 sıklığının ve seyrinin genel popülasyona benzer olduğu, artan yaş ve ek komorbid durumların mortalite riskini artırdığı gösterilmiştir. Romatizmal hastalıkların tedavisinde kullanılan anti-romatizmal ilaçların, hasta COVID-19 ile enfekte olmadıkça kesilmemesi önerilmektedir.
Anahtar kelimeler: COVID-19; romatizmal hastalıklar; sitokin fırtınası; anti-romatizmal ilaçlar.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an infection agent from the coronavirus family that started in Wuhan, China in December 2019 and spread to the world, causing a pandemic. The coronavirus disease 2019 (COVID-19) classically affects the respiratory tract and can spread very quickly because of its highly contagious nature. The most important cause of mortality in patients is complications such as acute respiratory distress syndrome (ARDS), which occurs after severe pneumonia. Although symptoms such as fever, cough, and dyspnea are the most common findings, they can be seen in findings related to arthralgia and myalgia in the musculoskeletal system (1,2).

It has been reported that comorbid conditions such as increasing age, male gender and hypertension increase the risk of mortality in COVID-19 (3). On the other hand, inflammatory rheumatic diseases are common in the public and it is known that both rheumatic disease itself and steroid and other immunosuppressive drugs used in treatment can increase the risk of infection by suppressing the immune system. This can reduce the compliance of drugs used in the treatment of primary rheumatic disease in people with rheumatic disease during the COVID-19 pandemic process. Recent findings indicate that the risk of COVID-19 is the same in people with and without rheumatic disease of similar age and gender. However, this situation may cause serious anxiety in those with rheumatic disease (4). Institutions such as European League Against Rheumatism (EULAR) and the European Rheumatology Association have published algorithms on the treatment and management of rheumatic diseases during the COVID-19 pandemic with their temporary recommendations (5).

Another issue is the use of some drugs used in the treatment of rheumatic diseases in the treatment of COVID-19. It has been suggested that these drugs, particularly chloroquine (CQ) and hydroxychloroquine (HCQ), can be effective in the treatment of COVID-19 infection and has entered treatment algorithms. Discussions about the use of these drugs in COVID-19 will continue until new findings are obtained in controlled studies in the coming period (6). Another interesting issue is the hyperinflammatory condition known as cytokine fever, which is more common in Juvenile Idiopathic Arthritis and Adult Still disease in rheumatology practice, but is known to be made by many infectious agents. It is thought that anti-cytokine treatments targeting cytokines such as IL-1 and IL-6 are used in the treatment of some rheumatic diseases and cytokine storm, which is an important cause of death, with ARDS and multi-organ failure caused by COVID-19 (7). In this article, the aspects of COVID-19 overlapping with rheumatic diseases, cytokine storm, frequency in rheumatic diseases, and the relationship between drugs used in the treatment of rheumatic diseases and COVID-19 will be discussed.

Prevalence of COVID-19 in Inflammatory Rheumatic Patients

The COVID-19 pandemic, which started in December 2019 in China and spread all over the world with its fast contagiousness, still affected a small part of the world proportionally in the summer of 2020. Considering that most of the population does not encounter this infection, concerns remain due to the negative clinical picture that it will create especially in risky disease groups. There are various immune system related problems in inflammatory rheumatic diseases, and especially immunosuppressive drugs used in treatment may increase the risk of infection. However, in the first published data, the prevalence of COVID-19 in inflammatory rheumatic patients was shown to be similar to the population (8). In a study conducted in Spain, it was shown that the risk may vary according to the disease subgroups. In this study, while patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) had a similar risk to the community, the risk was higher for the patients with spondyloarthritis (SpA), especially those using targeted synthetic disease modifying drug (tsDMARD) and biological disease modifying drug (bDMARD). In systemic lupus erythematosus (SLE), it was found to be similar to the population (9). In another study from Spain, the risk of COVID-19 was found similar to the general population, even in adult and pediatric patients with rheumatic disease even if they use tsDMARD (10). In a study conducted in Italy, the prevalence of COVID-19 was found at a rate similar to the general population in chronic inflammatory rheumatic patients (11).

Rheumatic Findings of COVID-19

COVID-19 is most often manifested by symptoms related to the respiratory system, such as cough, sore throat, dyspnea, along with fever. Although these are common symptoms, many system related findings have been associated with COVID-19. In the musculoskeletal system, it often causes myalgia and arthralgia, and these symptoms are detected in 14.4-44% of cases. More rarely, acute myositis, myocarditis, purpura, livedoid skin lesions and rash have been reported. There are case reports presenting with neurological findings such as stroke, Guillain-Barre syndrome associated with great vascular involvement at a young age, which can also be confused with rheumatic disease findings. In Italy, Kawasaki-like disease has been reported 30 times more in the pre-COVID period. In addition, cytokine storm or secondary hemophagocytic lymphohistiocytosis is a condition with high mortality with ARDS and multi-organ failure, which may occur approximately 8-9 days after the onset of COVID-19 symptoms. In addition, it has been reported that antinuclear antibody (ANA) and antiphospholipid antibodies can be found positive in relation to COVID-19 (12). In a study conducted in 306 patients proved to be COVID-19, arthralgia and myalgia were detected in 26.4% of the patients, and no arthritis was detected during admission. However, 4 patients (1.3%) developed acute arthritis after hospitalization, and it was observed that ankle, knee and foot metatars were mostly affected. Crystal arthritis was found in the synovial fluid examination of these 4 patients (13). In addition, COVID-19-associated reactive arthritis and acute arthritis with oligoarthritis have been reported as a rare presentation (14,15).

COVID-19 Immunopathogenesis and Cytokine Storm

Cytokine storm with thrombotic complications and disseminated intravascular coagulation (DIC) is the reason for this and is also known as macrophage activation

syndrome (MAS). Genetic factors, malignancies such as lymphoma and especially viral infections are among the diseases that play a role in MAS etiology. After entering the respiratory system, it is thought that it enters the cell by binding to angiotensin converting enzyme-2 (ACE-2) receptors in the host tissue with its COVID-19 glycoprotein components. Here it replicates and spreads to other cells by breaking down the cell. It enables the immune system to be activated by recognizing the immune system viral antigens to MHC antigens and acquired immune system cells such as Natural Killer (NK) and acquired immune system cells such as cytotoxic T cells. Thus, proinflammatory cytokines and chemokines are released into the environment. In some patients, when their production is uncontrolled and large, a so-called cytokine storm occurs (16). In a study from China investigating mortality associated with COVID-19, it was found that D-Dimer increase, ferritin increase, lymphopenia, LDH increase and Troponin increase were associated with high mortality in relation to the hyperinflammatory response (17).

Interferon (IFN) response, which has an important role in eliminating viral infections, is thought to play a role in COVID-19 related cytokine storm. In particular, the Type 1 IFN response has been shown to be weaker and unstable here than other viral infections, and as a result, more proinflammatory cytokines and chemokines are released into the environment (18). An intense inflammatory response occurs by causing more stimulation of cells such as macrophage and granulocyte, such as tissue damage, and exaggerated production of IL-1, IL-6, TNF-α, IL-8 in patients with high viral load. It is suggested that anti-cytokine treatments to be used in the treatment of hyperinflammatory response associated with cytokine storm against excessive cytokines such as IL-6 may be useful here (19). Apart from the delayed Type 1 IFN response in the hyperinflammatory response, there are many mediators such as NF-kB, inflamazone mediated inflammation, cellular immunity components. It may also play a role in cytokine storm in different mechanisms, such as increased neutrophil extracellular traps (NETs). Finally, after the decrease in viral load in patients who developed ARDS, a gradually increasing hyperinflammation appears as a typical course (16,20).

COVID-19 Prognosis and Treatment Management in Inflammatory Rheumatic Patients

There are contradictory publications regarding the prognosis of rheumatic diseases during the COVID-19 pandemic period, thus more evidence is needed. Although some studies have reported that the prognosis of rheumatic patients who have caught COVID-19 has not changed, there are publications advocating otherwise. In addition, regardless of primary rheumatic disease, older age, corticosteroid use and dosage, other immunosuppressive drugs and comorbidities accompanying it are thought to affect the prognosis (21,22). Another situation may be that the use of chronic conventional disease modifying drugs (cDMARD) may mask severe symptoms of COVID-19, especially in elderly patients, which may delay the diagnosis of COVID-19 (23). Another interesting view is whether the risk of developing severe symptoms is lower when rheumatic patients receiving immunosuppressive therapy are infected with COVID-19. It has been suggested that drugs such as HCQ and tocilizumab (anti IL-6 blocker) can prevent this by preventing the hyperinflammatory state (24). In addition, the hypothesis that autoimmune diseases such as RA and SLE may be triggered by COVID-19 infection and that these diseases may increase after pandemic is another situation to be considered in the coming period (25).

General opinion is that patients who have chronic inflammatory rheumatic disease and who use drugs should not stop their medication and continue treatment unless they are infected with COVID-19. Both the EULAR and the American Rheumatology Association; American College of Rheumatology (ACR) reported that the published guidelines should be updated with the emergence of new data. Here, it is recommended that treatment should not be discontinued on condition of complying with hygiene conditions. It has been suggested to take measures to ensure that patients go to health centers less, to use telemedicine methods, to reduce the frequency of follow-up as much as possible and to open the dose intervals between intravenous treatments. Glucocorticoids should be used at the lowest possible dose but not stopped suddenly. In patients with stable rheumatic disease, cDMARDs such as metotrexate, sulfasalazine, leflunomide and quinine, and immunosuppressors such as mycophenolate mofetil, azathioprine, JAK inhibitors and biological agents can be used. Immunosuppressant dosage should not be reduced in those with rheumatic disease threatening vital organs. After COVID-19 exposure, HCQ, sulfasalazine and nonsteroidal anti-inflammatory drugs (NSAID) can be continued. Apart from this, cDMARD, biological agents and other immunosuppressants should be temporarily discontinued. IL-6 blockers can be continued in certain situations by making a joint decision. Although the level of evidence is weak in those with severe respiratory symptoms, NSAIDs should not be given (5,26). Rituximab anti-CD20 antibody is used in various indications such as RA, SLE and Wegener granulomatosis in rheumatology practice and shows its effect by decreasing B cells. Rituximab is generally recommended not to be used or used with caution because it increases the risk of COVID-19 or may increase the severity of infection (27,28).

ANTI-RHEUMATIC DRUGS USED IN THE TREATMENT OF COVID-19

Hydroxychloroquine (HCQ) / Chloroquine (CQ)

Among the anti-rheumatic drugs, quinine is one of the most discussed drugs for COVID-19. In the COVID-19 pandemic, especially among biological drugs, it was an inaccessible drug because HCQ entered the COVID-19 treatment protocols at a time when the continuity was decreased (29). These antimalarial drugs used in rheumatology due to their immunomodulatory effects are thought to prevent in-vitro virus replication in COVID-19, thus reducing viral load, and they may be effective in pneumonia and cytokine storm (30). However, there are publications that say otherwise. In a study from Italy, they showed that patients who previously used HCQ due to rheumatic disease were similar to those who did not use it due to COVID-19, and that the use of prophylactic quinine did not prevent infection (31). Although it is the first drug used in the treatment of COVID-19, it is controversial whether quinine is effective in the treatment of COVID-19, and randomized controlled studies are needed (32).

IL-6 Blockers

IL-6 is one of the proinflammatory cytokines involved in COVID-19 associated MAS and cytokine storm. It has been shown that the use of IL-6 blockers such as tocilizumab in early period may be effective in the treatment of COVID-19 pneumonia and respiratory failure, and it can decrease the serum levels of ferritin and fibrinogen, which are markers of hyperinflammatory status. Here, optimizing the time to start the drug is considered an important factor in the success of treatment (33).

IL-1 Blockers

It is thought that IL-1 blockers may have potential benefits especially in viral pneumonia associated with hyperinflammatory status in the treatment of COVID-19. IL-1 is one of the major proinflammatory cytokines that play a dominant role in cytokine storm. Anakinra is a recombinant IL-1R antagonist, and high-dose intravenous anakinra therapy is thought to be effective and safe in COVID-19 pneumonia (34).

Other Medicines

JAK inhibitors such as low-dose steroids, NSAID, TNFα inhibitors, Baricitinib are drugs that are thought to be theoretically effective in suppressing inflammation associated with COVID-19 but without strong clinical evidence (35). Intravenous Immunoglobulin (IVIG) may be effective in preventing inflammation and protecting against superinfections before ARDS develops (36).

CONCLUSION

In severe COVID-19, an aggressive inflammatory response with excessive immune activity is observed although the exact mechanisms are not known exactly. Especially the disruption in the innate immune system and increased proinflammatory cytokines in the environment eventually lead to cytokine storm and ARDS. When the hyperinflammatory state triggered by this viral infection is detected early, it offers us a 'window of opportunity' in lung involvement with anti-cytokine treatments. Successful results have been reported here with tocilizumab, the IL-6 blocker. HCQ is an agent expected to be effective by reducing the viral load. It has been used in cytokine storm and mild-to-moderate COVID-19 cases, but it is in a position that is discussed and requires additional studies due to its low effectiveness in prophylaxis and treatment. Although corticosteroids, one of the frequently used drugs in rheumatology practice, are known to be effective in suppressing inflammation, they are associated with increased mortality in COVID-19 disease and should be used at the lowest possible dose. On the other hand, the risk of catching COVID-19 and death in inflammatory rheumatic diseases seems to be similar to the general population. It is generally recommended that anti-rheumatic drugs, including biological drugs, should not be discontinued during the COVID-19 pandemic unless the patients are infected with the virus. However, with the emergence of new data, the guides will be updated again.

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COVID-19 and Mental Health

COVID-19 ve Ruh Sağlığı

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ABSTRACT

Because of their epidemic nature, infections such as coronavirus disease 2019 (COVID-19) pandemic cause neuropsychological and social problems which are significantly different from other known infections. Many studies on the COVID-19 pandemic have shown higher levels of mental problems such as anxiety, depression, panic disorder, and obsessive compulsive disorder especially in patients and individuals who are in the risk group. Due to biopsychosocial characteristics of people, infections, especially epidemic infections, seriously impair the quality of life by dramatically affecting these three structures, namely biology, psychology and social quality of life of a person. As numerous studies have shown, the entire human innate and adaptive immune system and the psychological and mental state of an individual are directly linked. Many studies have reported that quarantine and social restrictions can trigger depressive symptoms such as anxiety, obsession, and anhedonia. Some researchers have claimed that information from unknown sources on social media increases the psychological and psychosocial symptoms of obsession, anxiety and fear of death. Consequently, a multidisciplinary study is necessary in the treatment and prevention of coronavirus pandemic.
Keywords: Coronavirus; anxiety; depression; stress.

ÖZ

Salgın doğaları nedeniyle; koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) pandemisi gibi enfeksiyonlar, bilinen diğer enfeksiyonlardan önemli ölçüde farklı olan nöropsikolojik ve sosyal sorunlara neden olur. COVID-19 pandemisi ile ilgili birçok çalışma, özellikle hastalarda ve risk grubunda yer alan bireylerde anksiyete, depresyon, panik bozukluğu ve obsesif kompulsif bozukluk gibi zihinsel problemlerin daha yüksek seviyelerde olduğunu göstermiştir. İnsanın biyopsikososyal özelliklere sahip olmasından dolayı; enfeksiyonlar, özellikle salgın enfeksiyonlar, kişinin biyoloji, psikoloji ve sosyal yaşam kalitesi olmak üzere, bu üç yapıyı da sarsıcı derecede etkileyerek yaşam kalitesini ciddi şekilde düşürmektedir. Çok sayıda çalışmanın gösterdiği gibi, insan doğal ve adaptif bağışıklık sisteminin bütünü ve bir bireyin psikolojik ve zihinsel durumu doğrudan bağlantı içindedir. Karantina ve sosyal kısıtlamaların anksiyete, takıntı ve anhedoni gibi depresif belirtileri tetikleyebileceği birçok çalışmada bildirilmiştir. Bazı araştırmacılar, sosyal medyadan elde edilen kaynağı belirsiz bilgilerin obsesyon, kaygı ve ölüm korkusunun psikolojik ve psikososyal belirtilerini artırdığını iddia etmişlerdir. Sonuç olarak, koronavirüs pandemisinin tedavisinde ve önlenmesinde multidisipliner çalışma gereklidir.
Anahtar kelimeler: Coronavirüs; anksiyete; depresyon; stres.

INTRODUCTION

It has been determined that psychological stress factors affect the immune system for many years. Changes in the immune system have also been found to affect the individual's psychology. Cytokines cause changes in monoamine metabolism, especially serotonin. Cytokines such as IL-1, IL-6, TNF-α lead to upregulation in serotonin transporter (SERT) mRNA and proteins. Thus, the neurotransmission of serotonin increases and the amount of serotonin decreases (1). Serotonin is synthesized from tryptophan. It is claimed that serotonin/SERT and inflammation interaction may be a common and important point in the development of depression, obsessions and anxiety. These cytokines form kinetic and linolenic acids, which are neurotoxic tryptophan metabolites thanks to the changes in the metabolism of tryptophan. 5-OH tryptophan and amino acid decarboxylase are key enzymes in the synthesis of serotonin. Tryptophan is converted to quinurine and quinolinic acid by the enzyme 2,3-dioxygenase (IDO). Cytokines (TNF-α, IL-1β, IL-6, INF-gamma) induce central and peripheral IDO enzyme activity. As a result, the formation of quinolinic acid, which has neurotoxic properties, increases and the conversion of tryptophan to serotonin decreases. These metabolites also cause glutamate neurotoxicity. The increase in the release of glutamate will also cause disruption of the brain's compatibility as the release of neuroprotective and neuroplastic agents such as brain-derived neurotrophic factor (BDNF) decreases (1,2).

COVID-19 AND STRESS

The stress-HPA axis relationship has been known for a long time. Stress stimulates the release of corticotropin releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), and this also stimulates the release of glucocorticoids from the adrenal glands. The control is provided by negative feedback. Proinflammatory cytokines disrupt negative feedback by causing desensitization at glucocorticoid receptors. Thus, HPA axis activity is constantly stimulated. Response to acute stress occurs with the activation of HPA axis, but long-term problems arise when the stress becomes chronic (3). In the studies, high stress burden resulted in post-traumatic stress disorder in the SARS process (4) and depressive disorders appeared as the most common long-term psychological problem (5).

EFFECTS OF SOCIAL ISOLATION ON MENTAL HEALTH IN COVID-19

The coronavirus disease 2019 (COVID-19) pandemic negatively affects human health, resulting in death, quarantine practices and restrictions on commute which lead to depression and stress (6). It also remarkably triggers the psychological crisis and increases the risks of permanent psychological distress (7). The uncertain and persistent threat in the COVID-19 outbreak can cause fear to become chronic and severe (8).

Due to this epidemic disease, denial, shock and surprise responses, which are typical trauma responses, are expected in individuals. Denial is a mental defense response that all people initially use as a coping tool, and reflects the difficulty in accepting the disease (9).

Tian et al. (10), in their research in China during the epidemic, have found that people under the age of 18 and over 50, individuals with a lower education level than higher education, individuals who are divorced or widowed, agricultural workers and those who are in the minority position have more obsessive compulsive symptoms, interpersonal sensitivity, phobic anxiety and psychotic symptoms. In general, older individuals who are more concerned about becoming infected and dying develop more serious and psychological symptoms that need to be focused on (11).

COVID-19 AND ANXIETY

Studies conducted in China during the COVID-19 outbreak reported that the level of anxiety of healthcare workers was very high. Compared to the normal population, it has been reported that they show significantly worse symptoms of depression, anxiety, and post-traumatic stress (12). The increase in the level of anxiety was found to be related to the high risk of infection of these individuals, whether their institution is providing adequate psychological support program, the lack of knowledge of the person's emergency response plans and high workload (13).

Cao et al. (14) stated that living in urban areas instead of rural areas, living with the family and having fixed and regular income were urban protective factors during the COVID-19 pandemic. In the same study, it was found that having family members, relatives or acquaintances infected with the COVID-19 virus increased anxiety.

The emptying of supermarket shelves in the first days of the outbreak, staying at home, interpretation of every bodily sensation as a sign of COVID-19, exposure of minds to misinformation due to social media posts, watching outbreak programs on the internet and television for long hours increased fear and panic. In a study in Mexico, after the influenza epidemic was widely covered in the media, it was found that individuals' risk perception and threat of uncertainty increased to a high level and their quality of life decreased (15).

In addition to all these factors, psychological resilience, which is defined as the ability to easily get rid of trouble and use positive emotions in negative conditions, is considered to be an important factor for COVID-19. Moreover, psychological resilience can be a protective factor against the development of psychopathology in individuals facing difficulties (16). Psychological resilience (6), which is generally associated with stress, is the most important factor in the process of adaptation to traumatic experiences such as epidemics, and it is a concept that requires individuals' efforts, time and continuity to deal with stress (17). In the research, a significant difference was found between post-epidemic thoughts and psychological resilience.

When the thoughts after the epidemic were examined, no significant difference was found between the thoughts stated as "my thoughts have not changed after the epidemic", "what do I do if myself, my child or my parents are infected", "we cannot get rid of the epidemic, the end of the world is coming" and "I don't want to die apart from my loved ones under quarantine". According to these results, it can be said that focusing on the thoughts after the epidemic reduces psychological resilience. Continuous focus on negative thoughts has negative effects on individuals' psychological health (18).

RISK GROUPS IN COVID-19

Some researchers suggest that people who will be exposed to more negative results in COVID-19 outbreak are the elderly, the youth, the women, the students, the immigrants (19), the prisoners and the homeless (18,20). The most painful and destructive effect of stigma is that people think that they are no longer a member of the society in which they used to feel connected to. Due to the exclusionary attitude of the society, the individuals feel increasingly lonely and withdraw from their environment. Thoughts such as social withdrawal, pessimism, hopelessness, inadequacy, helplessness, and guilt may trigger mental illnesses. After a while, most of those who experience stigma adopt these prejudiced, stereotyped thoughts themselves. In addition to those, some issues may start to arise and affect people's daily life after their being exposed to the feelings of pessimism, hopelessness, weakness, guilt and embarrassment, anxieties and fears about the future, intense anger and a desire to harm themselves or those around them as they think they deserve it. People may deny or hide the disease to avoid discrimination. Stigmatization may increase the anxiety of a person by preventing access to sufficient and accurate information about the disease. People may not want to access health services immediately and may apply in the late period. They may refuse treatment or may not comply with the treatment protocol due to the feeling of hopelessness. Those in the stigmatizing group, on the other hand, may neglect to take necessary protective measures, mistaking that they are protected against this disease, which is dangerous and contagious for everyone.

In another study, it was found that potentially high-risk individuals, people who were suspected of infection, and individuals who were in close contact with the infected people during the COVID-19 outbreak experienced negative psychological effects even if they did not develop the infection and remained physically well (22).

After the social isolation and quarantine processes that came with the COVID-19 outbreak, individuals started to spend more time at home with their families. Although social isolation is an effective policy for controlling infection, it increases domestic violence and alcohol use so that it brings serious social, psychological, economic and social consequences (23,24).

CONCLUSION

Under the light of all these findings, it seems rational to consider the pandemic as a psychological crisis and to accept that the uncertainty and unpredictability inherent in this crisis will have social, psychological and behavioral effects. Therefore, it is important to consider the negative effects of domestic violence as well as the individual consequences of the epidemic, and take steps to protect women, children and the elderly at risk. In conclusion, it is important to consider psychosocial factors in the treatment and prevention studies of COVID-19. Multidisciplinary work is essential for success when dealing with a pandemic, and taking necessary measures accordingly before, during and after is crucial.

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Evaluation of COVID-19 Thorax Computed Tomography Findings in Hemodialysis Patients

Hemodiyaliz Hastalarında COVID-19 Toraks Bilgisayarlı Tomografi Bulgularının Değerlendirilmesi

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) is an unprecedented cause of pandemics affecting all segments of society. It is not known whether hemodialysis patients form a different patient group in terms of susceptibility to COVID-19 infection or severe disease. In this study, thorax computed tomography (CT) findings were evaluated in hemodialysis patients diagnosed with COVID-19 infection during the pandemic period.

Material and Methods: CT findings of 32 hemodialysis patients diagnosed with COVID-19 with real-time polymerase chain reaction or thorax CT examination were evaluated retrospectively. Radiological findings were classified as ground glass, consolidation, mixed type involvement (ground glass and consolidation), crazy paving appearance, interlobular septal thickening, nodule, halo-reverse halo finding, air bronchogram finding, subpleural curvilinear opacities and tree-in-bud views.

Results: A total of 32 patients were included in the study. Twenty-one (65.6%) of the patients were male and 11 (34.4%) were female. The mean age was 67.5±8.5 years. All patients had chronic kidney failure. Thorax CT examination revealed ground-glass opacities in 14 (43.8%) patients, consolidation in 3 (9.4%) patients, and mixed type involvement (ground-glass opacities and consolidation) in 15 (46.9%) patients. The accompanying CT findings were pleural effusion in 23 (71.9%) patients, subpleural curvilinear opacities in 13 (40.6%) patients, bronchial wall thickening in 11 (34.4%) patients, lymphadenopathy in 7 (21.9%) patients, bronchiectasis in 4 (12.5%) patients and pleural thickening in 4 (12.5%) patients.

Conclusion: When hemodialysis patients are infected with COVID-19 infection, they differ significantly from other COVID-19 patients in terms of symptoms, clinical course, and prognosis, as well as imaging findings.

Keywords: COVID-19; hemodialysis; pneumonia; computed tomography.

ÖZ

Amaç: Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) toplumun her kesimini etkileyen benzeri görülmemiş bir pandemi sebebidir. Hemodiyaliz hastalarının, COVID-19 enfeksiyonuna ya da şiddetli hastalığa yatkınlık açısından farklı bir hasta grubunu oluşturup oluşturmadıkları bilinmemektedir. Bu çalışmada pandemi döneminde COVID-19 enfeksiyonu tanısı alan hemodiyaliz hastalarında toraks bilgisayarlı tomografi (BT) bulguları değerlendirilmiştir.

Gereç ve Yöntemler: Gerçek zamanlı polimeraz zincir reaksiyonu veya toraks BT incelemesi ile COVID-19 tanısı konulan 32 hemodiyaliz hastasının BT bulguları geriye dönük olarak değerlendirildi. Radyolojik bulgular; buzlu cam, konsolidasyon, karışık tip tutulum (buzlu cam ve konsolidasyon), kaldırım taşı görünümü, interlobüler septal kalınlaşma, nodül, halo-ters halo bulgusu, hava bronkogram bulgusu, subplevral kürvilineer opasiteler ve tomurcuklanmış ağaç görünümleri olarak sınıflandırıldı.

Bulgular: Çalışmaya toplam 32 hasta dahil edildi. Hastaların 21'i (%65,6) erkek, 11'i (%34,4) kadındı. Yaş ortalaması 67,5±8,5 yıl idi. Tüm hastalarda kronik böbrek yetmezliği mevcuttu. Toraks BT incelemesinde hastaların 14'ünde (%43,8) buzlu cam görünümü, 3'ünde (%9,4) konsolidasyon ve 15'inde (%46,9) karışık tip tutulum (buzlu cam görünümü ve konsolidasyon) görüldü. Eşlik eden BT bulguları 23 (%71,9) hastada plevral effüzyon, 13 (%40,6) hastada subplevral kürvilineer opasiteler, 11 (%34,4) hastada bronşiol duvar kalınlaşması, 7 (%21,9) hastada lenfadenopati, 4 (%12,5) hastada bronşektazi ve 4 (%12,5) hastada plevral kalınlaşma idi.

Sonuç: Hemodiyaliz hastaları COVID-19 enfeksiyonuna yakalandıklarında semptom, klinik seyir ve prognostik açıdan olduğu gibi görüntüleme bulguları açısından da diğer COVID-19 hastalarından önemli farklılıklar göstermektedir.

Anahtar kelimeler: COVID-19; hemodiyaliz; pnömoni; bilgisayarlı tomografi.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), known as coronavirus disease 2019 (COVID-19) has spread rapidly all over the world, causing a serious pandemic. The prognosis of the disease varies from asymptomatic or very mild course to unilateral or bilateral severe pneumonia and even respiratory failure that will require respiratory support in intensive care conditions. In severe cases, the severe inflammatory response accompanied by cytokine storm worsens respiratory symptoms and can even cause death. Although the mortality of the disease in the general population varies between 1.4% and 8%, the proportion of patients who need intensive care support rises to high values between 16% and 78% (1). Advanced age, male gender, and current comorbidity (especially cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and cancer history) are poor prognostic factors associated with the disease (1).

Since symptoms are non-specific for diagnosis in COVID-19 pneumonia, some diagnostic tests are required in addition to the patient's clinic. Real-time polymerase chain reaction (RT-PCR) is the standard test in diagnosis. However, since there is a waiting period for the detection of the virus and can be negative results at the beginning of the disease, radiological evaluation often plays a key role in the diagnosis (2).

Some specific radiological findings have been identified in computed tomography (CT) examination in COVID-19 pneumonia. These findings are in the form of bilateral, peripheral, and ground-glass opacities, consolidations, or a combination of these, which mainly hold the basal regions (3). CT findings were divided into 4 groups by the British Society of Thoracic Imaging (BSTI). This classification is used frequently by adapting it to our country, where the first case was seen on March 10, 2020. The course of the infection in chronic kidney patients is not clear. Mortality is expected to be higher in hemodialysis (HD) patients compared to the general population due to poor prognostic criteria such as advanced age, comorbidities, etc. Considering the high number of HD patients and the immune function of these patients is not normal, the condition of HD patients is of particular importance in the COVID-19 pandemic (1,4).

In this study, we aimed to evaluate the findings in the thorax CT examination of HD patients diagnosed with COVID-19 infection during the pandemic period.

MATERIAL AND METHODS

Patient Selection

Patients who were diagnosed with COVID-19 and admitted to our hospital with respiratory symptoms between 31 March and 25 May 2020 were evaluated. It was observed that 2513 patients had thoracic CT examinations at the time of admission. Among these patients, chronic HD patients diagnosed with COVID-19 were investigated. Patients were diagnosed with the presence of clinical signs (fever, cough, etc.) and positive thorax CT findings, or at least one positivity of RT-PCR test. Typical COVID-19 or possible COVID-19 categories were based on the classification determined by the BSTI as positive thorax CT findings. Finally, 32 patients who met the criteria were included in the study.

Comorbidities that patients carry in addition to chronic kidney failure were classified as a history of hypertension, diabetes, cardiovascular disease, COPD, and cancer.

The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (27.07.2020, 450).

Thorax CT Examination

In all patients, images were obtained with a multi-section CT device with 64 detectors (5 mm slice thickness, 512x512 matrix, 120 Kv automatic modulation mA; Aquilion64, Toshiba Medical Systems, Japan). Thorax CT examinations were evaluated by two independent radiologists (with 10 years of CT experience, Board-certified, and 4 years of CT experience). After the images were evaluated independently, the consensus was achieved in evaluation differences.

Image Analysis

Radiological findings were classified as ground glass, consolidation, mixed type involvement (ground glass and consolidation), crazy paving appearance, interlobular septal thickening, nodule, halo-reverse halo finding, air bronchogram finding, subpleural curvilinear opacities and tree-in-bud views. Also, the presence of accompanying findings such as cavitation, bronchiectasis, bronchial wall thickening, pleural changes (thickening, effusion), lymphadenopathy, and pneumothorax was evaluated. Opacities in which signs of the vascular or bronchial wall could be distinguished were defined as ground glass, and opacities that were not distinguishable were defined as consolidation. Round or irregular shaped, ground glass density with uniform or irregular borders, semi-solid, or solid densities measured at 3 centimeters and below were accepted as nodules.

Statistical Analysis

MedCalc v.12 (Ostend, Belgium) was used for statistical analysis. The descriptive statistics were given as mean±standard deviation. Categorical variables were stated as frequencies and percentages.

RESULTS

A total of 32 patients were included in the study. Twenty-one (65.6%) of the patients were male and 11 (34.4%) were female. The mean age of the patients was 67.5±8.5 years. All patients had chronic kidney failure. The comorbidities present in the patients in order of frequency include hypertension in 30 (93.8%) patients, diabetes in 16 (50.0%) patients, cardiovascular disease in 16 (50.0%) patients, chronic obstructive pulmonary disease in 8 (25.0%) patients and cancer history in 2 (6.3%) patients (Table 1). The malignancies present in these two patients were prostate and laryngeal cancers. In the follow-up, 11 (34.4%) patients died, while the remaining 21 (65.6%) patients were discharged after treatment.

Table 1. Comorbidities of the patients (n=32)

Comorbidities	n (%)
Hypertension	30 (93.8)
Diabetes	16 (50.0)
Cardiovascular Disease	16 (50.0)
Chronic Obstructive Pulmonary Disease	8 (25.0)
Cancer	2 (6.3)

In the thorax CT examination, 14 (43.8%) patients had ground-glass appearance (Figure 1), 3 (9.4%) patients consolidation, and 15 (46.9%) patients mixed type appearance (ground glass and consolidation). Air bronchogram was observed in 12 (37.5%) patients and all of them consisted of patients with consolidation or mixed type involvement. Nodules were observed in the lung parenchyma of 5 (15.6%) patients (Figure 2). Interlobular septal thickening was observed in 6 (18.8%) patients, but the crazy-paving pattern was not observed in any of the patients. Tree-in-bud pattern was observed in 6 (18.8%) of the patients, and 5 (83.3%) of these patients had mixed-type involvement, while only 1 patient had a ground-glass appearance, and none of them had pure consolidation. While the halo sign was not observed in any of the patients, the reversed halo sign was observed in one (3.1%) patient (Figure 3). The accompanying CT findings were pleural effusion in 23 (71.9%) patients, subpleural curvilinear opacities in 13 (40.6%) patients, bronchial wall thickening in 11 (34.4%) patients, bronchiectasis in 4 (12.5%) patients, and pleural thickening was observed in 4 (12.5%) patients. None of the patients had cavitation or pneumothorax (Table 2).

DISCUSSION

Our study is very important in terms of being one of the first studies showing the COVID-19 thorax CT findings in HD patients, which is a very special population. One of the most important results of our study was the presence of ground glass, consolidation, or mixed type (the most common) involvement in all patients. In our patient group, unlike the CT findings reported in the normal population in

Table 2. Computed tomography findings of the patients

	n (%)
Primary Findings	
Pure Ground Glass Opacity	14 (43.8)
Pure Consolidation	3 (9.4)
Mixed Type	15 (46.9)
Crazy Paving Pattern	0 (0.0)
Reticular Pattern (Interlobular Septal Thickening)	6 (18.8)
Nodule	5 (15.6)
Halo sign	0 (0.0)
Reverse Halo Sign	1 (3.1)
Air Bronchogram	12 (37.5)
Subpleural Curvilinear Lines	13 (40.6)
Tree in Bud	6 (18.8)
Accompanying Findings	
Cavitation	0 (0.0)
Bronchiectasis	4 (12.5)
Bronchial Wall Thickening	11 (34.4)
Pleural Effusion	23 (71.9)
Pleural Thickening	4 (12.5)
Lymphadenopathy	7 (21.9)
Pneumothorax	0 (0.0)

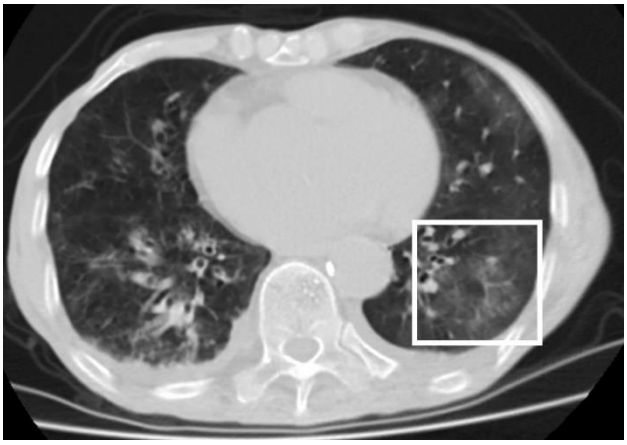

Figure 1. Axial non-contrast computed tomography image shows ground-glass opacity in the left lower lobe (frame).

Figure 2. Axial non-contrast computed tomography image shows a nodule in the right lower lobe (arrow).

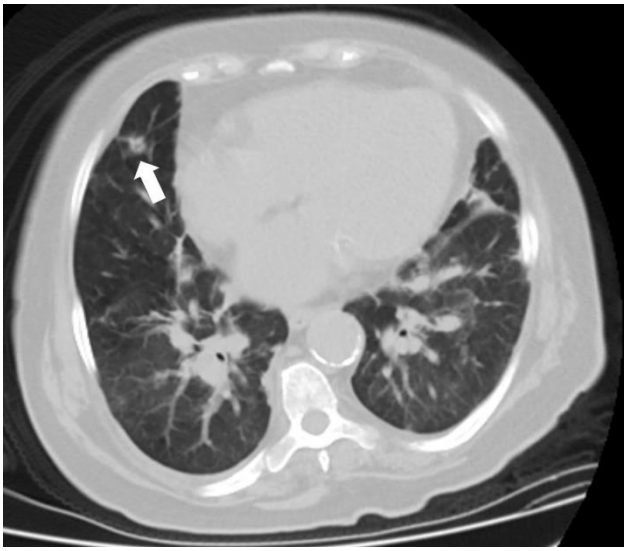

Figure 3. Axial non-contrast computed tomography image shows the reversed halo sign in the right middle lobe (arrow).

the literature, consolidations accompanying ground-glass appearance were more common than pure ground-glass opacities, and pleural effusion was also more frequent. These findings were evaluated in favor of the higher disease stage and more severe infection at the time of diagnosis in HD patients with COVID-19 infection. Besides, it was observed that the tree-in-bud appearance was more frequent in our patient group compared to the non-specific COVID-19 patient group in the literature. This finding suggests that bacterial pneumonia or aspiration pneumonia may have accompanied COVID-19 pneumonia in our patient group due to the presence of comorbidities in addition to chronic kidney disease, the more severe infection, and that the stage of the disease is more advanced than other patients. Similarly, a higher rate of pleural pathology may indicate that the infection is at an advanced stage in our patient group, or it may be a sign of poor prognosis.

COVID-19 disease, the cause of which is SARS-CoV-2, was declared as a pandemic by the World Health Organization on 12 March 2020. As of April 8, 2020, the virus has been reported to affect more than 199 countries worldwide, infecting more than one million people and causing around 81500 deaths. However, since some patients with asymptomatic and mild symptoms have not been tested, the stated figures are considered to be under reality (5).

Since the symptoms in COVID-19 pneumonia are non-specific for diagnosis, other diagnostic tests are required in addition to the clinical findings of the patients. RT-PCR is the standard test in diagnosis (2). However, thorax CT examination plays a complementary and key role in the diagnosis because RT-PCR does not give immediate results. It can give false-negative results due to low viral load and it is about 5 days between false-negative result and positive result. CT is very important in early diagnosis, especially in the patient group in which the patient's symptoms persist for more than 3 days and the RT-PCR test is negative due to the low viral load (5,6). However, it has been shown that CT findings may be normal in 56% of patients in the first 2 days from the onset of symptoms (7).

A wide variety of findings have been described in different studies of COVID-19 lung involvement. However, the most common CT finding in all studies was typically reported as ground-glass opacities with peripheral and subpleural distribution. In the majority of patients, multilobar involvement, especially the lower lobes, has been demonstrated. Ground-glass opacities are defined as fog-shaped density increases in which the vascular and bronchial walls are not erased and can be found alone, with areas of consolidation or in the form of a crazy-paving pattern with an interlobular septal thickening. Consolidations, on the other hand, are defined as increased density due to exudate filling into the alveoli and blurring the vascular and airway boundaries. They are usually observed in patients with multifocal, segmental and patchy involvement with COVID-19 infection (5,8). Other typical CT findings include nodules, reticular pattern (interlobular-intralobular septal thickening), air bronchogram, airway changes (bronchiectasis, bronchiolar wall thickening), halo and reverse halo sign, while atypical findings are a tree-in-bud pattern, subpleural curvilinear opacities, lymphadenopathy, pleural changes (thickening, effusion) and cavitation (2,8). Round or irregular shaped, ground glass density with uniform or irregular borders, semi-solid, or solid densities measured at 3 centimeters and below are defined as nodules (9). The reticular pattern refers to interlobular and intralobular septal thickening reflecting interstitial lymphocyte infiltration (10). While ground glass appearances surrounding the consolidation areas, halo finding, represents hemorrhage around the mass or nodule; the consolidation areas surrounding the ground glass areas, reverse halo finding, represents the dissolution of the debris from the central section (8,10).

HD patients form a special group of patients because they constitute a large patient population, have associated comorbidities, have impaired immune function, and have the potential to become super-infectious when infected (1,4). Some studies have shown that COVID-19 enters cells through the angiotensin-converting enzyme-2 (ACE-2) receptor, causing infection. The abundance of ACE-2 receptors in renal proximal tubule cells in uremic patients is one of the factors that predispose HD patients to infection (11).

After the SARS-CoV-2 virus infects the respiratory tract, it multiplies in the cells of the airway and activates the immune system and causes the release of massive levels of pro-inflammatory cytokines. The resulting cytokine storm can cause severe symptoms and even death. IL-6, IL-10, TNF-a, and other inflammatory cytokine increases are associated with poor prognosis in COVID-19 infection (12). Since lymphocyte and granulocyte functions are impaired in HD patients due to their uremic status, the immune response to COVID-19 infection is abnormal (13). In one study, T cells, B cells, and natural killer (NK) cells were found to be lower in patients who received HD treatment compared to patients who did not. In HD patients with COVID-19 infection, the number of these cells has been shown to decrease even more. Similarly, the number of cytokines such as IL-4, IL-6, and TNF-α increased in patients with COVID-19 infection compared to a healthy population, while the rate of these cytokines in HD patients with COVID-19 infection decreased significantly compared to other patients with COVID-19 infection. These results revealed that the impaired immune response in HD patients had a devastating effect on initiating an effective anti-viral response while limiting tissue damage as it reduced cytokine release. In the same study, the main causes of death of HD patients with COVID-19 were determined as cardiovascular and cerebrovascular complications or hyperkalemia. The reason for this has been shown to be shortened dialysis times to reduce the risk of COVID-19 infection of HD patients (4).

Considering the pathogenesis of lung involvement findings in COVID-19 infection and changes in the immune system response in HD patients, it is not known whether the frequency of lung involvement findings will differ in this group of patients. In the study by Wang et al. (14), bilateral diffuse consolidation or ground-glass appearances were observed in all 7 HD patients who were diagnosed with COVID-19, and death was reported in 3 of the patients. In the study of Du et al. (11) with 32 COVID-19 positive HD patients, ground-glass opacities were observed in 18 cases; unilateral consolidations were

observed in 7 patients, bilateral consolidations were observed in 7 patients; and pleural effusion was observed in 2 patients. In the study by Wang et al. (13) involving 5 patients, ground-glass opacities were observed in all patients, and it was reported that no severe complications or death occurred in any patient. In our study, a combination of ground glass and consolidation was observed in the majority (46.9%) of patients.

In the study conducted by Ma et al. (4), deaths were reported in 10 of 42 HD patients who were positive for COVID-19. In our study, the mortality rate was 11/32 (34.4%). Studies, including our study, show that HD mortality due to COVID-19 is quite high compared to the other population.

Ground glass opacities have been reported between 46% and 100% in COVID-19 infection and occur in the early phases of the disease or mild infection. As the severity of the disease increases, a crazy-paving pattern occurs with consolidation or interstitial thickening within the ground glass areas (15,16). In our study, the consolidations accompanying the ground-glass areas (mixed type involvement) were observed to be higher than pure consolidation with a rate of 46.9%, and the pure consolidation rate was lower than other COVID-19 CT studies, which were not specific to HD patients. This situation was interpreted in favor of the disease stage or severity of inflammation in HD patients when compared to the other patient population. It is associated with pure consolidation in COVID-19 infection, long time between symptom onset and thoracic CT examination, or advanced (>50 years) patient age (17,18). In our study, pure consolidation was observed in 3 (9.4%) patients. The crazy paving pattern is a common finding for COVID-19 infection and has been reported between 5% and 89% (15). In the later stages of the infection, it is stated that this pattern progresses to consolidation or causes the development of pleural effusion (17). The absence of a crazy-paving pattern and high pleural effusion in our patient group was associated with the advanced stage of infection in HD patients at the time of diagnosis.

Air bronchogram is also one of the frequently observed findings in COVID-19 infection, and it was reported as high as 80% (41/51) in a study by Song et al (19). Bronchial wall thickening has been reported to be higher in patients with severe clinical symptoms compared to patients with mild symptoms (20). In our study, air bronchogram findings were found in 12 (37.5%) patients, and bronchial wall thickening was found in 11 (34.4%) patients. Another frequently reported finding in COVID-19 infection is nodules. It was reported as 6% in the study by Shi et al. (21), and 7.2% (with or without halo sign) in the study by Li et al (22). In our study, nodules were seen in 5 (15.6%) patients and it was observed higher than these studies. It has been suggested that in the reticular pattern, reticulations increase with prolonged disease duration (17,23). Reticular pattern and linear opacities are reported in the literature at a very variable rate between 1% and 81% (15). Inter-intralobular septal thickening and linear opacities were observed in 14 (43.8%) patients in our study. Reverse halo finding is among the findings in COVID-19 infection. In the studies conducted, Bernheim et al. (7) reported as low as 2/121 (1.7%), while Wang et al. (24) reported a higher rate with 14/93 (15.1%). In our study, a reverse halo sign was observed in 1 (3.1%) patient.

Although it has been stated that tree-in-bud appearances, which are defined as bronchiolitis findings in the literature, can also be seen in COVID-19 infection, it is stated that bacterial infection superposition or aspiration should be considered first if this finding is observed (15). In our study, this finding was observed in 6 (18.8%) patients, and it was thought that bacterial pneumonia or aspiration pneumonia might accompany these patients due to the presence of comorbidities or advanced infection-disease stage in our patient group.

Mediastinal lymphadenopathy (LAP) is one of the rare CT findings in COVID-19 infection and has been stated to be a risk factor for severe and progressive pneumonia. LAP has been reported in the literature between 0% and 29%. It is stated that when it is seen with pleural effusion and tree in bud pattern views, it should be evaluated in favor of bacterial superinfection (15). In our study, mediastinal LAP was seen in 7 (21.9%) patients and is consistent with the rate reported in the general COVID 19 population in the literature.

Pleural pathologies (effusion and thickening) are rare, associated with pleural inflammation and observed in the late stages of the disease. They are also thought to be a poor prognostic marker and reported between 0% and 20% in COVID-19 infection (15,25). In our patient group, pleural effusion was observed in 23 (71.9%) patients, pleural thickening was observed in 4 (12.5%) patients, and pleural effusion and/or thickening was observed in 25 (78.1%) patients and was above the reported rates.

Our study has some important limitations. The first of these is that the study is retrospective, single centered, and not comparative. The presence of comorbid diseases in most HD patients appears to be another limitation in revealing the specific differences of these patients to chronic renal failure or regular dialysis treatment. Also, the low number of patients is an important limitation in terms of the adequacy of statistical data.

CONCLUSION

HD patients are a special group of patients due to differences in the immune system, a high number of comorbidities, and periodic HD requirements. When these patients are infected with COVID-19, they differ significantly from other COVID 19 patients in terms of symptoms, clinical course, and prognostic as well as imaging findings. In our study, it was shown that mixed patterns (ground glass and consolidation coexistence), nodules, budded tree views, and the presence of pleural pathology were more common than other COVID-19 patients.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (27.07.2020, 450).

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A Reason for Admission to the Sleep Outpatient Clinic during COVID-19 Pandemic: Insomnia

COVID-19 Pandemisi Sürecinde Uyku Polikliniğine Başvuru Nedeni: Uykusuzluk

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ABSTRACT

Aim: Sleep can be affected for various reasons such as social isolation, online education, shift work, etc. during the coronavirus disease 2019 (COVID-19) pandemic. People who have comorbid psychiatric or sleep disorders before the pandemic are thought to be more affected. The aim of this study was to investigate the effect of the COVID-19 pandemic on sleep quality and insomnia.

Material and Methods: Our study was a retrospective study, and patients who admitted to the sleep outpatient clinic with insomnia complaints during the COVID-19 pandemic were included. The complaints, sociodemographic characteristics, and diagnosis of the patients were obtained from medical records.

Results: Fifty-three patients diagnosed with insomnia according to the International Classification of Sleep Disorders third edition (ICSD-3) were included in the study. The mean sleep time before the pandemic was 6.8±1.2 hours, while it was 5.9±1.7 hours after the pandemic. After the pandemic, 13 (24.5%) patients had shortened sleep duration. There was no difference in clinical features between those whose sleep duration decreased and did not change during the pandemic. Twenty (37.7%) patients' complaints of insomnia started during the pandemic. Most of the patients whose complaints started during the pandemic were male (n=12, 60.0%). Their main complaint was difficulty in falling asleep (n=18, 90.0%). The anxiety symptoms were remarkable.

Conclusion: Sleep disorders during the pandemic are an important problem for everyone. However, some individuals have a higher risk of sleep problems. Therefore, the results of our study may contribute to the interventions aimed at improving sleep quality during pandemic.

Keywords: COVID-19; insomnia; pandemic.

ÖZ

Amaç: Uyku, koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) pandemisi döneminde sosyal izolasyon, çevrimiçi eğitim, vardiyalı çalışma gibi çeşitli nedenlerle etkilenebilir. Pandemiden önce eşlik eden psikiyatrik veya uyku bozukluğu olan kişilerin bu durumdan daha fazla etkilendiği düşünülmektedir. Bu çalışmanın amacı COVID-19 pandemisinin uyku kalitesi ve uykusuzluk üzerine etkisini araştırmaktır.

Gereç ve Yöntemler: Çalışmamız geriye dönük bir çalışma olup COVID-19 pandemisi sürecinde uyku polikliniğine uykusuzluk yakınmasıyla başvuran hastalar çalışmaya dahil edilmiştir. Hastaların başvuru şikâyetleri, sosyo-demografik özellikleri ve tanıları tıbbi kayıtlardan elde edildi.

Bulgular: Uluslararası Uyku Bozuklukları Sınıflandırmasının üçüncü baskısı (International Classification of Sleep Disorders third edition, ICSD-3)'na göre uykusuzluk tanısı almış 53 hasta çalışmaya dâhil edildi. Pandemiden önceki ortalama uyku süresi 6,8±1,2 saat iken, pandemiden sonra ortalama uyku süresi 5,9±1,7 saat idi. Pandemiden sonra 13 (%24,5) hastanın uyku süresi kısalmıştı. Pandemi sürecinde uyku süresi azalan ve değişmeyenler arasında klinik özellikler açısından fark yoktu. Yirmi (%37,7) hastanın uykusuzluk şikâyeti pandemi döneminde başlamıştı. Pandemi sırasında yakınmaları başlayan hastaların çoğu (n=12, %60,0) erkekti. Başlıca şikâyetleri uykuya dalmada güçlüktü (n=18, %90,0). Şikâyetleri arasında anksiyete belirtileri dikkat çekiciydi.

Sonuç: Pandemi sırasındaki uyku problemleri herkes için önemli bir sorundur. Ancak bazı bireylerin uyku problemi geliştirme riski diğerlerinden daha yüksektir. Bu nedenle, çalışmamızın sonuçları pandemi dönemlerinde uyku kalitesini artırmaya yönelik bazı müdahalelerin uygulanmasına destek sağlayabilir.

Anahtar kelimeler: COVID-19; uykusuzluk; pandemi.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a virus outbreak that appeared on 1 December 2019. The spread rate of the virus increased in January 2020 and has spread all over the world. The first detected COVID-19 case was announced by the Ministry of Health in Turkey on 11 March 2020 (1).

Social isolation was applied in countries during the pandemic process. People left their homes only for food shopping and medical needs. All these restrictions affected people's lifestyles and social relationships. Anxiety increased in many people for fear of being infected (2). Studies show that psychological stress and mental illnesses increase during the pandemic period (3). Although the speed of virus spread has been reduced by restriction of freedom, working from home, and online education, their psychological reflections have been quite high.

Homeostatic drive to sleep is important for sleep quality. The circadian rhythm keeps us awake all day and sleepy at night. Factors such as sunshine, eating patterns and exercise regulate the circadian rhythm. The melatonin hormone has an important role in regulating sleep. Exposure to light throughout the day is needed to increase of melatonin during the night. Physical activity throughout the day improves sleep quality (4). Low activity levels (e.g., due to depression, social confinement) and very high activity levels (e.g., due to stress, work overload) affect sleep negatively. Causes such as working in shifts, circadian rhythm disturbances, inability to provide sufficient sleep time due to work and social factors cause short sleep durations (5).

It can be thought that sleep will be affected for various reasons during the pandemic period. This study aimed to investigate the effect of the COVID-19 pandemic on sleep quality and insomnia.

MATERIAL AND METHODS

This retrospective study was performed at the sleep outpatient clinic of Erenköy Mental and Neurological Diseases Training and Research Hospital. Following the Helsinki declaration, approval was obtained from the Ethics Committee of Erenköy Mental and Neurological Diseases Training and Research Hospital (08.06.2020, 12). After the emergence of the first case in our country, on 27.03.2020, patient admission started with new measures and arrangements in our sleep outpatient clinic. After two months of the epidemic, as of 01.06.2020, the normalization process has started. All patients who admitted to the sleep outpatient clinic with insomnia complaints between 27.03.2020 and 01.07.2020 were screened. Inclusion criteria included patients with diagnosis of insomnia according to the third edition of the International Classification of Sleep Disorders (ICSD-3), and those without any other accompanying sleep disorder. Exclusion criteria included patients with diagnosis of a sleep disorder other than insomnia. Fifty-three patients diagnosed with insomnia according to the ICSD-3 were included in the study. The complaints, sociodemographic characteristics, and diagnosis of the patients were obtained from medical records.

Statistical Analysis

Statistical analysis was performed using the SPSS v.20. The Shapiro-Wilk test was used to determine whether the data were normally distributed. Continuous data were expressed as mean and standard deviation or median, interquartile range and minimum-maximum values, while categorical data were presented as numbers and percentages. A student t test or Mann Whitney-U test was used to compare continuous variables with and without normal distribution, respectively. Pearson chi-square and Fisher's exact tests were used for statistical analysis of the categorical variables. A p value <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 44.1±14.1 years. Twenty-nine (54.7%) of the patients were male. The duration of the patients' complaints of insomnia was between 1 and 240 months (31.0±44.6). The mean sleep time before the pandemic was 6.8±1.2 hours, while the mean sleep time after the pandemic was 5.9±1.7 hours. Of the 53 patients with insomnia, 48 (90.6%) patients described difficulty in falling asleep, 19 (35.8%) patients described difficulty in maintaining sleep, and 7 (13.2%) patients described the problem of waking up early. Seventeen (32.1%) patients complained of waking up tired in the morning. Twelve (22.6%) patients had excessive sleepiness during the day, 14 (26.4%) patients had depressive symptoms, 16 (30.2%) patients had anxiety symptoms, 5 (9.4%) patients had pain, 3 (5.7%) patients had somatic complaints, and 7 (13.2%) patients had irritability. Considering psychiatric comorbidities, there was a depressive disorder in 6 (11.3%) patients, an anxiety disorder in 8 (15.1%) patients, a psychotic disorder in 1 (1.9%) patient, and a bipolar disorder in 3 (5.7%) patients. Nineteen (35.9%) patients were using antidepressants, 8 (15.1%) patients were using anxiolytic, and 3 (5.7%) patients were using antipsychotics. When other sleep disorders were examined, 1 (1.9%) patient had REM behavior disorder, 1 (1.9%) patient had nightmare disorder, and 1 (1.9%) patient had sleep paralysis. When additional medical diseases were examined, 4 (7.6%) patients had hypertension, 3 (5.7%) patients had diabetes, 1 (1.9%) patient had asthma, 1 (1.9%) patient had chronic obstructive pulmonary disease, and 1 (1.9%) patient had hypothyroidism. There were 1 (1.9%) patient with alcohol use and 3 (5.7%) smoking patients.

Patients were divided into two groups according to the presence of shortened sleep duration after the pandemic. While 13 (24.5%) patients had shortened sleep duration, the sleep time of 40 (75.5%) patients did not change. Patients with shortened sleep duration had significantly short insomnia duration (p=0.048). There was no difference in clinical features between the groups (Table 1).

Patients were divided into two groups according to the duration of the patient's complaints. While 20 (37.7%) patients' complaints of insomnia started during the pandemic period, 33 (62.3%) patients' complaints of insomnia started before the pandemic period. There was no difference in clinical features between the groups (Table 2). Most of the patients whose complaints started during the pandemic were male (n=12, 60.0%). Their main complaint was difficulty falling asleep (n=18, 90.0%). Worry among their complaints was remarkable (n=10, 50.0%). Four of them had a diagnosis of anxiety disorder. Three of them had hypertension and two of them had diabetes mellitus.

Table 1. Comparison of the patients with reduced and unchanged sleep time in pandemic

	Reduced (n=13)	Unchanged (n=40)	p
Age (years)	44.4±10.3	44.0±15.3	0.937
Duration of insomnia (months)	2 (6) [1-96]	36 (52) [1-240]	**0.048**
Gender			
Male	5 (38.5)	24 (60.0)	0.175
Female	8 (61.5)	16 (40.0)	
Increased insomnia complaint	5 (38.5)	16 (40.0)	0.922
Waking up early	2 (15.4)	5 (12.5)	0.790
Difficulty maintaining sleep	7 (53.8)	12 (30.0)	0.183
Difficulty falling asleep	12 (92.3)	36 (90.0)	0.805
Tired waking up	7 (53.8)	10 (25.0)	0.086
Daytime sleepiness	2 (15.4)	10 (25.0)	0.707
Headache	1 (7.7)	4 (10.0)	0.805
Depressive symptoms	2 (15.4)	12 (30.0)	0.473
Anxiety symptoms	4 (30.8)	12 (30.0)	0.958
Ache	1 (7.7)	4 (10.0)	0.805
Somatic complaint	0 (0.0)	3 (7.5)	0.567
Irritability	0 (0.0)	7 (17.5)	0.174
Depressive disorder	1 (7.7)	5 (12.5)	0.635
Anxiety disorder	2 (15.4)	6 (15.0)	0.973
Psychotic disorder	1 (7.7)	0 (0.0)	0.245
Bipolar disorder	0 (0.0)	3 (7.5)	0.567
Hypertension	1 (7.7)	3 (7.5)	0.982
Diabetes Mellitus	2 (15.4)	1 (2.5)	0.145
Asthma	0 (0.0)	1 (2.5)	0.565
Chronic Obstructive Pulmonary Disease	1 (7.7)	0 (0.0)	0.245
Hypothyroidism	0 (0.0)	1 (2.5)	0.565

Reduced: patients with reduced sleep time in pandemic, Unchanged: patients with no change of sleep time in pandemic, data are presented as the number (%) of patients, mean±standard deviation or median (interquartile range) [minimum-maximum]

Table 2. Comparison of the patients according to the time of the complaints start

	During the pandemic (n=20)	Before the pandemic (n=33)	p
Age (years)	40.0±11.1	46.6±15.3	0.099
Duration of insomnia (months)	1 (1) [1-2]	36 (36) [13-240]	**<0.001**
Gender			
Male	12 (60.0)	17 (51.5)	0.547
Female	8 (40.0)	16 (48.5)	
Waking up early	3 (15.0)	4 (12.1)	0.764
Difficulty maintaining sleep	8 (40.0)	11 (33.3)	0.624
Difficulty falling asleep	18 (90.0)	30 (90.9)	0.913
Tired waking up	6 (30.0)	11 (33.3)	0.801
Daytime sleepiness	2 (10.0)	10 (30.3)	0.105
Headache	2 (10.0)	3 (9.1)	0.913
Depressive symptoms	5 (25.0)	9 (27.3)	0.856
Anxiety symptoms	10 (50.0)	6 (18.2)	**0.014**
Ache	2 (10.0)	3 (9.1)	0.913
Somatic complaint	1 (5.0)	2 (6.1)	0.871
Irritability	4 (20.0)	3 (9.1)	0.405
Depressive disorder	1 (5.0)	5 (15.2)	0.390
Anxiety disorder	4 (20.0)	4 (12.1)	0.457
Psychotic disorder	1 (5.0)	0 (0.0)	0.377
Bipolar disorder	2 (10.0)	1 (3.0)	0.549
Hypertension	3 (15.0)	1 (3.0)	0.145
Diabetes Mellitus	2 (10.0)	1 (3.0)	0.549
Asthma	0 (0.0)	1 (3.0)	0.432
Chronic Obstructive Pulmonary Disease	0 (0.0)	1 (3.0)	0.432
Hypothyroidism	0 (0.0)	1 (3.0)	0.432

During the pandemic: insomnia started in the pandemic, Before the pandemic: insomnia started before the pandemic, data are presented as the number (%) of patients, mean±standard deviation or median (interquartile range) [minimum-maximum]

DISCUSSION

Stress-related sleep problems are quite common (6). The group that is sensitive to stress-related sleep disorders generally develops chronic insomnia (7). Preexisting insomnia is an important risk factor for Posttraumatic Stress Disorder (PTSD) (8). This stressor causes the sleep disorder to increase even more (9). In our study, 37.7% of the patients had newly developed insomnia while 62.3% of the patients had insomnia before the COVID-19 pandemic. Studies on acute infectious diseases such as severe acute respiratory syndrome (SARS) show that both the infected and uninfected developed anxiety, depression, stress, and posttraumatic stress disorder (10,11). In previous studies, it has been shown that sudden developing events have negative effects on people's mental health and cause symptoms similar to post-traumatic stress disorder (12).

In a newly published study, 7% of people living in Wuhan, most of whom were female experienced PTSD symptoms during the COVID-19 pandemic (13). In our study, the majority of our patients who suffered from insomnia both during and before the pandemic period were female.

Anxiety levels of those who were younger than 35 years and followed more than 3 hours of COVID-19 news per day were found to be higher than those who were older than 35 and less exposed to COVID-19 news (13). We detected that patients who developed insomnia during the pandemic period were younger than those who developed insomnia before the pandemic (40.0±11.1 vs. 46.6±15.3). Studies have shown that PTSD symptoms develop less in the presence of good sleep quality and fewer early morning awakening (14). In our study, 7 of the patients diagnosed with insomnia had early morning awakening.

In a study by Taylor et al. (15) in 2008, it was shown that young age and female gender caused negative psychological effects in the quarantine period. In another study, the presence of psychiatric illness was shown to be associated with anxiety and anger 4-6 months after quarantine (16). There was a depressive disorder in 6 (11.3%) patients, an anxiety disorder in 8 (15.1%) patients, a psychotic disorder in 1 (1.9%) patient, and a bipolar disorder in 3 (5.7%) patients in our study.

Sleep has important effects on the immune system and emotion regulation. Studies on sleep deprivation have shown the relationship between the immune system and sleep. Cohen et al. (17) show that those with sleep time <7 hours or sleep efficiency <92% had more infections after virus exposure than those with sleep time >8 hours or sleep efficiency >98%. In a study, it was shown that the risk of having a cold after a virus exposure increased in those who sleep less than 6 hours a night (18). In our patients, the mean sleep time before the pandemic was 6.8±1.2 hours, while the mean sleep time after the pandemic was 5.9±1.7 hours. This is important for vulnerability to infection.

There is a review by the European CBT-I Academy that examines sleep and insomnia due to COVID-19 home confinement (19). Cellini et al. (20) evaluated the sleep structure, time perception, and use of electronic devices in 1310 people and saw an increase in the use of social media before bedtime. They saw that people go to bed later, get up later, and spend more time in bed, thus reducing sleep quality. Sleep problems have been shown to increase in the presence of depression, anxiety, and stress. Li et al. (21) demonstrated an increased prevalence of insomnia, including new-onset insomnia, during the COVID-19 pandemic. While time in bed and total sleep time increased, sleep efficiency decreased significantly (21). In our study, while patients described a higher rate of difficulty in falling asleep, early morning awakening rates were low.

As in the COVID-19 outbreak, traumatic events cause psychological stress and anxiety and affect sleep quality (22). For that reason, studies conducted during the COVID-19 pandemic focused on physical and mental health and sleep disorders. Consistent with these studies, in our study, 14 (26.4%) patients had depressive symptoms, 16 (30.2%) patients had anxiety symptoms, 7 (13.2%) patients had irritability, and 3 (5.7%) patients had somatic complaints.

In most studies conducted during the COVID-19 pandemic period, a specific sleep scale was not used. Most of the studies have been done by medical staff, who are exposed to or suffered from the virus itself (22). In our study, a specific sleep scale was not used, either. However, since patients who admitted to the sleep outpatient clinic are examined, it is important in terms of providing information about the society.

CONCLUSION

Sleep disorders during the pandemic period are an important problem for everyone. However, some individuals are riskier for sleep problems. Female gender, comorbid psychiatric disorders, and medical illness are important risk factors. Since sleep affects both emotional regulation and the immune system, it is very important during the pandemic period. Good sleep is necessary for psychological well-being and a strong immune system.

Therefore, the results of our study may contribute to interventions aimed at improving sleep quality during pandemic periods. Providing psychological support in risky groups such as female gender, additional medical and psychiatric diseases, and training to improve sleep quality is very important. It is necessary to maintain the normal routine during pandemic periods to regulate the circadian rhythm.

Ethics Committee Approval: The study was approved by the Ethics Committee of Erenköy Mental and Neurological Diseases Training and Research Hospital (08.06.2020, 12).

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Myalgia Frequency in Patients with COVID-19 and Its Relationship with Creatine Kinase Levels

COVID-19 Hastalarında Myalji Sıklığı ve Kreatin Kinaz Düzeyleri ile İlişkisi

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ABSTRACT

Aim: Many studies have showed that myalgia is a common onset symptom in coronavirus disease 2019 (COVID-19). This study aimed to determine the frequency of muscle pain in patients followed with COVID-19 diagnosis, and to investigate the relationship between muscle pain and creatine kinase (CK), pH, lactate and lactate dehydrogenase (LDH) levels.
Material and Methods: One hundred ten patients diagnosed with COVID-19 in our hospital were included retrospectively in this study. Presence of myalgia at the time of admission and on the 14th day of control were investigated. The first admission laboratory findings, 3rd day CK values and 14th day control CK values of all patients were recorded retrospectively from their files.
Results: The study included 110 patients diagnosed with COVID-19. Fifty patients (45.5%) had muscle pain at the time of admission, and it was one of the most common musculoskeletal complaints. High CK results were obtained in 48 (43.6%) of the 110 patients at the time of admission. Thirty-two (66.7%) of 48 patients with high CK had muscle pain ($p<0.001$). In the patients with muscle pain, the CK levels observed on 1st, 3rd, and 14th day of the disease were found to be significantly higher than in those without muscle pain ($p<0.001$, $p=0.003$, $p=0.029$). No significant relationship was found between complaints of muscle pain and lactate, pH, and LDH values.
Conclusion: Since some patients may only present with musculoskeletal symptoms such as myalgia, it is important that clinicians consider COVID-19 in patients presenting with myalgia and high CK levels.
Keywords: COVID-19; myalgia; creatine kinase.

ÖZ

Amaç: Birçok çalışma miyaljinin koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'da sık görülen bir başlangıç semptomu olduğunu göstermiştir. Bu çalışmada COVID-19 tanısıyla takip edilen hastalarda kas ağrısı sıklığının belirlenmesi ve kas ağrısı ile kreatin kinaz (creatine kinase, CK), pH, laktat ve laktat dehidrogenaz (LDH) düzeyleri arasındaki ilişkisinin araştırılması amaçlandı.
Gereç ve Yöntemler: Bu çalışmaya hastanemizde COVID-19 tanısı almış olan 110 hasta geriye dönük olarak dahil edildi. Başvuru sırasında ve 14. gün kontrolde miyalji yakınması olup olmadığı incelendi. Tüm hastaların ilk başvurudaki laboratuvar bulguları, 3. gün CK değerleri ve 14. gün kontrolündeki CK değerleri dosyalarından geriye dönük olarak kaydedildi.
Bulgular: COVID-19 tanısı almış 110 hasta çalışmaya alındı. Elli hastada (%45,5) başvuru anında kas ağrısı vardı ve en sık görülen kas iskelet sistemi şikâyetlerinden biriydi. Yüz on hastanın 48'inde (%43,6) başvuru anında CK yüksekliği saptandı. CK yüksekliği saptanan 48 hastanın 32'sinde (%66,7) kas ağrısı vardı ($p<0,001$). Kas ağrısı olan hastalarda 1., 3. ve 14. günde bakılan CK düzeyleri kas ağrısı şikayeti olmayanlara göre anlamlı derecede yüksek bulundu ($p<0,001$; $p=0,003$; $p=0,029$). Kas ağrısı yakınması ile laktat, pH ve LDH değerleri arasında anlamlı ilişki bulunmadı.
Sonuç: Başvuru sırasında yalnızca miyalji gibi kas iskelet sistem semptomları bulunan hastalar olabileceğinden, miyalji ile başvuran ve CK yüksekliği saptanan hastalarda COVID-19'un akılda tutulması önem arz etmektedir.
Anahtar kelimeler: COVID-19; miyalji; kreatin kinaz.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease caused by a new type of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This coronavirus has genetic similarities with severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), which was responsible for the epidemic of severe acute respiratory syndrome (SARS) in 2013. SARS-CoV-2 first emerged in China in December 2019 and soon spread to the rest of the world. The most common symptoms in adults are fever, cough, fatigue, dyspnea, anorexia, diarrhea, and myalgia (1,2). Many studies have shown that myalgia is a common (36%) onset symptom in COVID-19 (3).

Similar to other types of coronavirus causing acute respiratory failure, the spike (S) proteins of SARS-CoV-2 bind to the angiotensin-converting enzyme 2 (ACE2) receptors, and proteolytic cleavage occurs via the serine protease transmembrane protease serine 2 (4-6). ACE2 receptors have been shown in the brain, kidney, vascular smooth muscle, and skeletal muscles (7,8). SARS-CoV-2 can spread through the bloodstream or vascular endothelium, causing infection in all ACE2 receptor-containing tissues, including the musculoskeletal system. SARS-CoV-2 can affect skeletal muscle cells by binding with ACE2 alone or with the proinflammatory cytokines interleukin-6 (IL-6), interleukin-10 (IL-10) and tumor necrosis factor-alpha (TNF-α). Increased creatine kinase (CK) and lactate dehydrogenase (LDH) levels during COVID-19 infection are indicative of muscle involvement. As a result of cell damage, lactate levels increase (7), and the oxygen-carrying capacity of erythrocytes and the transport of oxygen to tissues are significantly reduced due to hyperlactatemia. The muscles, therefore, remain ischemic during the COVID-19 infection period (9). The expression of growth factors and inflammatory cytokines increases in the ischemic muscle tissue, and these endogenous substances cause excessive stimulation of the dorsal root ganglions. This stimulation is interpreted as pain by projection into the thalamus and cortex via ascending pathways (10). Myalgia is thought to reflect the systemic inflammation and cytokine response found in patients with COVID-19 (11). In addition, TNF-α is responsible for the intense fragmentation of muscle proteins by direct action (12). This can cause focal muscle fiber necrosis and diffuse muscle fiber atrophy, as previously demonstrated in studies of SARS-CoV-1 infection (13,14). Muscle pain that does not respond to classic analgesics decreases with a reduced viral load, decreased inflammation, and lower muscle lactate levels. This study aimed to determine the frequency of muscle pain in patients followed with a diagnosis of COVID-19 and to investigate the relationship between muscle pain and CK, pH, lactate, and LDH levels.

MATERIAL AND METHODS

In this retrospective single-center study, the medical records of patients diagnosed with COVID-19 between April and May 2020 in our hospital were screened retrospectively. In total, 110 patients with confirmed diagnosis of COVID-19 by reverse-transcription polymerase chain reaction (RT-PCR) assays from throat and nasal swab samples used for SARS-CoV-2 virus analysis and chest computed tomography findings were included in the study. The demographic, clinical, and laboratory findings of the patients were recorded in their files. The patients were asked about the presence of myalgia at the time of admission and on the 14th day of control. The CK, LDH, lactate, and pH laboratory findings of all the patients were recorded on the 3rd day and again on the 14th day of control and reviewed retrospectively. CK values over 171 U/L are considered high in our laboratory. The relationship between myalgia and the laboratory parameters was examined. The study was carried out in accordance with the principles of the Declaration of Helsinki with the approval of the Ministry of Health following approval by the local ethics committee. The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (10.07.2020, 416).

Statistical Analysis

Kolmogorov-Smirnov test was used to evaluate whether the distribution of numerical variables was normal. Accordingly, Mann-Whitney U test was used to compare the numerical variables, and Chi-square test was used to compare the categorical variables between the groups. The numerical variables were presented as median, interquartile range, minimum-maximum, and categorical variables were presented as a count and percentage. A p-value <0.05 was considered statistically significant. Analyses were performed using IBM SPSS Statistics v.22.

RESULTS

The study included 110 patients (63 male, 47 female) who had been diagnosed with COVID-19. The mean age of the patients was 47.13±15.06 (range, 18-73) years. The demographic characteristics of the patients are shown in Table 1. Fifty (45.5%) patients had muscle pain at the time of admission, and it was one of the most common musculoskeletal complaints. On the 14th day, 12 (10.9%) patients had ongoing muscle pain. In our study, 5 (4.5%) patients had only myalgia at the time of admission. High CK results were obtained in 48 (43.6%) of the 110 patients at the time of admission. Thirty-two (66.7%) of these patients had muscle pain (p<0.001).

Table 1. Demographic and clinical features of the patients

Patients diagnosed with COVID-19	n (%)
Gender	
Male	63 (57.3)
Female	47 (42.7)
CK level at admission	
High	48 (43.6)
Normal	62 (56.4)
CK level on 3rd day	
High	31 (28.2)
Normal	79 (71.8)
CK level on 14th day	
High	13 (11.8)
Normal	97 (88.2)
Myalgia at admission	
Yes	50 (45.5)
No	60 (54.5)
Myalgia on the 14th day	
Yes	12 (10.9)
No	98 (89.1)

COVID 19: coronavirus disease 2019, CK: creatine kinase

A significant difference was not observed on admission and on the 14th day of control according to the gender (p=0.360 and p=0.188, Table 2). On days 1 and 3, the CK values for the male patients were significantly higher than those of the female patients (both p<0.001). On day 14, there was no significant difference in CK values between the female and male patients.

The median CK values observed on days 1, 3, and 14 of control were 248.5, 150.5 and 80.0 U/L in the patients with muscle pain, respectively, while the median CK values of those without muscle pain were 96.0, 74.5 and 68.0 U/L respectively. In the patients with muscle pain, the CK levels observed on days 1, 3, and 14 of the disease were found to be significantly higher than in those without muscle pain (p<0.001, p=0.003, p=0.029). No significant relationship was found between complaints of muscle pain and lactate, pH, and LDH values (Table 3).

In the patients with muscle pain, high CK results were observed on 1st, 3rd, and 14th day of the disease to be significantly higher than in those without muscle pain (p<0.001, p=0.001, p=0.003, Table 4).

Table 2. Myalgia and creatine kinase levels according to the gender of the patients

	Male (n=63)	Female (n=47)	p
Myalgia at admission	31 (49.2)	19 (40.4)	0.360
Myalgia on the 14th day	9 (14.3)	3 (6.4)	0.188
High CK level at admission	39 (61.9)	9 (19.1)	**<0.001**
High CK level on the 3rd day	27 (42.9)	4 (8.5)	**<0.001**
High CK level on the 14th day	12 (19.0)	1 (2.1)	**0.007**

CK: creatine kinase

Table 3. Comparison of laboratory values of patients with and without myalgia at admission

	M (+) (n=50)	M (-) (n=60)	p
CK at admission	248.5 (459) [39-2103]	96.0 (115) [24-353]	**<0.001**
CK on the 3rd day	150.5 (301) [28-1266]	74.5 (83) [22-359]	**0.003**
CK on the 14th day	80 (73) [27-315]	68 (54) [20-198]	**0.029**
Lactate	1.6 (1.2) [0.8-4.3]	1.7 (1.0) [0.2-3.4]	0.794
pH	7.39 (0.06) [7.27-7.47]	7.38 (0.05) [7.30-7.55]	0.693
LDH	235 (95) [151-574]	234 (100) [97-596]	0.147

M (+): patients with myalgia at admission, M (-): patients without myalgia at admission, CK: creatine kinase, LDH: lactate dehydrogenase, descriptive statistics were given as median (interquartile range) [minimum-maximum]

Table 4. Comparison of creatine kinase levels of patients with and without myalgia at admission

	M (+) (n=50)	M (-) (n=60)	p
High CK level at admission	32 (64.0)	16 (26.7)	**<0.001**
High CK level on the 3rd day	22 (44.0)	9 (15.0)	**0.001**
High CK level on the 14th day	11 (22.0)	2 (3.3)	**0.003**

M (+): patients with myalgia at admission, M (-): patients without myalgia at admission, CK: creatine kinase

DISCUSSION

The biochemical parameters used in the diagnosis of COVID-19 play a major role in predicting the course and prognosis of the disease and directing its treatment. Since the emergence of the pandemic, researchers have concentrated their work on determining easily applicable practical parameters. Myalgia is known to be common in the early stages of COVID-19. We therefore evaluated CK levels, which we predicted could be a favorable parameter for evaluating myalgia.

Myalgia can occur as a symptom of many diseases, and viral infections are one of the main causes. In the course of a viral infection, IL-6 most frequently mediates myalgia (15). Since the SARS-CoV-2 agent causes a strong inflammatory response, high cytokine levels (IL-6, IL-10, and TNF-α) are detected, especially in patients with a moderate or severe disease course (16,17). Although the exact mechanism of myalgia during viral infection is not known, it is thought that proinflammatory cytokines cause muscle pain directly (i.e., TNF-α on muscle proteins) and indirectly (i.e., PGE2 stimulates nociceptive pathways causing a pain sensation). Myalgia caused by COVID-19 lasts longer and is more severe than myalgia caused by other viral infections. In patients with COVID-19, myalgia and fatigue do not respond to classic analgesics.

There is a relationship between high CK levels and muscle damage. CK levels begin to rise approximately 2-12 hours after the onset of muscle damage and start to decrease to their basal values in 3-5 days (18).

In our study, 110 patients diagnosed with COVID-19 were evaluated retrospectively. Among these, 50 (45.5%) patients had myalgia on admission, and 48 (43.6%) patients had CK elevation on admission. The control CK values on days 1, 3, and 14 were higher among the patients presenting with myalgia than those without myalgia. Although we found a significant relationship between myalgia and high CK levels, there was no significant relationship between myalgia and lactate, pH, and LDH values.

Several studies (19-22) have reported that patients with a diagnosis of COVID-19 and high serum levels of ferritin, leukocytes, total bilirubin, and IL-6 (CK) have higher mortality rates. Patients with rhabdomyolysis present with myalgia and high CK levels without typical COVID-19 symptoms; however, patients with COVID-19 diagnosed with very high CK levels due to the direct muscle damage caused by the virus have reportedly developed rhabdomyolysis following viral myositis (17). In our study, although very high CK levels were detected in only two patients, a rapid decrease was observed in the follow up, and kidney functions remained within normal limits. Patients with myalgia and high CK should be followed up more closely for the development of rhabdomyolysis.

It is clear that the SARS-CoV-2 virus affects the musculoskeletal system. In 25 of 33 related studies, weakness, myalgia, and increased CK levels, indicating

muscle damage, have been reported as symptoms of COVID-19 (23,24). Similarly, in our study, the incidence of high CK levels accompanying muscle pain was statistically significant.

In several studies from China, CK elevation has been reported in patients with COVID-19 who did not develop rhabdomyolysis. In a study of 91 adults, the CK levels of 14 patients were higher than 190 U/L, and 15 had myalgia (2). However, there was no relationship with myalgia in the patients with CK elevation. In another study involving 161 adults diagnosed with COVID-19, 17 patients had CK levels higher than 190 U/L, and 18 had myalgia (1). However, no relationship was found between the CK levels and myalgia. In contrast to these studies, myalgia and high CK levels were correlated in our series.

In another study on the relationship between myalgia and CK levels in patients diagnosed with COVID-19, 140 of 239 patients had high CK results, and 32 patients with CK elevation had myalgia (25). In the patients with myalgia, the mean CK values were 241.05±137.02 U/L (min 45.00 U/L, max 721 U/L), while the mean CK levels in the patients without myalgia were 139.67±83.80 U/L (min 21 U/L, max 451 U/L). Similarly to our study, the study found a significant relationship between myalgia and increased CK levels.

A limitation of our study was the lack of analgesic responses among the patients with myalgia because of an inadequate filing system. Furthermore, this was a cross-sectional study based on retrospective data. We recommend that it be supported by future multicenter studies with larger patient groups.

CONCLUSIONS

The typical clinical features associated with COVID-19 include fever, cough, and respiratory distress from the first day, but fatigue and myalgia are also common symptoms. Since some patients may only present with musculoskeletal symptoms such as myalgia, it is important that clinicians consider and evaluate COVID-19 in patients presenting with myalgia and high CK levels.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (10.07.2020, 416).

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Concordance of PCR and Early Thorax Computed Tomography Findings in COVID-19 Patients

COVID-19 Hastalarında Erken Dönemde Çekilen Akciğer Bilgisayarlı Tomografi Bulguları ile PCR Testinin Uyumluluğu

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ABSTRACT

Aim: The aim of this study was to investigate concordance between polymerase chain reaction (PCR) test results and early thorax computed tomography (CT) findings of the patients in whom coronavirus disease 2019 (COVID-19) was suspected after evaluation of their complaints and physical examination findings.

Material and Methods: One hundred and fourteen patients with suspicion of COVID-19, evaluated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) existence with PCR test and performed thorax CT in the first 48 hours, between April and July 2020, were enrolled in this study retrospectively. Demographic characteristics, laboratory parameters and thorax CT findings of PCR positive and negative patients were compared. If patients had negative PCR test results, but clinical suspicion for COVID-19 persisted, additional PCR samples were tested at 48-hour intervals.

Results: Interlobular septal thickening was more frequent in PCR positive patients (p=0.043). There was no significant thorax CT finding in 16 (28.6%) PCR positive and 14 (24.1%) PCR negative patients. Bilateral, peripheral and multilobar ground glass opacifications, consolidation and interlobular septal thickening were the most frequent findings in both groups. Neutrophil (p<0.001) and platelet counts (p=0.038) were significantly lower in PCR positive group.

Conclusion: The thorax CT findings of the patients whose PCR tests were positive or negative were greatly similar except for interlobular septal thickening, thus thorax CT should not be used alone in the diagnosis of COVID-19 especially in early stages. In decision making, symptoms, laboratory and CT findings and PCR tests of patients must be evaluated all together.

Keywords: COVID-19; ground glass opacity; interlobular septal thickening; thorax computed tomography; polymerase chain reaction.

ÖZ

Amaç: Bu çalışmanın amacı yakınmaları ve fizik muayene bulgularının değerlendirilmesi sonrasında koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) ön tanısı konulan hastaların erken dönemde çekilen akciğer bilgisayarlı tomografi (BT) bulguları ile polimeraz zincir reaksiyonu (polymerase chain reaction, PCR) testi sonuçları arasındaki uyumluluğun araştırılmasıdır.

Gereç ve Yöntemler: Nisan ile Temmuz 2020 tarihleri arasında COVID-19 şüphesi olan, PCR testi ile şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) varlığı açısından değerlendirilen ve ilk 48 saatte akciğer BT yapılan 114 hasta geriye dönük olarak bu çalışmaya alındı. PCR testi pozitif ve negatif olan hastaların demografik özellikleri, laboratuvar parametreleri ve akciğer BT bulguları karşılaştırıldı. PCR testi negatif saptanıp klinik şüphesi devam eden hastalarda 48 saatlik aralıklar ile yeni PCR örnekleri alındı.

Bulgular: PCR pozitif hastalarda interlobüler septal kalınlaşma daha fazla bulundu (p=0,043). PCR pozitif olan 16 (%28,6) ve PCR negatif olan 14 (%24,1) hastada tomografide anlamlı bir bulgu saptanmadı. Her iki grupta da en sık bulgular; bilateral, periferal ve multilober yerleşimli buzlu cam görünümü, konsolidasyon ve interlobuler septal kalınlaşma idi. PCR pozitif olan grupta nötrofil (p<0,001) ve trombosit sayısı (p=0,038) anlamlı olarak daha düşük saptandı.

Sonuç: PCR testi pozitif veya negatif saptanan hastaların interlobular septal kalınlaşma dışındaki akciğer BT bulguları oldukça benzer idi, dolayısıyla COVID-19 tanısında özellikle erken dönemlerde akciğer BT tek başına kullanılmamalıdır. Karar verme esnasında, hastaların semptom, laboratuvar ve BT bulguları ile PCR testi hep birlikte değerlendirilmelidir.

Anahtar kelimeler: COVID-19, buzlu cam görünümü; interlobüler septal kalınlaşma; akciğer bilgisayarlı tomografi; polimeraz zincir reaksiyonu.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is now a global pandemic. Early diagnosis and isolation of infected people are important factors in controlling the spread of the disease (1). Diagnosis of COVID-19 depends on detection of viral ribonucleic acid (RNA) by real time reverse transcriptase polymerase chain reaction (rRT-PCR) test. Polymerase chain reaction (PCR) test requires special equipment and it cannot be performed in every health center, and a relatively long time is needed to get results. There are difficulties in proper sample gathering and transporting specimens to a test laboratory which may cause inaccurate results (2).

Symptoms, signs and some laboratory findings in COVID-19 were reported to be associated with thorax computed tomography (CT) findings (3). Poor prognosis for disease may be predicted by thorax CT findings (4). However, many infectious and non-infectious diseases may cause similar findings in thorax CT, thus CT findings may be falsely regarded as positive results. A study reported specificity of thorax CT as low as 25.0% (5).

The most frequent laboratory findings in COVID-19 are lymphocytopenia, thrombocytopenia, elevations in hepatic transaminase levels and inflammatory markers (6). Lymphocyte counts are usually decreased, but neutrophil counts may be varying; some patients may have low and some may have high neutrophil counts (7).

The aim of this study was to evaluate concordance between PCR test results and early thorax CT findings in PCR positive and PCR negative patients.

MATERIAL AND METHODS

This study was conducted in the Lokman Hekim University Hospital as a single center study. Data of participants admitted between April and July 2020 were inspected retrospectively. A hundred and fourteen patients admitted to the hospital with complaints similar to those of COVID-19 patients such as high fever (>38.0 Celsius), sore throat, cough, dyspnea, headache, myalgia, loss of taste or smell senses were enrolled in the study. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) PCR tests were performed in patients who had at least two of these symptoms. Thorax CT was performed to the patients who had presence of newly developed infiltration on chest X-ray and/or new onset of cough and dyspnea and/or changes in breath sounds on physical examination. Patients who had thorax CT performed in the first 48 hours after hospitalization were enrolled in the study. The laboratory parameters and thorax CT findings of PCR positive and negative patients were compared. Patients below 18 years of age and patients in whom thorax CT images could not be examined or patients in whom CT was performed 48 hours after hospitalization were excluded. This study was approved by the Clinical Research Ethics Committee of Lokman Hekim University (27.05.2020, approval no: 2020/038). Informed written consent was obtained from all of the patients participated in the study.

Demographic characteristics, accompanying diseases, laboratory findings and thorax CT images of the patients were inspected through hospital computer systems. Whole blood counts (lymphocyte, neutrophil, platelet), alanine aminotransferase (ALT), aspartat aminotransferase (AST), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, D-dimer, prothrombin time, troponin I levels, creatinine, creatine kinase (CK), procalcitonin, and PCR test results were recorded. PCR samples were obtained at 48-hour intervals when previous tests were negative, but clinical suspicion for COVID-19 persisted. Patients in whom COVID-19 diagnosis was concluded after recurrent PCR analyses were also accepted as COVID-19 positive.

Whole blood count tests were measured using the Sysmex XN-1000 analyzer (USA). ALT, AST, creatinine, LDH, CK, D-dimer, CRP tests were performed using the Roche Hitachi Cobas 501 analyzer (Switzerland). Ferritin, troponin I and procalcitonin tests were measured using the Roche Hitachi Cobas 601 analyzer (Switzerland). PT-INR tests were performed using the Tokra Novae analyzer (Turkey). Thorax tomography was performed by a Siemens Emotion 16 Scanner (Siemens Healthineers; Erlangen, Germany, 2010) using the following parameters: 110 kV, 258 mA, a slice thickness of 1.5 mm. All scans were performed without intravenous contrast with the patient in the supine position during end-inspiration.

Tomography images were evaluated by a 13-year experienced radiologist. Ground glass opacifications, consolidation, unilateral/bilateral involvement, posterior and multilobar distribution, interlobular septal thickening, pleural thickening, bronchiectasis, pleural effusion, lymph node, cavity, halo sign, nodule and vascular thickness existence were inspected in tomography.

COVID-19 diagnosis was confirmed after the detection of specific viral RNA sequences in rRT-PCR by nucleic acid amplification test (NAAT).

Statistical Analysis

Data were analyzed by SPSS v.25.0 statistical package. Data distributions were evaluated by Shapiro-Wilk test. Data were presented as mean±standard deviation for normal distributed variables, as median, interquartile range, minimum-maximum for non-normal distributed variables. Comparisons between groups in normally distributed variables were done by independent samples t-test and Mann-Whitney U test for not normally distributed variables. Chi-square test was used for the comparison of qualitative data. Fisher's exact test was used when chi-square test cannot be used. A p value below 0.05 was considered significant.

RESULTS

The study was conducted with 114 patients. Fifty-six (49.1%) patients were male and 58 (50.9%) patients were female. The mean age of patients was 47.8±15.8 (45.3±15.0 for males, 50.1±16.0 for females) years. The mean ages of patients in the PCR positive group and PCR negative group were 45.8±16.2 and 49.6±15.4 years, respectively (p=0.205). In the PCR positive group, 27 (48.2%) patients were male, and 29 (51.8%) were female. In the PCR negative group, 29 (50.0%) patients were male, and 29 (50.0%) were female.

Accompanying diseases in PCR positive patients were as follows: hypertension in 13 (23.2%) patients, diabetes mellitus in 6 (10.7%) patients, coronary artery disease in 2 (3.6%) patients, malignancies in 2 (3.6%) patients and chronic pulmonary obstructive disease in 1 (1.8%) patient. When PCR negative patients were inspected, the following accompanying diseases were recorded: hypertension in 11 (19.0%) patients, diabetes mellitus in 10 (17.2%) patients, coronary artery disease in 4 (6.9%) patients, chronic

pulmonary obstructive disease in 4 (6.9%) patients and malignancy in 1 (1.7%) patient.

In comparison of the thorax CT findings of PCR positive and negative patients, only interlobular septal thickening was more frequent in PCR positive patients (p=0.043). Other thorax CT findings were similar in both groups. Bilateral, peripheral and multilobar ground glass opacifications, consolidations and interlobular septal thickenings were the most frequent findings in both groups (Figure 1 and 2). Both ground glass opacifications and consolidations were detected in 14 (25.0%) PCR positive patients. There were no pathologic thorax CT findings in 16 (28.6%) PCR positive patients and 14 (24.1%) PCR negative patients. Cavity formation, pleural thickening, halo finding, pleural effusion and vascular thickening were less frequent findings in thorax CT. The pathological findings detected in thorax CT were reported in Table 1.

Table 1. Computed tomography results of PCR positive and negative patients, n (%)

	PCR (+) (n=56)	PCR (-) (n=58)	p
Ground glass opacity	34 (60.7)	29 (50.0)	0.250*
Bilateral involvement	26 (46.4)	20 (34.5)	0.194*
Unilateral involvement	10 (17.9)	12 (20.7)	0.702*
Peripheral involvement	26 (46.4)	22 (37.9)	0.358*
Posterior involvement	13 (23.2)	10 (17.2)	0.427*
Multilobar involvement	27 (48.2)	20 (34.5)	0.136*
Consolidation	21 (37.5)	19 (32.8)	0.596*
Interlobular septal thickening	20 (35.7)	11 (19.0)	**0.043***
Pleura thickening	1 (1.8)	3 (5.2)	0.619†
Bronchiectasis	5 (8.9)	4 (6.9)	0.740†
Pleural effusion	2 (3.6)	3 (5.2)	0.999†
Lymphadenopathy	2 (3.6)	6 (10.3)	0.272†
Halo sign	1 (1.8)	3 (5.2)	0.619†
Vascular thickness	3 (5.4)	2 (3.4)	0.676†
Nodule formation	7 (12.5)	14 (24.1)	0.109*
Cavitation	0 (0.0)	1 (1.7)	0.999†

PCR: polymerase chain reaction, *: Chi-square test, †: Fisher's exact test

When the laboratory findings in both groups were compared, neutrophil and platelet counts were lower in PCR positive patients (p<0.001 and p=0.038, respectively). Other laboratory findings were similar in both groups. The laboratory findings of the patients were reported in Table 2 and the frequency of abnormal laboratory findings was shown in Table 3.

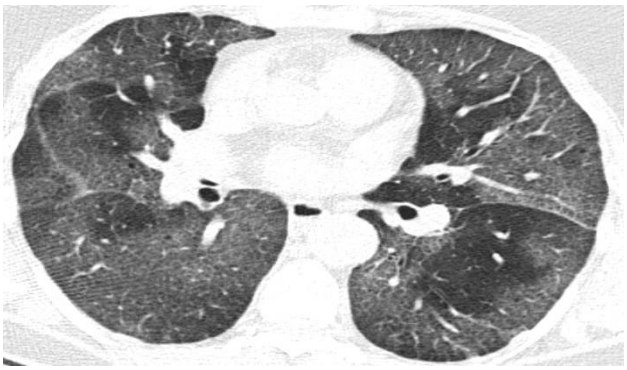

Figure 1. Tomography of 84 years old female patient whose PCR was negative. Peripheral localized ground glass opacifications in left lung are remarkable

Figure 2. Tomography of 65 years old female patient whose PCR was positive. Bilateral widespread ground glass opacifications are remarkable

Table 2. Laboratory results of PCR positive and negative patients

	PCR (+) (n=56)		PCR (-) (n=58)		p
	Mean±SD	Median (IQR) [min-max]	Mean±SD	Median (IQR) [min-max]	
Lymphocyte (x10^9/L)	1.6±0.8	1.4 (0.8) [0.4-4.3]	1.5±0.7	1.4 (0.9) [0.5-4.1]	0.709*
Neutrophil (x10^9/L)	4.4±2.9	3.2 (1.0) [0.7-15.0]	6.8±4.2	5.6 (3.0) [2-21]	**<0.001†**
Platelet count (x10^9/L)	227±67	219 (165) [124-375]	258±88	236 (158) [106-545]	**0.038***
ALT (U/L)	26.1±16.7	22 (27) [8-81]	29.1±30	21 (33) [6-197]	0.798†
AST (U/L)	26.8±16.5	22 (53) [8-82]	27.5±21.3	20 (34) [8-123]	0.733†
LDH (U/L)	219±108	181 (94) [122-712]	250±117	211 (98) [106-619]	0.066†
CRP (mg/L)	39±69	10 (136) [1-135]	61±87	23 (107) [1-462]	0.082†
Ferritin (µg/L)	300±350	143 (198) [4-1200]	329±463	120 (841) [13-1737]	0.729†
D-dimer (nmol/L)	557±347	311 (1133) [9-5125]	875±709	415 (701) [55-7625]	0.146*
PT-INR	1.1±0.4	1.8 (0.3) [0.4-3.2]	1.5±1.6	1.1 (0.2) [0.9-9.0]	0.118*
Troponin I (µg/L)	0.2±0.7	0.1 (0.1) [0.1-5.0]	0.1±0.1	0.1 (0.1) [0.1-1.0]	0.741†
Creatinine (µmol/L)	0.8±0.2	0.8 (0.2) [0.5-2.3]	0.9±0.3	0.9 (0.1) [0.1-2.3]	0.093†
CK (U/L)	202±355	88 (145) [30-1790]	150±198	78 (91) [15-1067]	0.547†
Procalcitonin (ng/mL)	0.7±2.9	0.1 (0.2) [0.1-15.0]	1.4±5.2	0.1 (0.2) [0.1-24.0]	0.274†

PCR: polymerase chain reaction, SD: standard deviation, IQR: interquartile range, min-max: minimum-maximum, *: Independent samples t test, †: Mann-Whitney U test, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, PT-INR: prothrombin time international normalized ratio, CK: creatine kinase

Table 3. Frequency of abnormal laboratory results of PCR positive and negative patients, n (%)

	PCR (+) (n=56)	PCR (-) (n=58)	p
Lymphophenia (<1.2x10^9/L)	18/56 (32.1%)	23/58 (39.7%)	0.403*
Neutrophilia (>7x10^9/L)	9/56 (16.1%)	16/58 (27.6%)	0.137*
Thrombocytopenia (<150x10^9/L)	7/56 (12.5%)	3/58 (5.2%)	0.200†
ALT (>34 U/L)	14/54 (25.9%)	10/58 (17.2%)	0.263*
AST (>33 U/L)	10/53 (18.9%)	12/57 (21.1%)	0.775*
LDH (>214 U/L)	19/54 (35.2%)	27/56 (48.2%)	0.166*
CRP (>5 mg/L)	44/56 (78.6%)	45/58 (77.6%)	0.918*
Ferritin (>200 µg/L)	12/30 (40.0%)	12/31 (38.7%)	0.453*
D-dimer (>500 nmol/L)	12/53 (22.6%)	20/55 (36.4%)	0.118*
PT-INR (>1.2)	12/38 (31.6%)	14/35 (40.0%)	0.599*
Troponin I (>0.3 µg/L)	2/41 (4.9%)	2/45 (4.4%)	0.999†
Creatinine (>1.2 µmol/L)	2/56 (3.6%)	7/55 (12.7%)	0.094†
CK (>192 U/L)	7/43 (16.3%)	9/49 (18.4%)	0.792*
Procalcitonin (>0.5ng/ml)	2/28 (7.1%)	3/21 (14.3%)	0.639†

PCR: polymerase chain reaction, *: Chi-square test, †: Fisher's exact test, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, PT-INR: prothrombin time international normalized ratio, CK: creatine kinase

DISCUSSION

The present study reports that only interlobular septal thickening in thorax CT findings was more frequent in PCR positive patients. Neutrophil and platelet counts were lower in PCR positive patients. Other laboratory and tomography findings were similar.

After inoculation of SARS-CoV-2, in the incubation period, there may be no pathologic tomography findings. Thus, tomography performed in the early period of the disease may be reported as normal and with advancing disease, tomography findings may be prominent (8). In a study, the thorax tomographies performed in the first two days of hospitalization were reported to be normal in 56% of the patients. On days 3 to 5, they were normal only in 9% of patients, and on days 6 to 12, the tomography ratio reported to be normal was as low as 4% (9).

In a study from China inspecting 101 COVID-19 patients, it was reported that 82% of patients had bilateral involvement in thorax tomography and the most frequent finding was peripheral ground glass opacifications in lower lobes of lungs (10). Another study reported posteriorly and peripherally localized lesions as the most frequent thorax CT findings. In that study, the most frequent lesions were ground glass opacifications, interlobular septal thickening and consolidations (4). In this reported study, the most frequent thorax CT findings were ground glass opacifications, consolidations and interlobular septal thickening, all localized bilaterally, peripherally and multilobarly. Only interlobular septal thickening was more frequent in PCR positive patients. Viral infections other than COVID-19, especially influenza pneumonia may frequently result in ground glass opacifications and consolidation findings in thorax CT (11). Pulmonary nodule formation and halo findings are not specific lesions for COVID-19 but they have been reported to exist in thorax CTs of COVID-19 patients (12). In this reported study, both nodule formation and halo findings were rare in the thorax CTs of the patients.

In a distinct study, comparing PCR positive and negative patients by thorax tomography, 34 patients were evaluated, and bilateral ground glass opacifications were more frequent findings in PCR positive patients (13). A study from China inspected thorax CT findings of COVID-19 and H1N1 influenza patients, and there were no difference in ground glass opacifications, consolidation, pathologic lymph node and nodule existence and localization of lesions between these groups (14). A normal thorax CT does not rule out COVID-19 diagnosis (13). A study reported normal thorax CT findings in 18% of COVID-19 confirmed patients (15). Chinese radiologists' expert consensus report emphasized that PCR results may not be concurrent with thorax CT findings (16). In this reported study, 28.6% of all participants had normal thorax CT findings. There were no significant differences between the thorax CT findings in PCR positive and negative patients. There may be some explanations for this situation. Before all, thorax CTs were performed in the early disease period, in the first 48 hours after hospitalization. Therefore, some lesions may not have been detected. Second, patients were younger in age and there were not much accompanying diseases, so they may have a milder course of the disease. Third, false negative PCR results should also be considered.

The most frequently detected thorax tomography findings in PCR negative patients were reported to be ground glass opacifications and co-existence of ground glass opacifications and consolidations in some patients that were peripherally localized (17,18). This study, concordantly, revealed that PCR negative patients had ground glass opacifications and consolidations as the most frequent CT findings which were bilateral and peripherally localized. Ground glass opacifications has been reported to be a frequent finding in tomography, which could be explained as a nonspecific lesion that may be found in many malignant or benign conditions (19).

A meta-analysis, inspecting studies reported from China, evaluated 8697 patients. The most frequently reported laboratory findings were elevations in CRP, hepatic transaminases, D-dimer, erythrocyte sedimentation rate, troponin and CK myocardial band tests and decreases in neutrophil and lymphocyte counts (7). Laboratory findings in COVID-19 disease may be similar to other viral infections. A study comparing patients having COVID-19 and influenza revealed no difference between the groups in leukocyte, lymphocyte and platelet counts, CRP and erythrocyte sedimentation rates (14). In this reported study, neutrophil and platelet counts were lower in PCR positive patients. SARS-CoV-2 infection may be the reason for decreases detected in neutrophil and platelet counts.

In a study reported from USA, the mean age of COVID-19 confirmed patients was 63 (20). In this reported study, the

mean patient age was 47 and mean ages for the PCR positive and negative groups were similar. A study reported 46% of the patients had at least one accompanying disease (21), but in this reported study, accompanying disease rate was 30.4%. Participants in this study were younger and had less accompanying diseases.
There are some limitations in this study. This is a retrospective study and thorax CTs were performed in the early period of the disease. Thus, the thorax CT findings may have been changed in the later periods of the disease. For the patients in whom the PCR test was negative, no further etiologic evaluation was performed. But in order to eliminate false negative results, additional PCR tests were performed if clinical suspicion for COVID-19 persisted.

CONCLUSION

In conclusion, the thorax CT findings of COVID-19 positive and negative patients were greatly similar in this study, except for interlobular septal thickening. The benefit of thorax CT in early periods of the disease seems to be limited, for this reason, it should not be performed in the first days after the onset of symptoms. Thus, thorax CT should not be relied alone, in the diagnosis of COVID-19, but symptoms, laboratory findings and PCR tests must be considered all together.

Ethics Committee Approval: The study was approved by the Ethics Committee of Lokman Hekim University (27.05.2020, 2020/038).

Conflict of Interest: None declared by the authors.

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The Relationship of Headache with Inflammatory Serum Parameters and Disease Severity in COVID-19 Patients

COVID-19 Hastalarında Başağrısının Enflamatuvar Serum Parametreleri ve Hastalık Şiddeti ile İlişkisi

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ABSTRACT

Aim: Most of the coronavirus disease 2019 (COVID-19) patients have respiratory symptoms; however, various neurological symptoms, such as headache, can be seen. The pathophysiological mechanism of headache in COVID-19 is unknown completely. In our study, we aimed to investigate the relationship between headache and inflammatory markers and disease severity in COVID-19 patients.

Material and Methods: Two hundred and three hospitalized patients with a polymerase chain reaction (PCR)-confirmed COVID-19 diagnosis between 15 March and 01 June 2020 were retrospectively investigated. A total of 62 patients with headache symptoms (n=31) and without headache symptoms (n=31), who were age and gender-matched, were included in the study. The demographic characteristics, inflammatory serum parameters, neutrophil/lymphocyte ratio (NLR), C-reactive protein (CRP)/albumin ratio (CAR), hospitalization times, and disease severity were determined.

Results: Of the 203 COVID-19 patients, 36 (17.7%) had a headache, and it was the fourth most common symptom. Headache accompanied other symptoms in all patients. Of the patients with headache, 14 (45.2%) were female, 17 (54.8%) were male, and the mean age was 37.74±16.65 years. In our COVID-19 patients, the neutrophil count, NLR, CRP, CAR were significantly higher, and hospital stay was longer in patients with headache than those without headache (p=0.023, p=0.041, p=0.034, p=0,048 and p=0.049, respectively).

Conclusion: As a result, the increased inflammatory response may play a role in the pathogenesis of headache in COVID-19 patients. Our study is the first study that evaluated the relationship between headache symptom and inflammation in COVID-19 patients. Further research is needed on this subject.

Keywords: COVID-19; headache; neutrophil-lymphocyte ratio; C-reactive protein; albumin.

ÖZ

Amaç: Koronavirüs hastalığı 2019 (coronavirüs disease 2019, COVID-19) hastalarının çoğunun solunum semptomları vardır; ancak baş ağrısı gibi çeşitli nörolojik semptomlar da görülebilir. COVID-19'daki baş ağrısının patofizyolojik mekanizması tam olarak bilinmemektedir. Çalışmamızda COVID-19 hastalarında baş ağrısının enflamatuvar belirteçler ve hastalık şiddeti ile olan ilişkisini araştırmayı amaçladık.

Gereç ve Yöntemler: 15 Mart ve 01 Haziran 2020 tarihleri arasında polimeraz zincir reaksiyonu (polymerase chain reaction, (PCR) ile doğrulanmış COVID-19 tanısıyla hastaneye yatırılan 203 hasta retrospektif olarak incelendi. Baş ağrısı semptomu olan (n=31) ve baş ağrısı semptomu olmayan (n=31) yaş ve cinsiyet eşleştirilmiş toplam 62 hasta çalışmaya dahil edildi. Hastaların demografik özellikleri, enflamatuar serum parametreleri, nötrofil/lenfosit oranı (neutrophil-lymphocyte ratio, NLR), C-reaktif protein (C-reactive protein, CRP)/albümin oranı (CRP-albumin ratio, CAR), hastanede yatış süreleri ve hastalık şiddeti belirlendi.

Bulgular: İki yüz üç COVID-19 hastasının 36 (%17,7)'sında baş ağrısı semptomu vardı ve en sık dördüncü semptomdu. Baş ağrısı, hastaların tümünde diğer semptomlara eşlik ediyordu. Baş ağrısı olan hastaların 14 (%45,2)'ü kadın, 17 (%54,8)'si erkekti ve yaş ortalamaları 37,74±16,65 yıl idi. COVID-19 hastalarımızda baş ağrısı olanlarda baş ağrısı olmayanlara göre nötrofil sayısı, NLR, CRP, CAR anlamlı düzeyde yüksekti ve hastane yatış süreleri daha uzundu (sırasıyla, p=0,023; p=0,041; p=0,034; p=0,048 ve p=0,049).

Sonuç: Sonuç olarak, COVID-19 hastalarında baş ağrısı patogenezinde artmış enflamatuvar yanıtın rolü olabilir. Çalışmamız, COVID-19 hastalarında baş ağrısı semptomu ile inflamasyon arasındaki ilişkiyi değerlendiren ilk çalışmadır. Bu konuda daha fazla araştırmaya ihtiyaç vardır.

Anahtar kelimeler: COVID-19; başağrısı; nötrofil-lenfosit oranı; C reaktif protein; albümin.

INTRODUCTION

In December 2019, many cases of pneumonia that were later found to be caused by a new type of coronavirus (CoV) were seen in Wuhan, China, and it quickly spread to different parts of China (1). The new CoV was reported to show symptoms like severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003, and both act using the angiotensin-converting enzyme 2 (ACE2) receptor (2). Therefore, the World Health Organization (WHO) named the disease caused by the virus called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the International Committee on Taxonomy, as coronavirus disease 2019 (COVID-19) in February 2020. On March 11, 2020, the COVID-19 outbreak was proclaimed as a pandemic. As of July 12, 2020, the total number of cases of COVID-19 is 12.7 million in the world the number of deaths due to the disease is more than 560 000 in the world, and the disease continues to spread rapidly (3,4).

SARS and COVID-19's "spike proteins" use ACE2 to bind to cells (2,5). The ACE2 receptor in the body is usually found in the lungs, mouth and nasal mucosa, and in many areas such as the skin, heart, arteries, kidneys, reproductive system and brain (6). Coronavirus infections defined in humans are mostly in the form of respiratory infections and can cause deadly pneumonia, described typical clinical symptoms such as fever, cough, shortness of breath, diarrhea, and fatigue in COVID-19 (7). COVID-19 also has typical laboratory findings and lung computed tomography (CT) abnormalities (8). In COVID-19 patients, not only respiratory symptoms but also neurological symptoms such as dizziness, headache, myalgia, inability to taste and smell, polyneuropathy, myositis, cerebrovascular diseases, and rarely encephalitis have been reported (9). Headache is a common symptom of COVID-19 at rates ranging from 10.0-40.0% in patients (10,11). The exact mechanisms of headache have not yet been fully studied in COVID-19 patients. In our study, whether the headache symptom was associated with inflammatory serum parameters, disease severity, and length of hospital stay in COVID-19 patients were investigated. This study focused on the presence of headache in COVID-19 infection, and it was aimed to examine the relationship between headache symptom and inflammation and disease severity.

MATERIAL AND METHODS

Prior to the study, approval was obtained from the Clinical Research Ethics Committee of Atatürk University Faculty of Medicine of (01.10.2020, 37). Two hundred and three patients who were hospitalized with a poliymerase chain reaction (PCR)-confirmed diagnosis of COVID-19 between 15 March and 01 June 2020 were retrospectively investigated. Five patients (3 with tension headache, and 2 with migraine) with previous recurrent headaches among 36 patients aged 18 years and over with headache were excluded from the study. A total of 62 patients with headache symptoms (n=31) and without headache symptoms (n=31), who were age and gender-matched, were included in the study. Patient data were analyzed retrospectively by screening files, and their demographic characteristics were recorded. In the patients included in our study, complete blood count (neutrophil, lymphocyte, platelet, hemoglobin), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), albumin, ferritin, procalcitonin, D-dimer levels, neutrophil/lymphocyte ratio (NLR), CRP/albumin ratio (CAR), and hospitalization times were compared. The relationship between headache and disease severity was investigated. The disease severity in COVID-19 was classified as mild (no pneumonia, slightly symptomatic), as moderate (there are signs of COVID-19 compatible pneumonia in CT, no need for respiratory support) and severe (patient with severe pneumonia findings in CT, in need of invasive or non-invasive mechanical ventilation (MV) according to clinical and lung CT abnormalities).

Statistical Analysis

Data were analyzed with SPSS v.22.0 program. The distribution of numerical variables was investigated by Shapiro-Wilk normality test. Categorical variables were expressed as numbers and percentages, and the numerical variables with normal distribution were expressed as mean and standard deviation, and those that were not normally distributed were expressed as median, interquartile range (IQR) and minimum-maximum. Normally distributed data were analyzed with Student's t-test, and Mann-Whitney U test was used for data without normal distribution. Chi-square and Fisher's exact tests were used for the analysis of categorical variables. The significance level was set at $p<0.05$.

RESULTS

In this study, the data of 203 PCR-confirmed COVID-19 patients were investigated retrospectively. Headache symptom was present in 36 (17.7%) patients and was the fourth most common symptom followed by cough in 78 (38.4%), fever in 57 (28.1%), weakness-fatigue in 41 (20.2%) patients. Neurological symptoms were present in 61 (30.0%) of the patients and headache was the most common among neurological symptoms such as loss of sense of taste and smell, myalgia, dizziness (Table 1).

The data of the patients with headache (n=31) and without headache (n=31) were compared. Of the patients with headache, 14 (45.2%) were female and 17 (54.8%) were male, and the mean age was 37.74±16.65 years. Headache accompanied other symptoms in all patients, and it was most commonly together with cough and fever. There were no patients presenting with isolated headache (Table 2).

Table 1. Demographic data of COVID-19 patients (n=203)

Age (years), mean±SD	46.98±19.71
Gender, n (%)	
Female	93 (45.8)
Male	110 (54.2)
Frequent symptoms*, n (%)	
Cough	78 (38.4)
Fever	57 (28.1)
Fatigue	41 (20.2)
Headache	36 (17.7)
Neurological symptoms, n (%)	
Total	61 (30.0)
Headache	36 (59.0)
Myalgia	15 (24.6)
Loss of taste and smell	7 (11.5)
Dizziness	3 (4.9)

COVID-19: coronavirus disease 2019, SD: standard deviation, *: There were total 212 symptoms

The comorbid symptoms and comorbidities, smoking status, disease severity of the COVID-19 patients with and without headache were compared. The most common symptoms accompanied by headache were fever and cough, and at the same time, these symptoms were the most common. There was no significant difference between patients with and without headache in terms of accompanying symptoms. Complaints of smell or taste loss were present only in patients who did not have a headache (Table 2).

While 5 (16.1%) of the patients with headache had concomitant disease, 4 (12.9%) of the patients without headache had concomitant disease, and there was no statistical difference between the groups (p=1.000). These diseases accompanying headache were hypertension (HT) in 2 (6.4%) patients, chronic obstructive pulmonary disease (COPD) in 1 (3.2%) patient, chronic kidney disease (CKD) in 1 (3.2%) patient, and hypothyroidism in 1 (3.2%) patient, in patients with headache. In patients without headache, each of the comorbid diseases of HT, COPD, CKD and coronary artery disease (CAD) were seen in 1 (3.7%) patient. Overall 6 (9.7%) of the patients had a history of smoking, and this ratio was equal in patients with and without headache (Table 2).

When the COVID-19 patients with headache were evaluated in terms of disease severity, 8 (25.8%) patients had a mild clinical condition without pneumonia, while 19 (61.3%) patients were moderate and 4 (12.9%) patients were severe. Non-invasive MV was performed in patients who were severe in our study and none of them were intubated. There were no patients with exitus. There was no statistically significant difference between the patients with and without headache in terms of disease severity. In one of the patients with headache symptom, a brain MRI was taken due to the development of respiratory distress and lethargy during follow-up and the results were normal. The patient was discharged after non-invasive MV treatment. The median duration of hospitalization was statistically significantly longer in patients with headache than those without headache (median 11 vs. 8 days, p=0.049, Table 2).

In patients with COVID-19, the neutrophil count was significantly higher in the group with headache than the group without headache (median 3.80 vs. 2.70 $x10^3/\mu L$, p=0.023). NLR was significantly higher in the patient group with headache than in the group without headache (p=0.041, Table 3).

No significant difference was found between white blood cell, lymphocyte, and platelet counts, hemoglobin, D-dimer, procalcitonin levels between the groups (p=0.071, p=0.602, p=0.502, p=0.794, p=0.612, p=0.873, respectively).

The ESR in patients with headache was higher than it was in patients without headache, but this difference was not statistically significant (median 15 vs. 10, p=0.345, Table 3). In patients with COVID-19, the CRP in the group with headache was significantly higher than it was in the group without headache (median 12.1 vs. 4 mg/dL, p=0.034). The albumin values in the group with headache were lower than those in the group without headache, but this difference was not statistically significant (median 3.76 vs. 3.9 g/dL, p=0.438). The CAR value was significantly higher in patients with headache compared to the group without headache (median 3.16 vs. 1.01, p=0.048, Table 3).

Table 2. Demographic and clinical features of COVID-19 patients with and without headache

	Total (n=62)	**With Headache (n=31)**	**Without Headache (n=31)**	**p**
Age (years), mean±SD	37.85±16.64	37.74±16.65	37.97±16.91	0.958
Gender, n (%)				
Female	28 (45.2)	14 (45.2)	14 (45.2)	1.000
Male	34 (54.8)	17 (54.8)	17 (54.8)	
Frequent symptoms that accompany headache				
Cough	28 (45.2)	17 (54.8)	11 (35.5)	0.126
Fever	23 (37.1)	14 (45.2)	9 (29.0)	0.189
Sore throat	14 (22.6)	6 (19.4)	8 (25.8)	0.544
Fatigue	13 (21.0)	5 (16.1)	8 (25.8)	0.349
Shortness of breath	6 (9.7)	4 (12.9)	2 (6.5)	0.671
Myalgia	7 (11.3)	3 (9.7)	4 (12.9)	1.000
Abdominal pain, diarrhea	7 (11.3)	4 (12.9)	3 (9.7)	1.000
Loss of taste and smell	5 (8.1)	-	5 (16.1)	0.053
Nausea	6 (9.7)	4 (12.9)	2 (6.5)	0.671
Comorbid diseases, n (%) (HT, CAD, CKD, COPD, Hypothyroidi)	9 (14.5)	5 (16.1)	4 (12.9)	1.000
Smoking, n (%)	6 (9.7)	3 (9.7)	3 (9.7)	1.000
Disease severity, n (%)				
Mild	19 (30.6)	8 (25.8)	11 (35.5)	
Moderate	37 (59.7)	19 (61.3)	18 (58.1)	0.556
Severe	6 (9.7)	4 (12.9)	2 (6.5)	
Hospital stay (days), median (IQR) [min-max]	10 (6) [3-28]	11 (8) [3-28]	8 (5) [4-16]	**0.049**

COVID-19: coronavirus disease 2019, SD: standard deviation, IQR: interquartile range, min-max: minimum-maximum, HT: hypertension, CAD: coronary artery disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease

Table 3. Comparison of serum parameters of COVID-19 patients with and without headache

	Total (n=62)	With Headache (n=31)	Without Headache (n=31)	p
White Blood Cell ($x10^3/\mu L$)	5.30 (2.42) [2.50-20.70]	6.10 (2.40) [2.50-20.70]	4.80 (2.36) [3.30-12.10]	0.071
Neutrophil ($x10^3/\mu L$)	3.17 (2.42) [1.20-17.90]	3.80 (2.40) [1.30-17.90]	2.70 (1.91) [1.20-9.20]	**0.023**
Lymphocyte ($x10^3/\mu L$)	1.42 (0.94) [0.44-4.00]	1.45 (0.99) [0.44-2.43]	1.40 (1.00) [0.75-4.00]	0.602
Platelet ($x10^3/\mu L$)	222.79±50.34	227.12±54.15	218.45±46.71	0.502
Hemoglobin (g/dL)	14.56±1.78	14.50±1.60	14.62±1.96	0.794
NLR	2.32 (2.73) [0.74-19.27]	2.81 (3.78) [0.74-19.27]	1.82 (2.11) [0.75-7.07]	**0.041**
D-dimer (mg/L)	431 (438) [56-4600]	414 (373) [56-4600]	450 (635) [105-3860]	0.612
ESR (mm/h)	14 (19) [2-91]	15 (29) [2-91]	10 (14) [5-85]	0.345
CRP (mg/L)	7.2 (15.3) [3-138]	12.1 (40.7) [3-138]	4.0 (7.4) [3.0-101]	**0.034**
Albumin (g/dL)	3.82 (0.53) [2.30-4.78]	3.76 (0.50) [2.30-4.40]	3.90 (0.65) [2.45-4.78)	0.438
CAR	1.76 (4.22) [0.63-69.80]	3.16 (9.74) [0.68-60]	1.01 (1.85) [0.63-69.8]	**0.048**
Ferritin (ng/mL)	83.5 (165.5) [5.2-2734]	94.8 (188) [7.2-2734]	75 (100.5) [5.2-1148]	0.564
Procalcitonin (ng/mL)	0.04 (0.04) [0.01-0.33]	0.04 (0.04) [0.01-0.33]	0.04 (0.02) [0.01-0.20]	0.873

COVID-19: coronavirus disease 2019, NLR: neutrophil/lymphocyte ratio, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, CAR: CRP/albumin ratio, data were presented as mean±standard deviation or median (interquartile range) [minimum-maximum]

DISCUSSION

In our study, the headache symptom was the fourth most common symptom with 17.7% of the patients with COVID-19, after cough, fever, weakness-fatigue symptoms. When the serum parameters of the patients were compared, the neutrophil count, NLR, CRP, CAR rates were significantly higher in the patients with headache compared to the group without headache. As far as we know, our study is the first study to show the relationship of headache symptoms with inflammation in COVID-19 patients.

Neurological involvement has been reported in 36.4-67.0% of COVID-19 patients (12,13). In our study, 30.0% of the patients had neurological involvement. Neurological symptoms of SARS-CoV-2 include headache, dizziness, cerebrovascular disease, seizure, altered consciousness, lack of taste and smell, visual disruption, neuropathic pain, Guillain-Barre Syndrome and muscle damage (13). In the study in Wuhan, the most common neurological symptoms of COVID-19 patients were dizziness 16.8% and headache 13.1% (13-17), while in the studies conducted, headache symptoms have been reported at the rates of %8.0, 11.0%, 14.0%, and 34.0% (18-21). In our study, headache was in the fourth place with 17.7% of all symptoms, and the first among neurological symptoms in 203 COVID-19 patients. Our findings have similar features to the literature.

Respiratory viruses can cause neurological symptoms in general and headache is among the most common symptoms, as in our study (18). Headache due to systemic viral infection is included as a separate title in the International Classification of Headache Disorders (ICHD)-III. Accordingly, it is defined as a headache that occurs with other symptoms and/or clinical signs of a systemic viral infection in the absence of meningitis or encephalitis (19). In our study, the patients with chronic headaches were excluded. Headache was one of the initial symptoms of COVID-19 and accompanied other symptoms. There were no patients presenting with isolated headache. In a patient with headache symptom, a brain MRI, which was taken due to the development of lethargy during follow-up, was normal. Our patients with and without headache symptoms did not have meningitis, encephalitis, stroke, or cerebral venous thrombosis (CVT) that may indicate a secondary headache. When all of the COVID-19 patients were discharged, the headache had passed, that is, the headache improved with the healing of the disease. In addition, the increase in NLR, CRP, and CAR in patients with headaches showed that the pain was associated with inflammation. With these features, headache in COVID-19 disease was compatible with the headache attributed to systemic viral infection.

The exact mechanisms of systemic infection headache are not still exactly known. Likely reasons include fever and activation of various immuno-inflammatory mediators such as endogenous or exogenous pyrogens, cytokines, and direct effects of microorganisms themselves (19).

Neutrophils are the most important cells that cause an inflammatory response during acute phase reactions. Lymphocytes are the main constituents of both humoral and cellular responses (20,21). The stress response of circulating lymphocytes results in an increase in neutrophil count and a decrease in lymphocyte count. Therefore, the ratio of these two white blood cell subgroups, NLR, is used as an inflammatory marker. In various studies, NLR was found to be higher in migraine patients than in the control group (22). NLR level has been previously shown to be a marker of a more severe infection in COVID-19 patients; however, there is no study in the literature showing the relationship between NLR and headache (23). In our study, the COVID-19 patients with headaches had a significantly higher neutrophil count and NLR than those without headaches.

CRP is an acute-phase protein synthesized in hepatocytes in reply to pro-inflammatory cytokines during inflammatory and infectious states (24). There are studies reporting increased serum CRP levels during migraine attack periods (25). Albumin is a negative acute-phase protein whose serum levels decrease in inflammatory conditions. Recently, CAR, which is a marker for systemic

inflammation, has been investigated as an independent prognostic marker in patients with infectious and other diseases (26). Similar to NLR, CAR has previously been shown to be high in migraine patients and it has been emphasized that peripheral inflammation may play a role in migraine pathogenesis (27). Similarly in our study, CRP and CAR were significantly higher in the COVID-19 patients with headache than those without headache, and according to our results, inflammation may play a role in the pathogenesis of headache in COVID-19.

The cytokine release syndrome seen in various viral diseases such as SARS, MERS, influenza, is another significant consideration for the headache mechanism (28). High pro-inflammatory cytokine concentrations in plasma were measured in patients with serious SARS-CoV-2 (14). These cytokines are known to cause direct tissue damage and another inflammatory cascade various immuno-inflammatory mediators (13). Neuroinflammation and various inflammatory mediators are well known to play a part in trigeminovascular activation (29). The headache in COVID-19 infection may have been caused by the release of proinflammatory mediators and cytokines triggering the perivascular trigeminal nerve endings (30). In our study, the increase in inflammatory parameters such as neutrophil count, NLR, CRP, and CAR, suggests that headache in COVID-19 disease may be associated with an increase in proinflammatory cytokines.

As is known, ACE2 has been identified as the main receptor for SARS-CoV-2 entry (31). It has been suggested that direct invasion of trigeminal nerve endings in the nasal cavity by SARS-CoV-2 may be another possibility for the headache mechanism associated with COVID-19 (30). However, ambiguity remains in this issue since ACE2 expression has not yet been demonstrated in the peripheral trigeminal nerve endings (32). In our study, headache was not an accompanying symptom in any of our five patients who had complaints of lack of taste and smell.

Headache can occur as a result of neurological damage caused by the virus directly infecting the central nervous system (CNS). Neurotropism of SARS-CoV-2 has been demonstrated in autopsy samples of COVID-19 patients (13,14). As previously shown in other coronaviruses (33,34), SARS-CoV-2 can enter the brain through systemic circulation or retrograde neuronal dissemination (35,36). SARS-CoV-2 in the systemic circulation can enter the brain through ACE2 receptors in capillary endothelium and cause neuronal damage (35). Similar to SARS-CoV, SARS-CoV-2 can also enter into the brain through the olfactory tract (37). The presence of anosmia in COVID-19 patients suggests an olfactory nerve invasion (38). Although there are opinions that it can directly invade the CNS through the olfactory nerve, this is not fully clarified (28,39). In our study, the patients with olfactory disorders were in the group without headache. In COVID-19 patients, the headache symptom may be associated with meningitis, encephalitis, or encephalopathy. Although the frequency of headache due to viral meningitis remains uncertain, a limited number of encephalitis cases in COVID-19 (40). Encephalopathy is likely to develop in patients with severe infection and comorbidities in COVID-19 (41). In our study, none of our patients had meningitis, encephalitis, or encephalopathy.

Increased D-dimer is common in COVID-19 patients (42). Elevations in the D-dimer can lead to headache-causing neurological complications such as CVT and stroke (43). Previously, stroke in COVID-19 patients (3%) and CVT (0.5%) have been reported (44,54). In our study, there was no statistically significant difference in D-dimer levels between patients with headache and patients without headache. No stroke or CVT was detected in our COVID-19 patients with and without headache symptoms.

In a recent study, headache was 17% in serious cases and 10% in milder cases, and it was emphasized that inflammation and hypoxia associated with disease seriousness may have a role in headache (13,16). In our study, there was no significant difference between patients with headache (25.8% mild, 61.3% moderate, and 12.9% severe) and without headache (35.5% mild, 58.1% moderate, and 6.5% severe) in disease severity. However, non-invasive MV was performed in patients with severity in our study, none of them were intubated and there were no patients with exitus. Therefore, there is a need for larger studies involving patients with more severe clinics on this subject. In addition, the duration of hospital stay of patients with headaches was higher in our study than those without headaches. It can be said that the recovery process of patients with headache takes longer.

As a result, there was a significant increase in neutrophil count, NLR, CRP, and CAR levels in COVID-19 patients with headache symptoms compared to those without headache. According to our study, the increased inflammatory response may play a role in the pathogenesis of headaches in COVID-19 patients. As far as we know, our study is the first to show the relationship of headache with inflammation in COVID-19 patients. In this regard, more comprehensive studies are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of Atatürk University Faculty of Medicine (01.10.2020, 37).

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Investigating the Frequency of Stroke in SARS-CoV-2 Cases in Sakarya City, Turkey

Sakarya İli SARS-CoV-2 Olgularında İnme Sıklığının Araştırılması

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ABSTRACT

Aim: The aim of this study is to identify the frequency of stroke among severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases in Sakarya city, to find out the clinical characteristics of patients diagnosed with stroke and to contribute to the national database.
Material and Methods: This retrospective study was carried out with 783 cases diagnosed with SARS-CoV-2 between April-June 2020 at the pandemic hospital in Sakarya city. Patients were compared in terms of age, National Institute of Health Stroke Scale (NIHSS), risk factors, radiological findings, inpatient treatment, intubation, and mortality rates.
Results: Out of 26 cases of ischemic stroke, 11 (42.3%) were male and 15 (57.7%) were female. In terms of infarction localization, the cause was medial cerebral artery (MCA) in 4 (15.4%) patients, top of the basilar in 2 (7.7%) patients, basilar artery in 1 (3.8%) patient, lacunar in 9 (34.6%) patients and anterior system in 10 (38.5%) patients. There was no significant difference in terms of D-dimer and C-reactive protein (CRP) levels according to disease severity (both p=0.262). Three (0.38%) patients presented with stroke findings and were diagnosed with SARS-CoV-2. Cryptogenic stroke was detected in 8 (30.8%) of the SARS-CoV-2 cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.
Conclusion: This is the first study to identify the frequency of stroke among SARS-CoV-2 patients in Sakarya city and Turkey. Our study is important as it shows that preventing or treating ischemic stroke in SARS-CoV-2 cases contributes greatly to the reduction of mortality.
Keywords: Sakarya city; SARS-CoV-2; stroke; frequency.

ÖZ

Amaç: Bu çalışmanın amacı Sakarya ilindeki şiddetli akut solunum yolu sendromu koronavirüsü 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) olgularında inme sıklığını tespit etmek, inme tanısı almış olan hastaların klinik özelliklerini ortaya koyabilmek ve ulusal veri tabanına katkıda bulunmaktır.
Gereç ve Yöntemler: Bu çalışma, Sakarya ilindeki pandemi hastanesinde Nisan-Haziran 2020 tarihleri arasında SARS-CoV-2 tanısı alan 783 olgu ile geriye dönük olarak yürütüldü. Hastalar, yaş, Ulusal Sağlık Enstitüleri İnme Skalası (National Institute of Health Stroke Scale, NIHSS), risk faktörleri, radyolojik bulgular, yatarak tedavi, entübe olma durumları ve mortalite oranları bakımından karşılaştırıldı.
Bulgular: Yirmi altı iskemik inmeli olgunun 11 (%42,3)'i erkek ve 15 (%57,7)'i kadın idi. Enfarkt lokalizasyonu bakımından 26 hastanın 4 (%15,4)'ü orta serebral arter (medial cerebral artery, MCA), 2 (%7,7)'si baziller tepe, 1 (%3,8)'i baziller arter, 9 (%34,6)'u laküner, 10 (%38,5)'u arka sistemden kaynaklanmaktaydı. D-Dimer ve C-reaktif protein (C-reactive protein, CRP) düzeyleri bakımından hastalık şiddetine göre anlamlı bir farklılık yoktu (her iki p=0,262). Üç (%0,38) hasta inme bulgusuyla gelip SARS-CoV-2 tanısı almıştı. SARS-CoV-2 olgularının 8 (%30,8)'inde kriptojenik inme tespit edildi. Sakarya ilinde SARS-CoV-2 olgularında inme sıklığı %3,3 olarak hesaplandı.
Sonuç: Bu çalışma SARS-CoV-2 hastalarında inme sıklığını tespit etmeye yönelik Sakarya ilinde ve Türkiye'de yapılmış ilk çalışmadır. Çalışmamız, SARS-CoV-2 olgularında iskemik inmenin önlenebilmesi ve tedavi edilebilmesinin mortalitenin azalmasına belirgin katkı sunduğunu göstermesi bakımından önemlidir.
Anahtar kelimeler: Sakarya ili; SARS-CoV-2; inme; sıklık.

INTRODUCTION

Even though respiratory symptoms are usually focused on in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) cases, we predicted that there may be accompanying neurological symptoms due to our familiarity with the coronavirus family. Stroke in SARS-CoV-2 cases is caused by changes in the body due to infection and or the presence of risk factors (1). The study that reported the first cases of stroke in Wuhan also noted that there were risk factors present in these cases. On the other hand, stroke was also reported in young cases without any risk factors. This appears to be evidence suggesting that both ways are possible (1-3). Some studies on SARS-CoV-2 reported that stroke was much more frequent in severe cases with pulmonary involvement (4-6). In cases of SARS-CoV-2, the most commonly reported condition in the literature has been ischemic stroke. Less often, hemorrhagic stroke and sinus vein thrombosis have been reported. In SARS-CoV-2 cases, young cases with stroke along with cases presented with only stroke reveal that stroke can also occur at the onset of the disease (6-8). The fact that thrombotic complications were identified in 31% of the cases despite systematic thrombosis prophylaxis shows the importance of evaluating patients in intensive care in terms of thromboembolism prophylaxis. One of the most important markers of this progression is thought to be the D-dimer level (9-11). Antithrombotic treatment such as low molecular weight heparin and aspirin has been recommended for SARS-CoV-2 patients with low D-dimer level (11,12). Starting from March 11, 2020, the day when the first positive case was detected in Turkey, antithrombotic treatment has been a part of the routine procedure as per the treatment guidelines of the Ministry of Health (13). We think that the reason behind the low mortality rates in Turkey could be this prophylactic treatment. The objective of our study is to identify the frequency of stroke among SARS-CoV-2 cases in Sakarya city and to contribute to the national database and literature.

MATERIAL AND METHODS

In this study, 783 cases diagnosed with SARS-CoV-2 at the emergency department, wards and intensive care units between April 1 and June 15, 2020 at Sakarya Training and Research Hospital, which was declared a pandemic hospital in March, were retrospectively reviewed. The diagnosis was made by evaluating nasopharyngeal swaps with polymerase chain reaction (PCR) and thorax computed tomography (CT), which presented atypical viral pneumonia. The study was approved by the Ethics Committee of the Sakarya University Faculty of Medicine (27.07.2020, 437) and the General Directorate of Health Services of the Ministry of Health. SARS-CoV-2 cases over the age of 18, who required neuroimaging due to stroke pre-diagnosis, were screened from the hospital registration system. Hemorrhagic stroke cases, cases with previous stroke history, and cases with missing data were excluded from the study. Demographic data, medical history, neurological examination result, electrocardiogram (ECG), brain CT, diffusion-weighted magnetic resonance imaging (MRI), PA chest radiograph, blood biochemistry, hemogram test, C-reactive protein (CRP), D-dimer and fibrinogen values of the cases, ischemic stroke diagnosis of which was confirmed by clinical and radiological sources, were recorded. Known or newly-identified accompanying chronic diseases such as cardiac failure, arrhythmia, myocardial infarction, diabetes, hypertension, chronic obstructive pulmonary disease, pulmonary hypertension, pulmonary embolism, and chronic renal failure were recorded. Stroke localization was performed by evaluating ischemic territories in the brain based on brain CT and diffusion-weighted MRI findings. Infarction areas were divided into three groups, namely anterior cerebral artery (ACA), posterior cerebral artery (PCA) and medial cerebral artery (MCA), taking into account arterial watershed areas. The National Institute of Health Stroke Scale (NIHSS) levels, which determine the severity of the disease based on neurological examination of patients, were recorded. Those with a NIHSS score of 1 to 8 were classified as mild, 9 to 15 as moderate, higher than 16 as severe.

Statistical Analysis

Statistical analysis was performed by using statistical package SPSS v.25.0. Continuous data are described by mean±standard deviation (SD) or median interquartile range (IQR) and (minimum-maximum), categorical data are presented as numbers and percentages. Shapiro-Wilk test was used to evaluate the normality assumption for numerical variables. In the evaluation of the data, a Student's t-test was used for the data with normal distribution in order to compare numerical variables, a Mann-Whitney U test was used for the data that were not normally distributed, and a Pearson Chi-square or Fisher's exact test was used in the analysis of categorical variables. Statistical significance was considered as 0.05.

RESULTS

SARS-CoV-2 patients were showing clinical stroke findings and were diagnosed with ischemic stroke with neuroimaging. Out of 26 cases of ischemic stroke, 11 (42.3%) were male and 15 (57.7%) were female. The mean age of the patients was 71.7±12.3, the mean age of the male patients was 72.0±10.8 and the mean age of the female patients was 71.5±12.7 years. Only 2 (7.7%) of the patients were 45 years of age and under. Seventeen (65.4%) of the patients had a medical history of hypertension, 9 (34.6%) patients had diabetes and 3 (11.5%) patients had cardiac disease. Nine (34.6%) of the patients were smokers and 1 (3.8%) patient consumed alcohol. There was no significant difference in terms of advanced age, and comorbidities according to the disease severity. Demographic characteristics and risk factors of patients are shown in Table 1.

In terms of the sub groups of infarction localization, the cause was MCA in 4 (15.4%) patients, top of the basilar in 2 (7.7%) patients, basilar artery in 1 (3.8%) patient, lacunar in 9 (34.6%) patients and anterior system in 10 (38.5%) patients. In terms of the anatomical localization of lesions of ischemic stroke patients, 4 (15.4%) patients had partial anterior CI, 13 (50.0%) had posterior CI, 9 (34.6%) had lacunar while no patients had total anterior CI.

Patients were compared in terms of their NIHSS score, which was calculated using the NIHSS during admission to the clinic, risk factors, radiological localization findings,

duration of stay at hospital, duration of intubation, and mortality rates. In terms of risk factors of the patient group, the relationship between age/sex and glucose level at arrival, HbA1C, diabetes, hypertension, heart disease, smoking and alcohol use was not statistically significant. Patients requiring intensive care were grouped under severe cases and those followed-up in wards were grouped under non-severe cases. Sixteen (61.5%) cases were followed-up in intensive care, 10 (38.5%) cases were intubated and 8 (30.8%) cases died. CRP and D-dimer levels of 26 patients that were included in the study did not show a significant difference between severe and non-severe cases (both p=0.262). There only was a significant difference in NIHSS according to the disease severity between severe and non-severe cases (p<0.001, Table 2). Three (0.38%) patients presented with stroke findings and were diagnosed with SARS-CoV-2. Cryptogenic stroke was detected in 8 (30.8%) of the SARS-CoV-2 cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.

Table 1. Clinical characteristics of patients with SARS-CoV-2

	Total (n=26)	Severe (n=16)	Non-severe (n=10)	p
Age (years), mean±SD	71.7±12.3	71.6±14.0	71.4±12.7	0.971
Age, n (%)				
<45	2 (7.7)	1 (6.3)	1 (10.0)	0.730
≥45	24 (92.3)	15 (93.8)	9 (90.0)	
Sex, n (%)				
Male	11 (42.3)	8 (50.0)	3 (30.0)	0.428
Female	15 (57.7)	8 (50.0)	7 (70.0)	
Comorbidities (any), n (%)	8 (28.6)	3 (16.7)	5 (50.0)	0.091
Hypertension, n (%)	17 (65.4)	8 (50.0)	9 (90.0)	0.087
Diabetes mellitus, n (%)	9 (34.6)	4 (25.0)	5 (50.0)	0.234
Cardiac disease, n (%)	3 (11.5)	2 (12.5)	1 (10.0)	0.846
Smoke, n (%)	9 (34.6)	3 (18.8)	6 (60.0)	**0.046**
Alcohol, n (%)	1 (3.8)	0 (0.0)	1 (10.0)	0.385

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, SD: standard deviation

Table 2. Laboratory findings of patients with SARS-CoV-2

	Total (n=26)	Severe (n=16)	Non-severe (n=10)	p
C-reactive protein (mg/L)	23.3 (64.2) [1.1-288]	33.2 (59.8) [1.1-288]	7.6 (45.4) [3-231]	0.262
D-dimer (mg/L)	1505 (2247) [331-29400]	1660 (3652) [373-29400]	1450 (1879) [331-3220]	0.262
NIHSS	23 (20) [5-39]	27 (12) [23-39]	9 (6) [5-16]	**<0.001**
Imaging Pattern, n (%)				
Lacunar	9 (34.6)	4 (25.0)	5 (50.0)	0.234
Other	17 (65.4)	12 (75.0)	5 (50.0)	

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2, NIHSS: national institutes of health stroke scale, data were presented as median (interquartile range) [minimum-maximum]

DISCUSSION

First, from Zhongnan Hospital in Wuhan, China, where the pandemic first emerged, then, from around the world, as of February 7, 2020, neurologists have started to report common neurological symptoms including stroke (6,14-16). It has been reported that blood coagulation tests (prothrombin and D-dimer) of SARS-CoV-2 patients showed abnormal results, which increased the possibility of ischemic stroke. Initial publications reported stroke in 5% of the cases (4,17). Among 388 patients, who applied to a university hospital in Italy, 2.5% had ischemic stroke and the mean age of these patients was 68.4±5.9 years (18). A study involving over 2000 SARS-CoV-2 patients found that the rate of cerebrovascular presentations was higher in severe cases (19). In our study, we investigated 783 SARS-CoV-2 positive patients at a pandemic hospital in Sakarya city and ischemic stroke was detected in 26 of these cases. Stroke frequency was calculated as 3.3% among the SARS-CoV-2 cases in Sakarya city.

Literature reports that in stroke cases, hypertension, diabetes and cardiovascular diseases increase the severity of disease (6,14,17,20). Especially in cases where risk factors for stroke are present such as hypertension, diabetes and smoking, SARS-CoV-2 is much more frequent and severe. In our study, only 8 (30.8%) cases developed stroke without having any risk factor. In cryptogenic cases, transthoracic echocardiogram and Doppler ultrasonography of the carotid vertebral artery could not be performed due to pandemic restrictions, which led to a limitation in determining stroke etiology.

The age range of SARS-CoV-2 patients with ischemic stroke has varied in studies. In a most comprehensive study carried out on more than 26 thousand SARS-CoV-2 cases in 99 centers, the mean age of ischemic stroke was 71 (6). In our study, the age range was in line with the literature. Only 2 (7.7%) cases were below the age of 45.

Subtyping, which is the next step after a stroke diagnosis, is

of vital importance in predicting prognosis, determining discharge and treatment strategies and preventing recurrence. In literature, large vascular occlusion has been reported in the majority of the cases (6,21). Only 6 (23.1%) of our stroke patients had large vascular occlusion. 3 (11.5%) cases arrived at the hospital presenting with stroke. Out of these, 2 cases actually started having fever and fatigue symptoms a few days back but refrained from going to the hospital because of the pandemic. Another case applied to another hospital presenting with weakness of the left side. Upon suspicion at the ER, this case was tested and was referred to the pandemic hospital after being diagnosed with SARS-CoV-2.

Literature reports that stroke can also occur at the onset of SARS-CoV-2 in cases who only present with stroke manifestations without showing any other symptoms such as fever, cough and loss of appetite (19). Only one case in our study presented with stroke at the onset of SARS-CoV-2.

SARS-CoV-2 can enter the brain via retrograde neuronal or hematogenous propagation (9,17). Due to its direct damage on the nervous system and inflammation, hypoxia, immobilization and disseminated intravascular coagulation it causes, this virus is thought to make people susceptible to venous and arterial thromboembolic events. Due to the known fact that the disease makes people susceptible to thromboembolic events, prophylactic antithrombotic treatment is recommended for patients with high D-Dimer levels (13,22-24). Twenty three (88.5%) of our cases were receiving prophylactic subcutaneous heparin and acetylsalicylic acid treatment at two equal doses before the diagnosis. CRP and D-dimer levels of our stroke cases significantly decreased over time. This significant decrease over time is thought to be due to the antithrombotic and infection treatment patients were receiving. We found a positive correlation between D-dimer and CRP levels of stroke cases in our study and the severity of SARS-CoV-2, and the majority of these cases were followed up under intensive care conditions with respiratory support. We were not able to find a relationship between NIHSS, which is used to identify the severity of stroke, and D-dimer and CRP levels. We predict one reason for this to be the regular and early administration of subcutaneous heparin in all SARS-CoV-2 cases with high D-dimer levels.

In Turkey and all around the world, rigorous and diligent efforts are being exerted to prevent death in SARS-CoV-2 cases. A patient presenting with cerebrovascular event findings during the pandemic should be suspected for SARS-CoV-2, a detailed medical history should be taken and the patient should be tested, if necessary. This is highly important both for diagnosing the disease early and for preventing the spread of the infection in the hospital and in the community. In our study, only 1 case presenting with stroke was tested after suspecting SARS-CoV-2 due to a routine thorax CT, which then resulted in this case to be diagnosed early with SARS-CoV-2.

The most important limitation of our study was that etiological subtyping could not be done in stroke cases. Etiology could not be established in cases due to pandemic-related restrictions. The cases were only compared based on risk factors for stroke. Another limitation was that our results only cover moderate and severe SARS-CoV-2 cases requiring hospitalization. Another limitation was that the association of medication used for SARS-CoV-2 with stroke cases could not be investigated. As we are facing with a new disease, medications used for treatment should also be investigated for cerebrovascular side effects.

CONCLUSION

It could be noted that our study is significant as it will contribute to the literature by providing information on cerebrovascular events observed in SARS-CoV-2 positive cases and will further improve experience on this issue.

Our study supports the need for patients suffering from stroke, even if they are cryptogenic, regardless of the etiology of stroke, to be suspected of SARS-CoV-2 during the pandemic and for testing suspected cases.

Ethics Committee Approval: The study was approved by the Ethics Committee of Sakarya University Faculty of Medicine (27.07.2020, 437).

Conflict of Interest: None declared by the authors.

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Evaluation of Computed Tomography, Clinical and Laboratory Findings of COVID-19 in Cancer Patients

Kanser Hastalarında COVID-19 Bilgisayarlı Tomografi, Klinik ve Laboratuvar Bulgularının Değerlendirilmesi

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ABSTRACT

Aim: The aim of this study was to evaluate the computed tomography (CT), clinical and laboratory findings of coronavirus disease 2019 (COVID-19) in cancer patients and to compare the findings between polymerase chain reaction (PCR) positive and negative patients.
Material and Methods: Twenty-three cancer patients with positive PCR tests and 22 diagnosed as COVID-19 with clinical and radiological findings were included in the study. CT images of the patients were evaluated simultaneously by two radiologists. Presence of comorbid diseases, symptoms and laboratory values were evaluated.
Results: The most common CT involvement pattern was peripheral with 88.9% (n=40). Bilateral lung involvement rate was 57.8% (n=26). The most common finding was ground glass opacities (n=38, 84.5%). 35.6% (n=16) of these were accompanied by consolidation. Multifocal involvement was present in 62.2% (n=28) of the cases. The most frequently involved lobes were lower lobes. Other relatively common findings were septal thickening, subpleural streaking, and air bronchogram. The median neutrophil, lymphocyte, D-dimer, procalcitonin, C-reactive protein and lactate dehydrogenase values of the patients were 2000 mm^3, 1200 mm^3, 1990 ng/mL, 30.7 mcg/L 15.8 mg/dl, 161 IU/L, respectively.
Conclusion: Multifocal and bilateral involvement, and ground glass opacities were the most common findings. However, higher rates of septal thickening, which is generally less common, suggest that the findings may be more severe in cancer patients. Most of the inflammatory markers were higher in PCR negative cases. Studies with more patients in multiple centers will provide better comparison of the findings in cancer patients with the general population.
Keywords: COVID-19; cancer; computed tomography; laboratory; PCR.

ÖZ

Amaç: Bu çalışmanın amacı kanser hastalarında koronavirus hastalığı 2019 (coronavirus disease 2019, COVID-19) bilgisayarlı tomografi (BT), klinik ve laboratuvar bulgularının değerlendirilmesi ve polimeraz zincir reaksiyonu (polymerase chain reaction, PCR) pozitif ve negatif hastaların bulgularının karşılaştırılmasıdır.
Gereç ve Yöntemler: Çalışmaya PCR testi pozitif olan 23, klinik ve radyolojik bulgularla COVID-19 tanısı almış 22 kanser hastası alındı. Hastaların BT görüntüleri iki radyolog tarafından eşzamanlı değerlendirildi. Komorbid hastalık varlığı, semptomlar ve laboratuvar değerleri değerlendirildi.
Bulgular: En sık BT tutulum paterni %88,9 (n=40) ile periferaldi. Bilateral akciğer tutulumu oranı %57,8 (n=26) idi. En sık saptanan bulgu buzlu cam dansiteleri idi (n=38, %84,5). Bunların %35,5 (n=16)'ine konsolidasyon da eşlik etmekteydi. Vakaların %62,2 (n=28)'sinde multifokal tutulum mevcuttu. En sık tutulan loblar alt loblar idi. Diğer nispeten sık bulgular septal kalınlaşma, subplevral çizgilenme ve hava bronkogramı idi. Hastaların ortanca nötrofil, lenfosit, D-dimer, prokalsitonin, C-reaktif protein ve laktat dehidrogenaz değerleri sırasıyla 2000 mm^3, 1200 mm^3, 1990 ng/mL, 30.7 µg/L 15.8 mg/dl, 161 IU/L idi.
Sonuç: Multifokal ve bilateral tutulum ile buzlucam dansiteleri en sık bulgulardı. Ancak genelde daha az saptanan septal kalınlaşmanın yüksek saptanması kanser hastalarında bulguların daha ciddi olabileceğini düşündürmektedir. PCR negatif vakalarda inflamatuvar markerların birçoğu daha yüksekti. Çok merkezde daha fazla hasta ile yapılacak çalışmalar kanser hastalarındaki bulguları genel popülasyonla daha iyi karşılaştırmayı sağlayacaktır.
Anahtar kelimeler: COVID-19; kanser; bilgisayarlı tomografi; laboratuvar; PCR.

INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first detected in a group of patients with pneumonia in Wuhan, China in December 2019, and it is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). COVID-19 has spread rapidly across the world within a couple of months, and the World Health Organization (WHO) assessed that COVID-19 can be identified as a pandemic on 11 March 2020. COVID-19 may result in severe clinical conditions, such as pneumonia, necrotizing encephalopathy, acute respiratory distress syndrome, respiratory failure, systemic inflammatory response and sepsis, as well as in asymptomatic patients (1-3). Cancer patients have become more susceptible to COVID-19 due to immunosuppression, malnutrition and treatment-related toxicities due to the underlying disease. It has also been stated that mortality is higher in cancer patients (4). Therefore, we planned this study with the idea that CT and laboratory findings of COVID-19 may differ in cancer patients. Also, we aimed to compare these findings in cancer patients with and without positive polymerase chain reaction (PCR) results.

MATERIAL AND METHODS

This retrospective study was conducted using non-contrasted computed tomography (CT) images and laboratory values of patients infected with SARS-CoV-2 that were performed between March and September 2020 at Adana City Training and Research Hospital. The study was approved by the Ethics Committee of Adana City Training and Research Hospital (08.07.2020, 61/992) and was carried out in accordance with the provisions of the Declaration of Helsinki and the Good Clinical Practice guidelines. Pediatric patients (0-18 age) were excluded from the study. Overall, 45 patients were included in the study. Of these, 23 patients had a positive PCR test, and 22 patients' PCR test results were negative, but they had typical thorax CT features and typical clinical findings for COVID-19. Imaging was performed using a 128-detector MDCT unit (Philips Ingenuity 128, Eindhoven, The Netherlands) with technical parameters utilized as follows: 120 kvP, 75-400 mAs, rotation time 0.4 s, pitch 1.49 and slice thickness: 1 mm. In the other center, imaging was performed using a 16-detector MDCT unit (Toshiba Alexion, Japan) with technical parameters utilized as follows: 120 kvP, 100-400 mAs, rotation time 0.5 s, pitch 1.2 and slice thickness: 1 mm. CT images were evaluated in terms of ground glass opacity (GGO), consolidation, air bronchograms, halo and reverse halo signs (RHS), tree in bud, septal thickening, crazy paving pattern, lymphadenopathy, pleural effusion, nodules, and subpleural fibrous streaking findings, and multilobar-multifocal, unilateral or bilateral, peripheral-central and upper-lower side involvement was noted. Lymphadenopathy was considered when the short-axis diameter is >10 mm. The radiologic evaluation was performed by two radiologists simultaneously. The white blood cell (WBC), neutrophil, lymphocyte, D-dimer, ferritin, procalcitonin, C-reactive protein (CRP), lactate dehydrogenase (LDH), prothrombin time (PT), international normalized ratio (INR) and creatinine values of patients which were examined during the period of COVID-19 were noted.

Statistical Analysis

The data analysis was performed with SPSS v.20.0. All continuous data were presented as mean±standard deviation or median, interquartile range and minimum-maximum. The categorical data were presented as numbers and percentages. Shapiro Wilk's test was performed to analyze the distribution of continuous variables. Student's t-test was used to analyze variables showing normal distribution, and Mann-Whitney U test was used for variables not showing normal distribution. A Chi-square test or Fisher's exact test was used to compare the categorical variables. A p value of <0.05 was considered as statistically significant.

RESULTS

Overall, 45 patients, 19 (42.2%) female and 26 (57.8%) male, were included in the study. The mean age was 61.4±14.6 (range, 23-91) years (Table 1). The ratio of common parenchymal infiltration patterns was as follows: mixed GGO and consolidation 35.6% (n=16), pure GGO 48.9% (n=22) and pure consolidation 15.5% (n=7). Air bronchograms were present in 24.4% (n=11) of the patients. The detailed findings are shown in Table 2.

The evaluation of involvement patterns showed that 57.8% (n=26) of the patients had bilateral lung involvement and 62.2% (n=28) had multifocal involvement. The most common lobe involved was the left lung lower lobe with 73.3% (n=33). The evaluation of the involved area showed that only peripheral involvement pattern was the most common (n=23, 51.1%). However, both peripheral and central involvement were detected in 37.8% (n=17) of the patients. The frequency of other findings is specified in detail in Table 2.

The median WBC, neutrophil, lymphocyte, D-dimer, procalcitonin, CRP, PT, INR, LDH, creatinine and ferritin values of all patients were 9100 mm^3, 2000 mm^3, 1200 mm^3, 1990 ng/ml, 30.7 µg/L, 15.8 mg/L, 12.9 sec, 1.16, 161 U/L, 1.00 mg/dL and 7000 ng/mL, respectively.

Ferritin ($p<0.001$), procalcitonin ($p<0.001$) and creatinine ($p=0.014$) values were significantly lower in PCR positive patients, while neutrophil ($p<0.001$), CRP ($p=0.007$) and LDH ($p<0.001$) values were significantly higher in PCR positive patients than PCR negative patients.

DISCUSSION

During the COVID-19 pandemic, cancer patients have become more susceptible to this disease. Therefore, CT and laboratory findings may differ with the general population. In a study, it was found that the WBC was between 4-10000 in 60% of the cases, and over 10000 in 25%, while the mean WBC number was 5300. In our study, the mean WBC number was found to be 9100 mm^3. In the same study, while the mean lymphocyte count of the patients was 990 µg/L, lymphopenia was observed in 50% of the patients. In our study, while the lymphocyte count was detected as 1200 µg/L, lymphopenia was observed in 35% (4).

In different studies, it has been shown that the association of COVID-19 with solid tumors is higher than hematological malignancies. In the studies conducted by Yang et al. (4) and Meng et al. (5), it was shown that it is more common in patients with solid tumors. In our study, 43 of 45 patients were patients with solid tumors, in line with the literature. The most common accompanying solid tumor differs between studies. In the study of Yang et al. (4),

Table 1. Demographic and clinical features of the patients

	Total (n=45)	PCR (+) (n=23)	PCR (-) (n=22)	p
Gender				
Female	19 (42.2%)	11 (47.8%)	7 (31.8%)	0.273
Male	26 (57.7%)	12 (52.2%)	15 (68.2%)	
Age (years), mean±SD	61.4±14.6	59.1±15.8	63.8±13.0	0.277
Comorbidity	18 (40.0%)	5 (21.7%)	13 (%59.1)	**0.011**
Cancer type				
Lung	16 (35.5%)	7 (30.4%)	9 (40.9%)	0.189
Breast	7 (15.6%)	5 (21.7%)	2 (9.1%)	
Colon	7 (15.6%)	3 (13.0%)	4 (18.2%)	
Pancreas	3 (6.7%)	3 (13.0%)	0 (0.0%)	
Endometrium	4 (8.9%)	2 (8.7%)	2 (9.1%)	
Larynx	2 (4.4%)	0 (0.0%)	2 (9.1%)	
Prostate	1 (2.2%)	1 (4.3%)	0 (0.0%)	
Kidney	1 (2.2%)	0 (0.0%)	1 (4.5%)	
Stomach	2 (4.4%)	2 (8.7%)	0 (0.0%)	
Lymphoma	2 (4.4%)	0 (0.0%)	2 (9.1%)	
Symptom				
Fever	6 (13.3%)	4 (17.4%)	2 (9.1%)	0.231
Cough	6 (13.3%)	1 (4.3%)	5 (22.7%)	
Dyspnea	8 (17.8%)	3 (13.0%)	5 (22.7%)	
Diarrhea	3 (6.7%)	1 (4.3%)	2 (9.1%)	
Headache	2 (4.4%)	1 (4.3%)	1 (4.5%)	
None	7 (15.6%)	6 (26.1%)	1 (4.5%)	
Multiple symptoms	13 (28.9%)	7 (30.4%)	6 (27.3%)	

PCR: polymerase chain reaction, SD: standard deviation,

Table 2. Computed tomography findings of the patients

	Total (n=45)	PCR (+) (n=23)	PCR (-) (n=22)	p
Central	5 (11.1%)	0 (0.0%)	5 (22.7%)	**0.022**
Peripheral	23 (51.1%)	16 (69.6%)	7 (31.8%)	**0.011**
Central and peripheral	17 (37.8%)	7 (30.4%)	10 (45.5%)	0.299
GGO	22 (48.9%)	15 (65.2%)	7 (31.8%)	**0.025**
Consolidation	7 (15.6%)	3 (13.0%)	4 (18.2%)	0.699
GGO and consolidation	16 (35.6%)	5 (21.7%)	11 (50.0%)	**0.048**
Single lung involvement	19 (42.2%)	9 (39.1%)	10 (45.5%)	0.668
Bilateral lung involvement	26 (57.8%)	14 (60.9%)	12 (54.5%)	0.668
Right lung upper lobe	17 (37.8%)	7 (30.4%)	10 (45.5%)	0.299
Right lung middle lobe	20 (44.4%)	10 (43.5%)	10 (45.5%)	0.894
Right lung lower lobe	29 (64.4%)	15 (65.2%)	14 (63.6%)	0.912
Left lung upper lobe	12 (26.7%)	7 (30.4%)	5 (22.7%)	0.559
Left lung lower lobe	33 (73.3%)	17 (73.9%)	16 (72.7%)	0.928
Single lobe involvement	17 (37.8%)	9 (39.1%)	8 (36.4%)	0.848
Multifocal involvement	28 (62.2%)	14 (60.9%)	14 (63.6%)	0.848
Halo sign	1 (2.2%)	0 (0.0%)	1 (4.5%)	0.489
Reverse halo sign	1 (2.2%)	0 (0.0%)	1 (4.5%)	0.489
Tree in bud sign	1 (2.2%)	0 (0.0%)	1 (4.5%)	0.489
Septal thickening	23 (51.1%)	11 (47.8%)	12 (54.5%)	0.652
Effusion	12 (26.7%)	7 (30.4%)	5 (22.7%)	0.559
Crazy Paving pattern	6 (13.3%)	2 (8.7%)	4 (18.2%)	0.414
Air bronchogram	11 (24.4%)	4 (17.4%)	7 (31.8%)	0.260
Nodule	2 (4.4%)	1 (4.3%)	1 (4.5%)	1.000
Subpleural streaking	12 (26.7%)	6 (26.1%)	6 (27.3%)	0.928
Lymphadenopathy	3 (6.7%)	1 (4.3%)	2 (9.1%)	0.608

PCR: polymerase chain reaction, GGO: ground glass opacity

Table 3. Laboratory findings of the patients

	Total (n=45)	PCR (+) (n=23)	PCR (-) (n=22)	p
Ferritin (ng/mL)	7000 (12514) [30-32480]	441 (916) [30-32480]	11500 (6275) [1000-25200]	**<0.001**
WBC (mm^3)	9100 (7100) [100-31500]	9200 (8500) [1400-31500]	8850 (6225) [100-22600]	0.658
Neutrophil (mm^3)	2000 (7550) [100-27300]	8200 (8300) [680-27300]	850 (925) [100-3300]	**<0.001**
Lymphocyte (mm^3)	1200 (1013) [200-4550]	1200 (800) [200-2500]	1067 (1135) [289-4550]	0.510
Procalcitonin (µg/L)	30.7 (112.4) [0.2-407.0]	1.5 (10.7) [0.2-125.0]	94.1 (181.3) [7.6-407.0]	**<0.001**
CRP (mg/L)	15.8 (51.6) [1.2-405.3]	63.0 (199.8) [1.2-405.3]	13.8 (3.4) [11.2-30.3]	**0.007**
PT	12.9 (4.4) [9-28.0]	13.4 (4.2) [9.0-28.0]	12.4 (3.3) [10.0-26]	0.301
D-dimer (ng/mL)	1990 (3730) [272-40200]	1500 (3740) [272-40200]	3800 (4025) [400-30.200]	0.069
INR	1.16 (0.29) [0.80-2.62]	1.11 (0.35) [0.80-2.40]	1.17 (0.23) [0.97-2.62]	0.964
Creatinine (mg/dL)	1.00 (0.84) [0.44-18.60]	0.85 (0.61) [0.44-2.93]	1.05 (1.83) [0.70-18.60]	**0.014**
LDH (U/L)	161 (302) [4-7044]	313 (318) [161-7044]	20 (7) [4-60]	**<0.001**

PCR: polymerase chain reaction, WBC: white blood cell, CRP: C-reactive protein, PT: prothrombin time, INR: international normalized ratio, LDH: lactate dehydrogenase

it was mostly observed in patients with breast cancer (40%). Likewise, in another study, it was shown that it was more common in patients with breast cancer (6). In our study, the most common accompanying malignancy was lung cancer. There are not many studies comparing PCR positive and negative cancer patients. In the study of Assaad et al. (7), lung cancer was the most common accompanying solid tumor both in the PCR positive and negative groups. Our findings also support this study, and the most common accompanying cancer type was lung cancer.

Various symptoms can be seen during the course of COVID-19 infection. Common symptoms are fever, dyspnea and cough. In addition, gastrointestinal symptoms such as diarrhea, vomiting, and neurological symptoms such as loss of smell and sensation may accompany. Studies show that the most common symptoms vary. While the most common symptoms in some studies were fever and cough (4,6,7), the most common symptoms in our study were dyspnea and cough. In the study by Assaad et al. (7), the most common symptom in both PCR positive and PCR negative patients was fever. While 7 (26%) of the PCR positive patients in our study were asymptomatic, the most common symptom in symptomatic patients was fever. While 4.5% (n=1) of the PCR negative patients were asymptomatic, the most common symptom was cough and dyspnea.

Lymphopenia (lymphocyte count <1000 µg/L) can be seen in COVID-19. The decrease in lymphocyte count in these patients suggests that the immune system response may also be poor. The rate of lymphopenia in the studies performed varies between 35-70% (8). Lymphopenia was not detected both in the PCR positive and negative patients in our study.

In COVID-19, an increase in values such as procalcitonin and C-reactive protein, which are indicators of inflammation, can be seen (8). Procalcitonin is the prohormone of calcitonin and can be normal or elevated at the onset of the disease (9). In our study, procalcitonin and CRP values were found to be high in PCR positive and negative patients. Moreover, procalcitonin levels in the PCR negative group were statistically significantly higher than the PCR positive patients.

Ferritin is also a positive acute phase reactant and may increase in inflammation. In some studies, it has been shown that the ferritin level is higher in cancer patients compared to the normal population. In our study, ferritin level was higher in PCR negative patients compared to PCR positive patients. However, there is no clear information in the literature regarding ferritin level among PCR positive and negative patients.

When evaluated in terms of CT findings, GGO was found at a rate of 100% in a similar study, which was 84.5% in our study (10). Consolidation was detected at a rate of 14% in the same study, while it was 51.1% in our study, as a higher rate. Depending on whether the patients are in the early or late period of the infection, an organizational finding such as consolidation can be expected to vary. In this study, the rate of air bronchogram was found to be 4%, which is lower than the rate of 24.4% in our study. This features can also be considered as a finding correlated with the low consolidation rates of the patients in this study. In the same study, lower lobe involvement was more common, similar to the rates in our study. Bilateral involvement was also detected at a rate of 76%, which was slightly higher than the rate of 57.8% in our study. When we compared CT findings with a large review of the general population (11), GGO and bilateral involvement were common in our study as in the general population. However, while consolidation rate was 10% in this review, it was higher in our study, suggesting that the organization may be more pronounced in cancer patients. In addition, in the same study and in another large review (12), it was stated that septal thickening and subpleural streaking are rare. However, in our study, these findings were detected at 51.1% and 26.7%, respectively, suggesting that lung involvement may be more severe in cancer patients.

PCR positive and negative patients in our study were also compared in terms of CT findings. There are very few studies in the literature comparing these two groups even in the general population. In our study, the presence of GGO and peripheral involvement were statistically significantly higher in the PCR positive group. Similarly, in the study conducted by Chen D et al. (13), GGO was higher in those with PCR positive. In the same study, the air bronchogram was significantly higher in the PCR positive group, but in our study, there was no difference between the two groups. There was no significant difference in terms of other findings.

CONCLUSION

As a conclusion, COVID-19 is a disease with a relatively high fatality in the general population and may have a more severe course in cancer patients. Therefore, laboratory and CT findings vary compared to the general population. In our study, CT findings such as septal thickening, which can be detected in more severe cases, were found to be higher in cancer patients compared to the general population. However, studies with a larger number of cases are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of Adana City Training and Research Hospital (08.07.2020, 61/992).

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Dynamics and Determinants of Inflation During the COVID-19 Pandemic Period in European Countries: A Spatial Panel Data Analysis

COVID-19 Pandemi Döneminde Enflasyonun Belirleyicileri: Avrupa Ülkeleri Üzerine Bir Mekansal Panel Veri Analizi

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ABSTRACT

Aim: The recent macroeconomic problems in the global economy are highly related to the coronavirus disease 2019 (COVID-19) pandemic. Since the highest spread of the disease is observed in the European countries, it is worthwhile to investigate the macroeconomic indicators in the European Union (EU) member and the candidate countries. Inflation is one of the most important indicators to examine since it may directly affect many macroeconomic variables. In this study, the determinants of inflation in the 28 EU members and candidate states are investigated.
Material and Methods: In this study, the determinants of inflation in the 28 EU members and candidate states are investigated for January 2020-July 2020 using spatial panel data analysis.
Results: The empirical results indicated that the exchange rate and money supply ratios were reasons of the increase in inflation. There is also increasing pressure on the inflation rates due to the domestic money supply and exchange rate variables as well as the neighborhood relations between countries (positive spatial effects).
Conclusion: It is an important finding that macroeconomic problems in each sample country are also affected by developments in neighboring countries as well as internal dynamics. Continuous development of economic, social, and political cooperation between neighboring countries at the regional level is essential. It is reasonable for every country to develop self-sufficient strategies in the fields of agriculture, food, technology, and pharmaceutical industries in case of global disasters. Regional cooperation should not be limited to the development of sectors that stand out during the pandemic period.
Keywords: COVID-19; inflation; EU countries; spatial panel data analysis.

ÖZ

Amaç: Küresel ekonomide son dönemde yaşanmakta olan makroekonomik sorunlar, koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) pandemisi ile yakından ilgilidir. Hastalığın en yüksek yayılımı ağırlıklı olarak Avrupa ülkelerinde görüldüğünden, Avrupa Birliği (AB) üyesi ve birliğe aday ülkelerdeki makroekonomik göstergeleri araştırmak anlamlı olacaktır. Enflasyon, birçok makroekonomik değişkeni doğrudan etkileyebileceği için incelenmesi gereken en önemli göstergelerden biridir. Bu çalışmada 28 AB üyesi ve birliğe aday ülkede enflasyonun belirleyicileri araştırılmıştır.
Gereç ve Yöntemler: Bu çalışmada, Ocak 2020-Temmuz 2020 dönemi ele alınarak 28 AB üyesi ve birliğe aday ülkede enflasyonun belirleyicileri mekansal panel veri analizi kullanılarak araştırılmıştır.
Bulgular: Ampirik sonuçlar, döviz kuru ve para arzındaki değişimlerin enflasyondaki artışın en belirgin nedenleri olduğunu göstermiştir. Yurt içi para arzı ve döviz kuru değişkenlerinin yanı sıra ülkeler arası komşuluk ilişkileri nedeniyle de enflasyon oranları üzerinde artan bir baskı olduğu gözlenmiştir (pozitif mekansal etkiler).
Sonuç: Her örnek ülkenin yereldeki makroekonomik sorunlarının, iç dinamikler yanında komşu ülkelerdeki gelişmelerden de etkilendiği önemli bir bulgudur. Pandemi sürecinde, bölgesel düzeyde komşu ülkeler arasında ekonomik, sosyal ve politik işbirliğinin geliştirilmesi elzemdir. Pandemi döneminde, her ülkenin tarım, gıda, teknoloji ve ilaç endüstrileri alanlarında kendi kendine yeten stratejiler geliştirmesi akılcı bir strateji olacaktır. Bölgesel işbirliği, pandemi döneminde öne çıkan sektörlerin gelişimi ile sınırlı kalmamalı, geniş katılımlı işbirlikleri her alanda ele alınmalıdır.
Anahtar kelimeler: COVID-19; enflasyon; AB ülkeleri; mekansal panel veri analizi.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused unprecedented shocks in all sectors. Besides, the pandemic caused different and massive uncertainties both in developed and developing countries such as stock market volatility, economic policy uncertainty, uncertainty about employment, and future of GDP growth. The uncertainty became even worse during and after the shutdown (1). In his speech on the great uncertainty about the COVID-19 pandemic, Fed Chairman Jerome Powell (2) expressed that "In the best of times, predicting the path of the economy with any certainty is difficult. We are now experiencing a whole new level of uncertainty, as questions only the virus can answer complicate the outlook".

Related to the uncertainty, the impact of pandemic has not been the same in all sectors. While there is a great collapse in consumption during the lockdown, there are upward pressures on the reduction of real output (3). What is more, while contraction trends are emerging in sectors such as transportation and tourism, significant positive improvements are observed in the sectors that make a positive contribution to the process of combating the pandemic. For policymakers, not only the sectoral developments but also the improvements in the whole economy are important. When the positive and negative developments on the sectoral basis are evaluated collectively, it is possible to conclude that a recession has occurred in all economies during the pandemic process. Exacerbating recession and decreasing growth rates cause economic problems such as increases in unemployment and decreases in public income.

The contraction of total demand during the pandemic period and the sharp falls in prices of inputs used in production are positive factors to control inflation. Nevertheless, it should be emphasized that the supply of intermediate and capital goods has become very difficult. The disruption of the supply chain causes a decline in production. Under normal conditions, the contraction in demand causes the prices to decrease. However, if the supply shrinks as demand shrinks, price increases may occur. In this case, it is difficult to control inflationary trends due to the imbalance between supply and demand.

During the pandemic period, the deterioration of the supply chain, as well as the developments affecting inflation rates, can be discussed under the following headings.

Increase and Uncertainty in Exchange Rates

During the pandemic period, there is an increasing trend in exchange rates, especially in developing countries. Foreign capital outflow is the main reason for the increase in exchange rates. Besides, investors convert their cash in national currency into more reliable foreign currencies. The increase in foreign currency demand causes the national currency to depreciate. The unpredictability of when the pandemic will end increases the uncertainty in the exchange rate increase. The increase and uncertainty in exchange rates trigger production cost increases and ultimately price increases.

Monetary Expansion

During the pandemic period, one of the strategies for demand increase is monetary expansion. Most developed and developing economies resorted to monetary expansion in order to alleviate the contraction tendencies in their economies. Monetary expansion, which is not consistent with the increase in production, will increase inflationary pressure.

Massive shocks such as the pandemic to the global economy will probably bring turning points. Nowadays, it is a fact that the risks are difficult to assess and the stability of the global exchange rate system is getting more problematic. Ilzetzki et al. (4) expressed that systemic economic crises generally produce major turning points. The authors pointed out that the global exchange rate system has increasing stability at its core. However, due to the pandemic, the risks are hard to evaluate. The authors also indicated that the recent trend reflects the paralysis of monetary policy at the zero bound and today's stability might mask fragilities, but not strengths.

Actually, IMF (5) expressed that COVID-19 pandemic is the worst economic downturn since the Great Depression. The pandemic negatively impacted the local economies and the risk is rising in the countries more affected by the pandemic such as the EU countries. Inflation is one of the most important indicators that worths examining since it may directly affect many macroeconomic variables such as consumer expenditures, exchange rates, cost of production, and interest rates.

Inflation is not the only variable that needs to be carefully monitored during the pandemic period. Aside from inflation, the data obtained by investigating the impacts of the pandemic on economic growth, foreign trade, borrowing, and financial markets should be used in policy-making processes.

In most of the studies on the pandemic period, the effects of the policy implementations applied to reduce the negative effects of the Pandemic on the economy as well as the direct effect of the Pandemic on the economic indicators are discussed. Besides, all macroeconomic variables can be included in the analyzes of the studies on the pandemic period together. However, making each macroeconomic variable a subject of research separately will contribute to obtaining more specific results. During the pandemic period, it was observed that economic growth rates declined due to the recession. This process conveyed increasing unemployment rates. Many countries initiated expansionary monetary policies to alleviate the negative effects of recession. Therefore, it is important to predict the tendency of the inflation rate in the period of increasing unemployment for determining the policies to combat the recession.

At this point, two important questions arise: Does inflation increase while expansionary policies are implemented? Which variables affect the inflation rate in this period?

The aim of this study is to investigate the main determinants of inflation in the first 7 months of 2020 when the COVID-19 crisis was intense for 28 European Union (EU) members and candidate EU members. Spatial Panel Data Analysis was preferred in the study. There are two main reasons for including the European countries in the scope of the research. The first reason is that European countries take the first place regarding the number of cases and deaths due to the COVID-19 pandemic. The second reason is that we have a theoretical expectation that the spatial impact is high among the EU countries. Changes in

macroeconomic indicators are affected both by neighboring countries and local improvements. Also, the real-time effects of the pandemic on employment and spending are well documented, much less is known about how the pandemic is impacting inflation. As far as we know, there is no other study investigating the determinants of inflation during the COVID-19 pandemic period using the spatial data analysis method. This study will contribute to the literature by exploring the determinants of inflation during the Pandemic period using the spatial data analysis method.

The rest of the work consists of three parts. The first part includes the literature review, in the next part we explained the data set and methodology, and in the third part, we provided the empirical analysis and findings.

Literature Review

It is a fact that there is a change in consumption trends as well as increasing uncertainties due to COVID-19 pandemic and great lockdown. The continuing "low-touch" production and consumption can further lead to inflation. Some papers focused on uncertainty and spending, and some others on the most affected sectors. Nevertheless, there are few papers in the literature addressing the connectedness between the COVID-19 pandemic and inflation rates.

Eichenbaum et al. (6) applied the canonical epidemiology model to analyze the effects of the pandemic on economic decisions in the US. The researchers found that the pandemic cut back the consumption which exacerbated the severity of the recession due to the COVID-19.

Altig et al. (1) compared the economic uncertainty indicators such as stock market volatility, business growth uncertainty, and uncertainties on the GDP growth for the US and UK, before and after the COVID-19 pandemic period. The researchers found that great uncertainty jumps in reaction to the pandemic and its economic outcomes. They calculated a 35% increase in the US economic uncertainty to a 20-fold rise in forecasting disagreement about UK economic growth. They also concluded that volatility started to increase towards the end of February and reached to peak in mid-March. It fell down towards the end of March since stock price started to recover. The authors also indicated that there was a sharp decline in industrial production of 12-19%.

Andersen et al. (7) estimated the change in consumer spending during the COVID-19 pandemic in the Danish economy. The researchers calculated that aggregate spending was 27% below the counterfactual level without the pandemic. The spending fall was on the goods and services which are directly restricted during the lockdown. The spending drop was the highest among the people who lost their jobs, and the ones who lost their wealth during the pandemic.

Baker et al. (8) estimated the consumption response to the pandemic. They concluded that while household spending increased sharply in retail, credit card spending, and food in the early days of the pandemic, the spending showed sharp declines in restaurant and retail in the preceding months.

Dunn et al. (9) analyzed the effects of the COVID-19 pandemic on consumer spending. The researchers concluded that the greatest impact was on accommodation and restaurants with 80% and 70% respectively by the second week of March. On the contrary, there was a 100% increase in food and beverage sales. They concluded that there was an aggregate decline in spending of 13.7%. They estimated the pandemic effect as 27.8% due to the measures.

Coibion et al. (10) explored the spending patterns of households as well as their spending and macroeconomic expectations using the survey with more than 10.000 respondents. Half of the respondents reported income and wealth losses due to the pandemic. The respondent also expressed that they expected lower future inflation, higher uncertainty, and foreign stocks into liquid forms of savings.

Sharif et al. (11) examined the relationship between the COVID-19 pandemic, oil price volatility shock, the stock market, geopolitical risk, and economic uncertainty in the US using Granger causality tests. They found that the effects of the COVID-19 on the geopolitical risk are much higher than on the US economic uncertainty. The pandemic risk was perceived differently for the short and long run.

In a similar study, Pellegrino et al. (12) investigated the benefit of reducing policy uncertainty on GDP using a nonlinear VAR estimation for the Euro Area. The authors showed that the impact of the pandemic on the economy of uncertainty shocks is much higher during periods of a negative outlook for the future. They estimated the impact of COVID-19 induced uncertainty on industrial production as a peak value at a year-over-year growth loss of -15.4% in September 2020, and a fall in CPI inflation between 1%-1.5%.

Cavallo A. (13) investigated the changes in consumer expenditure patterns that caused the impact on the CPI. The author found that the inflation caused by the COVID-19 was higher than the official CPI in the US for both headlines and core indices. There were similar findings with COVID-19 baskets for 10 out of 16 countries. The author also concluded that while social distancing precautions and behaviors cause more spending on food and other categories with rising inflation, they cause losses on transportation and related categories which experience significant deflation.

In her speech, Tenreyro S. (14) expressed that during the COVID-19 period in the UK, there were large, temporary changes in relative prices and consumption expenditures which caused inflation data difficult to interpret. She explained that although price inflation was under control, there was labor cost growth during the pandemic which is related to structural changes in the economy.

Apergis et al. (3) investigated the role of COVID-19 on inflation expectations and their volatility on the US economy. By using swap rates, the authors concluded that inflation expectations and their volatility are increased by the COVID-19 pandemic.

Jaravel et al. (15) analyzed the inflation dynamics during the pandemic period in the UK. The researchers calculated the inflation rate as 2.4% in the first month of the lockdown which is 10 times more than the previous months. They explained this loss with fewer promotions and decreasing the purchasing power of consumers. They also concluded that while 96% of households experienced inflation, half of the households experienced deflation in the preceding years. They also indicated that there may be a risk of stagflation in the UK economy.

Seiler P. (16) investigated the connectedness between the COVID-19 and inflation for Switzerland. By using debit card transactions, the author tried to analyze the changes

in consumer spending and the Swiss consumer price index. He found that inflation was higher during the lockdown than suggested by CPI inflation.

Similarly, Lane T. (17) explained that during the quarantine process, inflation rates declined sharply particularly because of declines in prices of gasoline, travel services, and changes in spending in Canada. CPI-based on the cost of a fixed basket of goods has changed during the shutdown period. The fall in inflation experienced by consumers may be less than indicated by the official CPI measure. The author expressed the importance of the monetary policy to be forward-looking than usual.

Blundell et al. (18) examined the reflections of COVID-19 on the CPI. The spread of COVID-19 affected high-demand products such as medicine, nappies, rice, and pet food by a 1.1% rise. The findings indicated the increase in not only profit margin but also the cost of production due to the disruption of supply chains and production during the pandemic.

Bresser-Pereira L. (19) explained the government protections during the COVID-19 pandemic. Governments limited the expenditures not to increase public debt. The author also pointed out the contribution of central banks by buying securities from the Treasury to finance exceptional spending. The author also explained that while this policy does not contradict the inflation constraints, it may have conflicts with the fiscal constraints. However, it does not increase public debt. The researcher also explained that monetary financing of COVID-19 will not lead to excess demand that may increase imports, and current account deficit that may appreciate the national currency, accelerate inflation and lead to the currency crisis.

Ebrahimy et al. (20) examined the potential drivers and dynamics of inflation during the COVID-19 pandemic. For the early period of the pandemic, the researchers found evidence of inflation in food prices. However, there was no evidence of inflation in broader indexes.

Armantier et al. (21) explored consumer inflation expectation during the COVID-19 pandemic in the US. The researchers could not find a consistent upward or downward trend at the time they finalized the research. However, they pointed out that the data indicated unprecedented increases in individual inflation uncertainty.

MATERIAL AND METHODS

The present study deals with the main determinants of inflation during the first 7 months of 2020, when the COVID-19 crisis was in full swing, in the 28 European Union member and candidate states. In this way, the movement of inflation rates will be analyzed during the pandemic period. In the study, data on the European countries (Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Netherlands, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and Turkey) are discussed for the period between January 2020 and July 2020. The estimation model is shown in Equation [1].

$$inf = \beta_0 + \beta_1 money + \beta_2 pricre + \beta_3 exc + \beta_4 indust + \varepsilon_{it} \quad [1]$$

where *inf* is the domestic inflation rates of the countries, *money* is the amount of domestic money supply of the countries, *price* is domestic credit volume for the private sector, *exc* is the dollar-denominated exchange rate, *indust* is industrial production index and ε_{it} is error terms. Inflation rates represent the exchange rate of a basket related to the consumer price index of countries. The money supply shows the sum of cash and other liquid assets in circulation in the economy. Loans to the private sector show the volume of loans to non-financial private companies by commercial banks and other financial institutions that collect deposits. In the equation, i denotes units (1,….,N) and t denotes time (1,...,T). Data were collected from the statistical institutions and central banks of the respective countries.

The first reason for the selection of European countries in the study is that the spread of the pandemic to Europe following China, and the high number of cases in Europe. Considering the course of the pandemic, it is seen that European countries take the first place regarding the number of cases and deaths. Another important point is that we have a theoretical expectation that the spatial impact is high in the European Union countries.

Spatial econometrics is preferred when the effect is not only caused by the characteristics of the spatial unit itself but also by its neighbors. This method can be used in many areas. The important point here is how spatial relationships are incorporated into the model. Spatial relationships can be modeled over contiguity relations or distance if geographic data are available. In our study, the distance relationships for European countries are preferred for the creation of the weight matrix to measure spatial effects.

For the modeling of spatial relationships, the Spatial Autoregressive Model (SAR), Spatial Error Model (SEM), Spatial Durbin Model (SDM) and General Spatial Model (SAC) models are commonly preferred. There is dependence in the SAR model resulting from spatial interaction. The SAR model can be indicated as follows:

$$inf = \alpha_0 + \rho W inf + \alpha_1 X + \varepsilon_{it} \quad [2]$$

In Equation [2], *inf* is the dependent variable, *X* is nxk-size independent variables matrix, *W* is nxn size weight matrix. The matrix *W* represents the distance function. ε_{it} denotes error terms, i denotes units 1,…,N and t denotes time 1,…,T. The contiguity structure can be fully represented by a spatial weight matrix (W). Here W is a measure of the links between the positions of the spatial units i and j. Thus, the magnitude of interaction (direct effects) or spreading effects (indirect effects) between the neighbors can also be measured with the spatial dependence parameter.

Spatial effects in the SEM model arise from error terms. The spatial effects here are seen in the error term. The SEM model is included in Equation [3].

$$inf = \alpha_0 + \rho W inf + \alpha_1 X + \varepsilon_{it} \quad [3]$$

In Equation [3], $\rho = 0$. Since the spatial effects here are included in the error term, $\varepsilon_{it} = \lambda W \varepsilon + u, \quad u\, N(0, \sigma^2 I_n)$, where $\lambda \neq 0$. The SAC model is made up of the combination of SAR and SEM models.

$$inf = \alpha_0 + \rho W_1 inf + \alpha_1 X + \varepsilon_{it} \quad [4]$$

$$\varepsilon_{it} = \lambda W_2 \varepsilon + u \quad [5]$$

Spatial Weight Matrix

In our study, a weight matrix created with the inverse distance relationship is used to model spatial relationships.

The inverse distance spatial weight matrix was created using the latitude and longitude of different spatial units (positions). The inverse distance weight matrix is calculated as follows:

$$W_{ij} = \begin{cases} \frac{1}{d_{ij}^{\propto}} & if\ i \neq j \\ 0 & if\ i = j \end{cases}$$

RESULTS

In our study, firstly cross-section dependencies and stationarities of the series are investigated. It is observed that all the series have cross-section dependencies. The cross-sectionally IPS (CIPS) test, one of the second-generation panel unit root tests, is preferred to investigate the stationarity status of the series. The results of unit root test indicate that all series are stationary at level. Considering the country group in our study, particularly the spreading effect of the pandemic, we have a pre-expectation that there are strong spatial relations due to the close distance. Therefore, we use the Moran's I and Geary' C tests to investigate a priori the spatial effects for the inflation rates. According to the test results there is an effect in the context of the cross-section for the months included in the study. The results are shown in Table 1.

The results in Table 1 illustrates that there is a spatial effect for January, July, and June periods according to Moran's I test results, while there is a spatial effect for January, March, June, and July according to Geary 'C test results.

Considering the existence of spatial effects, we use spatial OLS methods in the study. Spatial OLS test results are shown in Table 2.

Table 1. Moran's I and Geary's C test results

Moran's I					
Months	**I**	**E(I)**	**sd(I)**	**z**	**p-value***
January	0.047	-0.037	0.031	2.686	0.004
February	-0.041	-0.037	0.030	-0.138	0.445
March	-0.011	-0.037	0.030	0.854	0.197
April	-0.039	-0.037	0.024	-0.064	0.474
May	-0.044	-0.037	0.030	-0.219	0.413
June	-0.092	-0.037	0.031	-1.786	0.037
July	0.010	-0.037	0.030	1.569	0.058
Geary's C					
Months	**C**	**E(c)**	**sd(c)**	**z**	**p-value***
January	0.912	1.000	0.035	-2.509	0.006
February	1.004	1.000	0.039	0.103	0.459
March	0.934	1.000	0.042	-1.580	0.057
April	0.967	1.000	0.064	-0.511	0.305
May	0.960	1.000	0.041	-0.991	0.161
June	1.050	1.000	0.038	1.342	0.090
July	0.928	1.000	0.041	-1.751	0.040

Table 2. Spatial OLS test results

SAR							
	Coef.	**Std. Err.**	**z**	**Prob.**	**Tests**	**Stat.**	**Prob.**
lnmoney	0.107	0.061	1.770	0.076	GLOBAL Moran MI	0.0529	0.0067
lnpricre	-0.100	0.070	-1.410	0.157	GLOBAL Geary GC	0.9137	0.0006
lnexc	0.068	0.021	3.240	0.001	GLOBAL Getis-Ords GO	-0.053	0.0067
indust	0.003	0.003	0.780	0.433	Moran MI Error Test	2.3251	0.0201
Cons	-0.049	0.187	-0.260	0.793			
rho	***0.392***	***0.121***	***3.240***	***0.001***			
Hausman Test	***chi2***	***10.830***	***Probability***	***0.055***			
SEM							
	Coef.	**Std. Err.**	**z**	**Prob.**	**Tests**	**Stat.**	**Prob.**
lnmoney	2.369	2.319	1.020	0.307	GLOBAL Moran MI	0.0529	0.0067
lnpricre	-0.229	3.167	-0.070	0.942	GLOBAL Geary GC	0.9137	0.0006
lnexc	-5.102	4.132	-1.230	0.217	GLOBAL Getis-Ords GO	-0.0529	0.0067
indust	-0.003	0.005	-0.480	0.633	Moran MI Error Test	2.3251	0.0201
Cons	0.531	0.1528	3.47	0.001			
lambda	***0.452***	***0.111***	***4.080***	***0.000***			
Hausman Test	***chi2***	***7.390***	***Probability***	***0.193***			
SDM							
	Coef.	**Std. Err.**	**z**	**Prob.**	**Tests**	**Stat.**	**Prob.**
lnmoney	0.093	0.059	1.580	0.114	GLOBAL Moran MI	0.0477	0.0137
lnpricre	-0.072	0.056	-1.280	0.200	GLOBAL Geary GC	0.9188	0.0012
lnexc	0.058	0.035	1.640	0.102	GLOBAL Getis-Ords GO	-0.0477	0.0137
indust	0.004	0.005	0.760	0.450	Moran MI Error Test	2.053	0.0401
Cons	-0.673	2.114	-0.320	0.750			
rho	***0.392***	***0.130***	***3.020***	***0.003***			
Hausman Test	***chi2***	***45.830***	***Probability***	***0.000***			

Based on the data in Table 2, it is decided that the spatial effect exists according to the rho test results estimated for the SAR and SDM models for the random-effects model and according to the lambda test result for the SEM model. For these models, when the results of Global Moran MI, Global Geary GC, Global Getis-Ords GO, Moran MI Error Test are examined, the null hypothesis claiming that there is no spatial effect is rejected and it is decided that there is a spatial effect. An important point here is the efficiency of the estimator of the random-effects model. The Hausman test results indicated that the random effects estimator is effective for the SAR and SDM models, and the fixed effects estimator is effective for the SEM model. The results obtained with the fixed effects estimator for the SEM model showed that there is no spatial effect. On the other hand, the results of the SDM model showed that the coefficients of the variables are not statistically significant. Finally, it was decided that the random effects estimator for the SAR model was effective and spatial effects exist. Spatial impacts can be either direct or indirect. Therefore, it is important to separate the effects. Spatial effects related to the SAR model are included in Table 3 as indirect and direct effects.

Table 3. Total, direct and indirect effects for the SAR model

Total Effects				
lnmoney	***0.107***	***0.061***	***1.770***	***0.076***
lnpricre	-0.100	0.070	-1.410	0.157
lnexc	***0.068***	***0.021***	***3.240***	***0.001***
indust	0.003	0.003	0.780	0.433
Cons	-0.049	0.187	-0.260	0.793
Direct Effects				
lnmoney	***0.111***	***0.063***	***1.770***	***0.077***
lnpricre	-0.104	0.073	-1.430	0.151
lnexc	***0.072***	***0.021***	***3.460***	***0.001***
indust	0.002	0.003	0.750	0.454
Indirect Effects				
lnmoney	0.073	0.059	1.240	0.214
lnpricre	-0.065	0.059	-1.100	0.271
lnexc	0.050	0.033	1.510	0.130
indust	0.002	0.003	0.550	0.582

Table 3 illustrates that the coefficients related to indirect effects are not statistically significant and there are direct effects for our estimated model. In this context, it is observed that the increases in money supply and exchange rate for the period considered stir up the increase in inflation. However, it has been observed that the credit increase for the private sector did not increase inflation. As a possible reason for this, it is thought that the loans extended to the private sector are used to get out of the difficult situation of the sector such as debt payment. Thus, the increase in credit supply does not have a positive effect on prices. On the other hand, the slowdown in industrial production caused the production-inflation relationship to break. Therefore, the effects of industrial production on inflation disappear during the pandemic period.

DISCUSSION and CONCLUSION

In our study, the determinants of inflation for European countries (Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Netherlands, Poland, Portugal, Romania, Serbia, Slovakia, Slovenia, Spain, Sweden, and Turkey) were investigated with spatial panel data methods taking into consideration the proximity of the countries for the period between January 2020 - July 2020. According to the empirical results, it was found that the exchange rate and money supply ratios were reasons of the increase in inflation. Behind the increase in inflation, there is increasing pressure on the inflation rates due to the domestic money supply and exchange rate variables as well as the neighborhood relations (positive spatial effects).

It is an important finding for the policy-making processes that macroeconomic problems in each sample country are also affected by developments in neighboring countries as well as internal dynamics. Continuous development of economic, social, and political cooperation between neighboring countries at the regional and global levels is essential. It is reasonable for every country to develop self-sufficient strategies in the fields of agriculture, food, technology, and pharmaceutical industries in case of global disasters. However, it is not possible to eliminate the effects of external shocks. While critical sectors that are vital in times of disaster are supported at the national level, initiatives at regional and global levels should not be ignored. Regional cooperation should not be limited to the development of sectors that stand out during the pandemic period. The framework of economic cooperation initiatives should be kept as broad as possible. It should not be forgotten that it is not possible for any country to solve its problems by completely isolating itself from the rest of the world.

Ethics Committee Approval: Since our study was not an experimental study including human or animal subject, Ethics Committee approval was not required.

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A Case Report about Diabetes Mellitus and COVID-19 Outbreak

Diabetes Mellitus ve COVID-19 Salgını Hakkında Bir Olgu Sunumu

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has almost collapsed most of the health systems of communities around the world. The rapid increase in the number of cases has brought this virus to the top of the agenda, and many issues such as the mode of transmission of the virus, how long it remains alive, how it should be protected have been the most researched topics in the last year. It is observed that mortality is high especially in patients with chronic diseases and elderly patients. In also diabetes mellitus, one of the chronic diseases, the risk of morbidity and mortality is high due to COVID-19. Our case report states that there are impairments in blood glucose regulation in the follow-up of patients with diabetes mellitus hospitalized due to COVID-19 infection and that they should be dealt with, and the course of COVID-19 infection with poor prognosis.
Keywords: Diabetes mellitus; coronavirus; pathogenesis; SARS-CoV-2.

ÖZ

Koronavirüs hastalığı 2019 (coronavirüs disease 2019, COVID-19) salgını, dünyanın dört bir yanında, toplumlarda sağlık sistemini nerdeyse çökertmiştir. Vaka sayısının çok hızlı bir şekilde artışı bu virüsü gündemin en üstüne taşımış ve virüsün bulaş şekli, ne kadar süre canlı kaldığı, nasıl korunulması gerektiği gibi birçok konu son bir yılın en çok araştırılan konuları olmuştur. Özellikle kronik hastalıkları olan ve ileri yaştaki hastalarda mortalitenin yüksek olduğu gözlenmektedir. Kronik hastalıklardan biri olan diyabetes mellitusta da COVID-19 nedeni ile morbidite ve mortalite riski yüksektir. Olgu sunumumuz, COVID-19 enfeksiyonu nedeni ile hastaneye yatırılan diyabetes mellitus tanılı hastaların takiplerinde kan şekeri regülasyonunda bozulmalar olduğunu ve bunlarla baş edilmesi gerektiğini ve COVID-19 enfeksiyonunun kötü prognozla gidişatını göstermektedir.
Anahtar kelimeler: Diabetes mellitus; koronavirüs; patogenez; SARS-CoV-2.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) case first appeared in Wuhan, China at the end of 2019 and was declared as a global pandemic in March 2020 after a very short time (1). Being an enveloped RNA virus, coronavirus gets its name from using the surface protein in the form of a crown (corona) when attaching to the host cell. Coronaviruses can infect animals and humans, causing respiratory, gastrointestinal, hepatic and neurological diseases.

Dry cough, high fever, and respiratory distress are among the most common symptoms of COVID-19 infection. These findings are generally mild. However, sometimes the disease can lead to multiple organ failure and severe pneumonia. The data show that the mortality rate is 1-2% (2). Although most patients progress asymptomatically, the condition may be more severe in the elderly and those with comorbid diseases. Hospitalization rates and the need for intensive care are also high in these people.

It is stated that people with diabetes are more likely to get COVID-19 than the general population, but we do not have enough data yet. The problem faced by people with diabetes is primarily a problem of worse outcomes, not chances of getting the virus. People with diabetes have much higher rates of serious complications and deaths than those without diabetes, and in general, the more health conditions (e.g. diabetes and heart disease) a person has, the more likely they are to suffer serious complications from COVID-19. Advanced age, obesity, and smoking are among the factors that increase the risk of complications (3).

In this case report, we aimed to discuss the problems experienced by a diabetic patient with COVID-19 infection during treatment and the factors that negatively affect her treatment.

CASE REPORT

A 76-year-old female patient with a previously known diagnosis of diabetes mellitus, hypertension and coronary artery disease visited our hospital. Her medications were as follows: gliclazide 30 mg, two tablets daily, losartan potassium/hydrochlorothiazide 50/12.5 mg, one tablet daily, metoprolol 50 mg, one tablet daily. She was using an oral antidiabetic for diabetes treatment. The patient presented with complaints of fever, back pain, and shortness of breath that started 1 day before admission. On her physical examination upon arrival, her general condition was moderate. She had mild tachypnea, a respiratory rate of 24, a temperature of 37.9 °C, blood pressure of 155/95 mmHg, and oxygen saturation (at room air) of 95%. On examination, her liver function tests and kidney function tests were normal. Her C-reactive protein (CRP) level was 11 mg/L, and her white blood cell count was 8600 mm^3 (neutrophil 95%, lymphocyte 2%). Her hemoglobin, ferritin and procalcitonin levels were 12.3 g/dL, 348 ng/mL and 0.29 ng/mL, respectively. Her platelet count was 156000 U/L. Her lactate dehydrogenase and D-dimer levels were 616 U/L and 670 µg/mL, respectively. Computed tomography (CT) was requested because of the complaints of fever, shortness of breath and comorbid disease. Peripheral multiple infiltration areas extending from apex to basal in a patchy pattern in bilateral lung parenchyma seen on thoracic CT (Figures 1 and 2) were found to be compatible with COVID-19 infection, and when the patient's history was deepened, there was a history of contact with another patient diagnosed with COVID-19. For this reason, the COVID-19 polymerase chain reaction (PCR) test was taken after being hospitalized and the test result was positive. In addition to her drugs, favipiravir 200 mg one tablet twice a day, heparin 0.6 mg, once a day SC, hydroxychloroquine 200 mg, one tablet twice a day, methylprednisolone 40 mg ampoule once daily, bronchodilator and symptomatic treatment were started. In the blood glucose monitoring, the regulated blood glucose values increased to 200-300 on the 3rd day of her hospitalization. For the treatment of the patient, it was planned to keep blood glucose in the range of 120-200 by adding crystallized insulin according to the blood glucose before meals. On the 5th day of her admission, the patient's respiratory distress increased and his oxygen saturation regressed to 90. She was followed up in the intensive care unit. During the follow-up in the intensive care unit, the insulin doses were continuously increased as the blood glucose levels remained at 300. The patient was not intubated. She was treated in intensive care for 3 days, and when vital signs stabilized she was followed up in the service again. The patient's treatment continued in the service for 7 days and was discharged with basal-bolus insulin therapy with recommendations.

DISCUSSION

The frequency of COVID-19 in individuals with comorbid disease also varies in different studies and country-based data. It has been reported that the diabetes prevalence in COVID-19 patients in different regions of China is at high values ranging from 7.4-20% (4). The prevalence of diabetes in COVID-19 patients hospitalized in Italy was found to be 8.9%, and this rate is above the prevalence of advanced age diabetes (5).

In different studies, COVID-19 patients with diabetes were found to be more frequently associated with serious or critical illness, ranging from 14% to 32% (6). Initial data reported that infection with COVID-19 and the development of severe pneumonia were higher in diabetics compared to those without diabetes, thus mortality rates

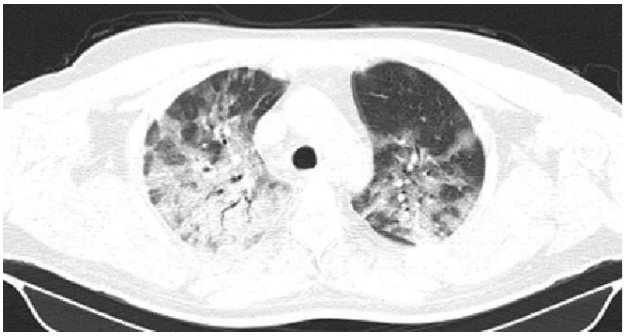

Figure 1. Peripheral multiple infiltration areas extending from apex to basal patchy in bilateral lung parenchyma seen on thorax computed tomography

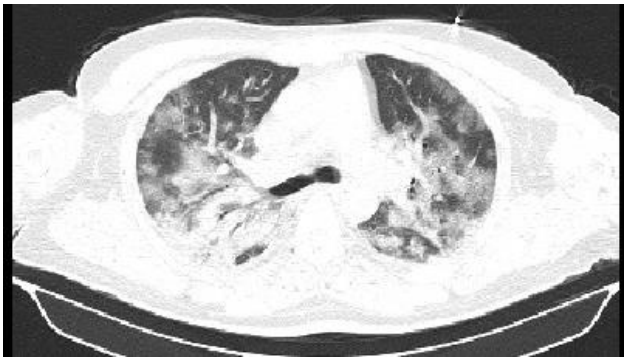

Figure 2. Peripheral multiple infiltration areas extending from the apex to basal in a patchy pattern in the bilateral lung parenchyma on thorax computed tomography

were also higher (7). While the need for intensive care is around 30% for those without chronic diseases, this rate can reach up to 70% for diabetic individuals. There is a significant correlation between COVID-19 severity and diabetes. It is also reported that mortality in diabetic individuals with COVID-19 varies between 22-31% (8). It is said that mortality in people with diabetes is approximately three times higher than in those without diabetes (9).

Glycemic control is important in every patient with COVID-19 because plasma glucose elevation is a risk factor for mortality and morbidity due to organ failure alone. The added effect of COVID-19 further increases the risk for organ damage in people with diabetes. It has been shown in previous studies that patients with poor glycemic control in other viral infections such as severe acute respiratory syndrome (SARS) and influenza H1N1 have an increased risk of complications and death (10,11). Data on COVID-19 is limited.

Although a diabetic individual receives outpatient oral antidiabetic therapy, most of the hospitalized patients due to COVID-19, especially those with respiratory distress, switch to insulin therapy. In addition, frequent monitoring of blood glucose in these patients, especially in diabetic patients hospitalized in the intensive care unit, due to intravenous insulin infusion, and measuring blood glucose every hour or every 2 hours bring additional costs. If each blood glucose care is considered as contact with the patient, this job is also a burden for the healthcare worker. As a matter of fact, our patient, whose blood glucose was regulated at home and who used oral antidiabetic drugs, was started on insulin treatment after her hospitalization and frequent blood glucose measurements were required because her blood glucose levels were high.

Treatment with angiotensin converting enzyme (ACE) inhibitors and ARB has the potential to cause upregulation of ACE-2 (12). Seeing improvement in mice with lung injury treated with losartan (13) and demonstrating reduced mortality and endotracheal intubation rates in patients with viral pneumonia who continue to use ACE inhibitors (14) suggest that the use of these drugs may be beneficial. The current antihypertensive treatment was continued in our patient using ARB.

As a result, COVID-19 proved to be a more serious disease than seasonal flu in a very short time by causing a pandemic including people with diabetes. All the standard precautions taken to avoid the commonly reported infection have become even more important when dealing with this virus. If your diabetes is well managed, your risk of being seriously ill from COVID-19 is likely lower. When people with diabetes don't manage their diabetes well and experience fluctuating blood glucose, they are often at risk for a range of complications related to diabetes. Having a heart disease or other complications in addition to diabetes can worsen the chances of getting seriously ill from COVID-19, like other viral infections, as the ability to fight the infection is compromised. Blood gkucose levels may rise rapidly in patients who are hospitalized and treated, especially as a result of steroid treatments. This can cause extra burden for both the patient and the healthcare worker. It can extend the hospital stay. It is important to determine specific treatment strategies for these patients.

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A Case Report of Delirium and Literature Review of Dementia in COVID-19 Process

COVID-19 Sürecinde Deliryum Olgu Sunumu ve Demansın Literatür Taraması

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ABSTRACT

Coronavirus directly infects the nervous system and may cause the course of the existing neurological disease to get worse in those with a chronic neurological disease. People with dementia, which is the most common chronic neurological disease over 65 years old, have serious difficulties in terms of follow-up and treatment of their diseases in the social isolation process. However, due to the risk factors caused by coronavirus disease 2019 (COVID-19), it has become easier for them to go into delirium. These risk factors can be listed as social isolation, inactivity, intense stress, as well as direct invasion of the virus to the central nervous system, the effect of inflammatory cytokines, the effect of sedative drugs used and the effect that develops secondary to other accompanying diseases. This paper provides an assessment regarding the problems experienced by dementia patients in the pandemic process, and their solutions, accompanied by a case presentation.
Keywords: COVID-19; dementia; delirium.

ÖZ

Koronavirüs doğrudan sinir sistemini enfekte etmesinin yanı sıra kronik nörolojik hastalığı olanlarda mevcut nörolojik hastalığın daha kötü seyretmesine neden olabilmektedir. Altmış beş yaş üstünde en sık görülen kronik nörolojik hastalık olan demans hastaları sosyal izolasyon sürecinde hastalıklarının takip ve tedavisi açısından ciddi zorluklar yaşamaktadır. Bununla birlikte koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19)'un sebep olduğu risk faktörleri nedeniyle deliryuma girmeleri de kolaylaşmıştır. Bu risk faktörleri sosyal izolasyon, hareketsizlik, yoğun stresin yanı sıra virüsün merkezi sinir sistemine direk invazyonu, inflamatuar sitokinlerin etkisi, kullanılan sedatif ilaçların etkisi ve eşlik eden hastalıkların ikincil etkileri olarak sıralanabilir. Bu yazı bir olgu sunumu eşliğinde, demans hastalarının pandemi sürecinde yaşadıkları problemler ve çözümleri üzerine bir değerlendirme sunmaktadır.
Anahtar kelimeler: COVID-19; demans; deliryum.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic overburdens the healthcare systems of the communities around the world, causing serious mortality and morbidity. Accumulated experiences show that the disease is not specific to lung only, and may progress with involvement of many organs and systems. Especially, the symptoms and findings of the central nervous system and the peripheral nervous system show a wide variety (1). Coronavirus directly infects the nervous system and it may cause the course of the existing neurological disease to get worse in those with a chronic neurological disease. Dementia patients are one of the most affected disease groups. It has been reported that the elderly with dementia are the main risk factor for the severity of COVID-19 infection (2).

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The recent papers discussed the possible difficulties to be experienced by dementia patients in the social distancing and home isolation period due to the pandemic (1). Understanding and evaluating difficulties experienced by dementia patients as from early stages cause them to have difficulties in acting and following restrictions as required in the pandemic process, leading to an increased risk of infection transmission. In addition to behavior problems, all patients with a chronic disease are considered to be at increased risk of COVID-19, regardless of age. The immunity system is weakened as the age advances and with the presence of accompanying chronic diseases, contributing to the risk of COVID-19. In the pandemic process, many clinics suspended healthcare services, which led to interruptions in the control and follow-up of dementia patients. Especially, the progression of dementia presentation and the presence of delirium caused serious difficulties for both patient relatives and caregivers.

During the COVID-19 pandemic process, new practices have been implemented, which can be also considered new for many clinics. The technological facilities such as smart phone applications or video conference have been introduced to support patients and their relatives. With the telemedicine method, somatic neurological evaluation is not fully possible, but neuropsychological tests can be applied. It was reported that especially the follow-ups by video conference are at least as effective as clinical follow-ups in evaluating cognitive functions and daily life activities of patients (3).

This paper aimed to review the status of patients with dementia representing a common chronic neurodegenerative disease group in the pandemic process, accompanied by a case presentation.

CASE REPORT

The following case illustrates the difficulty that may be experienced in treating excessive stress-induced delirium in patients with dementia, especially when stressors continue and the clinical support cannot be reached. It also illustrates the need in such cases for prolonged antipsychotic treatment and the ultimate good prognosis. The authors received informed consent to publish his case.

A 86-year-old man with a history of hypertension, atrial fibrillation, and mild Alzheimer dementia was accepted to the neurology outpatient clinic for altered mental status after his family noted a change in the patient's behavior.

His wife told that for about 3 months, in the social distancing and home isolation period due to the pandemic, he was deeply worried. For example, as soon as he woke up early in the morning, he was wearing his mask and was sitting with the mask on his face all day, although there was no one else at home but his wife. When he started acting aggressively and his sleep pattern was disrupted at night, they tried to contact their doctor, but failed because the clinic was closed due to the pandemic. However, they did not want to go to another medical center due to the concern that coronavirus could be transmitted. For the past few days, the patient's appetite waned, and he became progressively more lethargic, not eating for over 30 hours. There were no reported changes to the patient's medications which included donezepil, metoprolol, edoxaban, and hydrochlorothiazide. There was no significant history or complaint associated with the infection.

The patient appeared comfortable in bed. He was sleepy, but easily aroused. Initial vital signs were as follows: heart rate, 115 beats/minute; respiratory rate, 12 breaths/minute; blood pressure, 120/70 mmHg; and oral temperature, 36.3˚C. Oxygen (O_2) saturation was 97% in room air.

His systemic examination was normal. He was oriented to person only and responded appropriately to simple questions, intermittently following one-step commands. His orientation to place and time was impaired. He was unable to attend and required redirection throughout the interview (According to his wife, this behavior was different than his baseline). In his somatic neurological examination there were no focal neurological deficits. His reflexes were normal throughout.

His routine blood and urine tests were normal. Although his lungs were clear during his examination, radiological examinations of the lungs performed due to the pandemic were normal. No abnormality detected on computed tomography. Brain magnetic resonance imaging revealed global atrophy and no acute abnormality that could explain the patient's current condition was found.

Assessment of this patient suggested a diagnosis of delirium due to intense anxiety in the background of Alzheimer dementia.

Oral quetiapine 12.5 mg/day was began and it was gradually increased to 37.5 mg/day. Forty eight hours later his orientation and concentration had completely improved. Escitalopram 5 mg/day was began and planned to increase to 10 mg/day after 10 days. Thus, the patient was discharged, but continued to take quetiapine 25 mg/day in the evenings additionally to escitalopram and donepezil 10 mg/day. Four weeks later upon follow up, he was cheerful and willing to communicate. He was oriented to person, place and time. According to his wife, his behavior was back to his baseline. Mini mental state examination score was 24/30. It was planned to continue taking escitalopram 10 mg/day, donepezil 10 mg/day, and also quetiapine (as it removed night sleep interruptions) 12.5 mg/day in the evenings. Due to the ongoing COVID-19 pandemic and isolation, monthly phone calls and visits and a clinical check-up 6 months later were scheduled.

DISCUSSION

The symptoms and findings of the central nervous system and the peripheral nervous system caused by COVID-19 show a wide variety. A study from Wuhan, where the virus first emerged and spread, reported that 78 of 214 patients had findings suggesting a neurological system involvement, and the neurological system findings of the patients were divided into 3 groups. Accordingly (4);

- Findings suggesting central nervous system involvement (headache, dizziness, acute stroke, loss of consciousness, ataxia, seizure)
- Findings suggesting peripheral nervous system involvement (loss of taste and smell, blurred vision, neuropathic pain)
- Findings suggesting skeletal muscle involvement were found.

Although some of the pathogenetic studies about the diseases caused by the virus in the nervous system are explained, many studies are ongoing. Detection of the genetic material of the virus in CSF examinations as well

as of the coronavirus within the neuron in autopsy examinations is remarkable in terms of neurotropism of the disease (5,6).

It was reported that the virus causes the direct involvement of the nervous system as well as serious immune reactions and creates a cytokine storm, leading to organ or system damage (7).

It has been reported that the elderly with dementia are the main risk factor for the severity of COVID-19 infection (2). Considering several papers reporting that the renin angiotensin system adversely affects neurodegenerative processes, it may be suggested that the virus may also contribute to the neurodegenerative process using ACE2 receptors (8). The recent papers mentioned the contributions of the renin-angiotensin system to the neurodegenerative process in diseases with neurodegeneration such as dementia (9). Thus, the relationship between COVID-19 and the renin-angiotensin system is remarkable.

A study from the UK reported that regardless of pre-existing dementia, patients with ApoE e4e4 allele are at increased risk of COVID-19 infection (10). This is an important finding since it is known that especially those with the ApoE e4e4 (homozygous) genotype are at significantly increased risk of dementia and delirium (11). However, further studies are needed to understand the relationship between the severity of COVID-19 disease and ApoE genotypes.

Dementia often accompanies patients with delirium. However, in patients with COVID-19, the risk of delirium was found to be high due to direct invasion of central nervous system, induction of inflammatory cytokines, the effect of sedative drugs, prolonged mechanical ventilation duration, sedentary life, social isolation and the secondary effects of other accompanying organ failure (12).

In our case report, it is described that a patient diagnosed with Alzheimer's dementia, who was not infected with coronavirus infection, had delirium due to social isolation and intense stress during the pandemic process. Through this case report, we find it useful to review the literature on the problems and solutions experienced by dementia patients during the pandemic process.

Dementia patients have limited access to right sources about the COVID-19 pandemic. They may have difficulties in understanding and implementing the public health measures such as wearing a mask and maintaining the social distance. Ignoring the warnings and failing to comply with quarantine measures may put them at higher risk of infection (1). In many countries, old people tend to live at their homes or residential homes alone or with their partners. Increased social distancing prevents further spread of COVID-19; however, it puts further restrictions on individuals with limited knowledge about telecommunication and those in need of personal assistance. Reduced visits by family members, restriction of social activity programs or group activities as per the health policies to decrease the risk of infection may cause them to feel themselves lonely and abandoned (1).

The individuals with dementia are likely to have accompanying diseases, such as cardiovascular disease, diabetes and pneumonia, which would affect the progress and management of dementia (13). It was reported that pneumonia-related deaths were twice more in individuals with dementia in the non-pandemic period (14). Consequently, individuals with dementia are at increased risk of COVID-19 infection (15). The reported comorbid conditions were associated with bad outcomes, including death, in dementia patients with COVID-19 (16).

The need of follow-up of patients in wards or intensive care units due to COVID-19 may cause stress or behavioral problems in them. Hypoxia, as the typical clinical characteristic of COVID-19, may trigger delirium. All of these may increase the need for support of patients with dementia as well as their care costs (1).

Patients with mild cognitive impairment and mild dementia may fail to comply with the recommendations given by public health officials to prevent infection, such as paying attention to hand hygiene, closing mouth and nose while coughing, keeping social distancing with others or isolation (15,17). Those with more severe dementia will not understand most of these recommendations or not remember things to do when appropriate, due to general cognitive impairment. Behavioral and psychological symptoms of dementia such as motor agitation or wandering may weaken isolation and protection efforts.

With rapid increase in the number of COVID-19 cases, the healthcare systems around the world have been negatively affected with interruptions in the healthcare services. Elective and non-emergency care services have been suspended in many affected areas. Due to the social isolation, individuals with dementia, who rely on their families or healthcare providers to remember to take their medications or to get support, are at risk of abrupt discontinuation of their medications.

The COVID-19 outbreak disrupts the active care of individuals with dementia as well as their basic routines supporting their mental health. Social outcomes of the pandemic may cause fear, anxiety and anger. They will disrupt any social interactions after some time. The lack of physical intimacy may cause an increase in loneliness and sadness. Exercise is recommended for individuals with dementia, and confinement restricts access to exercise. Sleep disorders are common in those with dementia, which may get worse due to anxiety and loss of social zeitgebers. On the other hand, the lack of physical activity and sleep disorders may cause delirium, increasing morbidity and mortality (18).

The use of cholinesterase inhibitors and memantine is common in the treatment of individuals with Alzheimer and a related disease. The commonly used medications in the treatment of psychiatric symptoms associated with dementia include antipsychotic, antidepressant, antiepileptic and other psychotropic medications (19). Haloperidol, risperidone, olanzapine, quetiapine and ziprasidone are the antipsychotic agents used in the treatment of agitated delirium. In addition, it has been reported that the use of melatonin is beneficial in preventing delirium development and in sleep disorder during the COVID-19 process (20).

Starting a new medication during the pandemic may not be suitable due to insufficient clinical evaluations, blood tests or electrocardiographs. Also, an abrupt discontinuation of the medication or a lack of doctor's visits may play a negative role in the clinical course of such patients (17). Therefore, it will be essential not to interrupt and change the medical treatment of patients.

The treatment of dementia and related psychiatric symptoms generally involves social and physical interaction such as non-pharmacological interventions, involvement in social groups or exercise groups, and pet therapy. However, reduced social participation due to physical distancing, and patients' inability to use electronic tools and software may prevent these therapies. Therefore, it will be inevitable to encounter with individuals and their relatives with increased medical treatment at the end of the pandemic process (17). The infection symptoms, such as fever, cough, diarrhea, etc. in patients with dementia confirmed the expected worsening of neuropsychiatric symptoms during the COVID-19 outbreak. However, considering such causes and the complex nature of the interaction between COVID-19 and dementia, as per the international recommendations, the supportive care-based approach is recommended for dementia patients all around the world. In particular, the international guidelines include "telemedicine approaches", namely digital revolution recommendations based on multidisciplinary-approach (21).

As recommended by the International Alzheimer's Disease specialists, support is needed for dementia patients and their care givers all around the world. In addition to physical protection from virus infection, mental health and psychosocial support should be provided. For example, mental health care should be provided for psychiatrist-psychologists, social care specialists, residential home managers and volunteers, and people living with dementia. Some stress-relief activities such as relaxing or meditation exercises may be provided electronically (1). Dementia support teams may support behavior management via hot lines. Psychological counselors may provide online counseling to care givers at homes and nursing homes (22). Furthermore, patients with dementia should be encouraged to be in more frequent contact with their first-degree relatives or to spend more time with them and to take care of them (1). Especially, video conferences and video playing programs have been shown to be as effective as face-to-face visits in evaluating daily life activities and cognition (23). They are also guiding for the necessity of cerebrospinal fluid evaluation or PET scanning (24). Mobile dementia patients should be encouraged to walk at appropriate spaces such as corridors, while severe dementia patients should be encouraged to do passive exercise movements at their beds to prevent the formation of contracture or bedsores. With the support of their relatives, patients should continue exercises such as remembering loved ones, place-time-person orientation as well as bearing in mind (25). In this regard, patients are recommended to spend more time and share more things with their relatives (26). After the onset of the outbreak in France, a part of hospitalization units was dedicated to COVID-19 positive patients, as acute Alzheimer unit and behavior unit. The staff was provided training on safe management of such patients. They were informed about the fact that the patients may have specific behavior disorders due to quarantine, depending on cognitive impairment. It was planned to support caregivers who cannot visit their loved ones (27). The number of active working staff was reduced for the safety of patients. Thus, it was envisaged to support patients and their families against global disasters with fluent cooperation between risk reduction strategies and Alzheimer research institution -participants, caregivers, research personnel, regulatory agencies, sponsors and funders (28).

For hospitalized and treated dementia patients, one of the important points that should be considered by physicians is the probability of drug interaction. Since antivirals and quinine and azithromycin (less frequently) are metabolized in liver via cytochrome p-450 enzyme system, cholinesterase inhibitors may cause side effects on many systems, especially cardiac side effects, in patients receiving rivastigmine, donepezil and galantamine treatment. Memantine undergoes partial hepatic metabolism and has a low risk for pharmacokinetic/pharmacodynamic drug interaction, which is a more reliable alternative treatment for COVID-19 patients with dementia (29). Non-family personnel should completely use a mask and protective equipment when dealing with hospitalized dementia patients, regardless of their stages, and transfer them to intensive care unit rapidly. It should be also noted that agitation may develop in such patients, which may require sedation. It should be noted that the risk of mortality as well as the likelihood of stress disorders will increase in the patients after anesthesia. Since the number of patients who can understand the interventions is limited (except for mild cognitive impairment), time should not be wasted by serious discussions to obtain consent in order to protect the patient from being in hypoxic and stressful condition (30).

CONCLUSION

Dementia is the most common neurodegenerative disease in elder population. Increased inflammatory process and cytokine storm due to COVID-19 may adversely affect the course of the disease. Delirium can easily develop in patients with dementia with the addition of secondary diseases or the sociopsychological disadvantages of the pandemic. During the outbreak, the clinical follow-ups should be made via teleconferencing with such patients and their caregivers, and in-house nurse-assisted controls should be performed to continue the existing treatment of patients. It would also be appropriate to provide psychological counseling service to patients and their relatives.

Informed Consent: Written informed consent was obtained from the patient for publication.

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- Compliance with The Principles of Helsinki Declaration (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) is required in all studies including "human" factor. In this kind of studies, authors must state that they perform the study in compliance with these principles, they have taken the approval from ethics committee of their institution and the "informed consent" from people participating the study, in the MATERIAL AND METHODS section.
- If "animal" factor was used in the study, authors must state that they have protected the animal rights in line with the principles of Guide for the Care and Use of Laboratory Animals (https://grants.nih.gov/grants/olaw/guide-for-the-care-and-use-of-laboratory-animals.pdf) and they have taken the approval from ethics committee of their institution, in the MATERIAL AND METHODS section.
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- The information of the ethics committee approval should be indicated together with the name of the committee, approval date and number, in the MATERIAL AND METHODS section.
- If there is a direct-indirect commercial relation or an institution giving financial support in the study, authors must state that they have no commercial relationship with the commercial product, medicine, company etc. used, or if any, what kind of a relationship they have (consultant, other agreements), in the cover letter to the editor.
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SECTIONS THAT SHOULD BE USED ACCORDING TO THE TYPE OF ARTICLE

Research Article

TITLE (English and Turkish), SHORT TITLE, ABSTRACT (English and Turkish), Keywords (English and Turkish), INTRODUCTION, MATERIAL AND METHODS, RESULTS, DISCUSSION, CONCLUSION, REFERENCES
ABSTRACT and ÖZ should be compatible in terms of translation and each should be between 200-250 words.
ABSTRACT should be structured as "Aim, Material and Methods, Results, Conclusion".
ÖZ, should be structured as "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç".

Review (Invited Only)

TITLE (English and Turkish), SHORT TITLE, ABSTRACT (English and Turkish), Keywords (English and Turkish), INTRODUCTION, Subtitles Related to the Subject, CONCLUSION, REFERENCES
ABSTRACT and ÖZ should be compatible in terms of translation and each should be between 150-200 words.

Case Report

TITLE (English and Turkish), SHORT TITLE, ABSTRACT (English and Turkish), Keywords (English and Turkish), INTRODUCTION, CASE REPORT, DISCUSSION, REFERENCES
ABSTRACT and ÖZ should be compatible in terms of translation and each should be between 100-150 words.

Other

The general writing rules are applied for the preparation of the writings (letter to the editor, editorial comment/discussion, etc.) except these three basic types of article. There is no title and abstract sections in these writings. The number of references is limited to 5. The dedicated article should be specified by giving the number and date. The name, institution and address of the author should be included at the end of writing. Answer to the letter is given by the editor, or authors of the dedicated article, by publishing again in the journal.

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WRITING RULES

- Articles should be prepared as Microsoft Word® document.
- The required margins are 2.5 cm on all sides.
- Page numbers should be placed to bottom right corner of pages.
- All texts must be typed with double-space as left-aligned using 12 point Times New Roman font.

KEYWORDS

- Number of the keywords must be at least 2, words should be separated from each other by a semicolon (;).
- Keywords in Turkish must be given in accordance with Türkiye Bilim Terimleri (TBT) (http://www.bilimterimleri.com), and keywords in English must be given in accordance with Medical Subject Headings (MESH) (http://www.nlm.nih.gov/mesh/MBrowser.html).

STATISTICAL METHODS

- All research articles should be assessed in terms of biostatistics and indicated with appropriate plan, analysis and report. In these articles last subtitle of the MATERIAL and METHODS section should be the "Statistical Analysis".
- In this section, the statistical methods used in the study should be written by indicating the purpose of use, package programs and versions used for statistical analysis should be specified.
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ABBREVIATIONS

- The term should be written in full words with the abbreviation in parenthesis where first mentioned, and the same abbreviation should be used throughout the entire text.
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- Should be indicated at the end of the relevant sentence in the text as (Table 1) and/or (Figure 1).
- Tables (with headings) and figures (with captions) must be added after references at the end of the text as each to be on a separate page.
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ACKNOWLEDGEMENT

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Al-Habian A, Harikumar PE, Stocker CJ, Langlands K, Selway JL. Histochemical and immunohistochemical evaluation of mouse skin histology: comparison of fixation with neutral buffered formalin and alcoholic formalin. J Histotechnol. 2014;37(4):115-24.

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Book:

Buckingham L. Molecular diagnostics: fundamentals, methods and clinical applications. 2nd ed. Philadelphia: F.A. Davis; 2012.

Book Chapter:

Altobelli N. Airway management. In: Kacmarek R, Stoller JK, Heuer AJ, editors. Egan's fundamentals of respiratory care. 10th ed. St. Louis: Saunders Mosby; 2013. p.732-86.

YAZARLARA BİLGİLENDİRME

BİLİMSEL SORUMLULUK

Bilimsel yayıncılık standartları açısından, gönderilecek makaleler, Uluslararası Tıbbi Dergi Editörler Kurulu (ICMJE), Dünya Tıbbi Editörler Birliği (WAME) ve Yayın Etik Kurulu (COPE) kriterlerine uygun olarak hazırlanmalıdır.

- Gönderilecek makalelerde araştırma ve yayın etiğine uyulması zorunludur. Makalelerin sorumluluğu yazarlarına aittir.
- Makalelerin daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmaması gerekir.
- Değerlendirme sürecinin başlaması için makaleler, tüm yazarlar tarafından imzalanmış Telif Hakkı Devir Formu ile birlikte gönderilmelidir. Yazar sıralaması için Telif Hakkı Devir Formu'ndaki imza sırası dikkate alınır.
- Sorumlu yazar, tüm yazarlar adına makalenin son halinin sorumluluğunu taşır.

ETİK SORUMLULUK

- "İnsan" öğesini içeren tüm çalışmalarda Helsinki Deklerasyonu Prensipleri'ne (https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/) uygunluk aranır. Bu tip çalışmalarda yazarların, GEREÇ VE YÖNTEMLER bölümünde çalışmayı bu prensiplere uygun olarak yaptıklarını, kurumlarının etik kurullarından onay ve çalışmaya katılmış insanlardan "bilgilendirilmiş olur" (informed consent) aldıklarını belirtmeleri gerekmektedir.
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- Makalelerin bilimsel ve etik kurallara uygunluğu yazarların sorumluluğundadır.

BAŞVURU DOSYALARI

Makaleler aşağıda belirtilen şekilde ayrı dosyalar halinde sisteme yüklenmelidir.

Telif Hakkı Devir Formu: Başvuru sırasında sistemden alınacak Telif Hakkı Devir Formu tüm yazarlar tarafından makaledeki yazar sıralamasına uygun şekilde imzalanmış olmalıdır.

Başvuru Mektubu: Makalenin türü, daha önce hiç bir yerde yayınlanmamış ve/veya yayınlanmak üzere değerlendirme sürecinde olmadığı, varsa çalışmayı maddi olarak destekleyen kişi ve kuruluşlar ve bu kuruluşların yazarlarla olan ilişkileri (yoksa olmadığı) belirtilmelidir. Makalenin konusuyla ilgili olarak önerilen, yazarlarla ve kurumlarıyla ilgisi olmayan en az iki hakemin adları, akademik unvanları, kurumları, iletişim bilgileri ve e-posta adresleri yazılmalıdır. Editörlerin hakemleri seçme hakkı saklıdır.

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Ana Metin: Makalenin başlığı (İngilizce ve Türkçe), 40 karakteri geçmeyen kısa başlık, Öz (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), Ana Metin (gönderilen makalenin türüne uygun olarak bölümlere ayrılmış), Kaynaklar, Tablolar ve Şekil açıklamaları yer almalıdır.

Etik Kurul Onay Belgesi: Tüm araştırma makaleleri için Etik Kurul Onay Belgesi ayrı bir dosya olarak yüklenmelidir.

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MAKALE TÜRÜNE GÖRE KULLANILMASI GEREKEN BÖLÜMLER

Araştırma Makalesi

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, GEREÇ VE YÖNTEMLER, BULGULAR, TARTIŞMA, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 200-250 kelime arasında olmalıdır.

ABSTRACT, "Aim, Material and Methods, Results, Conclusion" şeklinde yapılandırılmalıdır.

ÖZ, "Amaç, Gereç ve Yöntemler, Bulgular, Sonuç" şeklinde yapılandırılmalıdır.

Derleme (Sadece Davetli)

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, Konu ile İlgili Alt Başlıklar, SONUÇ, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 150-200 kelime arasında olmalıdır.

Olgu Sunumu

BAŞLIK (İngilizce ve Türkçe), KISA BAŞLIK, ÖZ (İngilizce ve Türkçe), Anahtar kelimeler (İngilizce ve Türkçe), GİRİŞ, OLGU SUNUMU, TARTIŞMA, KAYNAKLAR

ÖZ ve ABSTRACT çeviri açısından uyumlu olmalı ve her biri kendi içinde 100-150 kelime arasında olmalıdır.

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Bu üç temel makale türü dışındaki (editöre mektup, editöryel yorum/tartışma vb.) yazıların hazırlanmasında da genel yazım kuralları geçerlidir. Bu tür yazılarda başlık ve öz bölümleri yoktur. Kaynak sayısı 5 ile sınırlıdır. İthaf olunan makale sayı ve tarih verilerek belirtilmelidir. Yazının sonunda yazarın ismi, kurumu ve adresi yer almalıdır. Mektuba cevap, editör veya makalenin yazarları tarafından, yine dergide yayınlanarak verilir.

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YAZIM KURALLARI
- Makaleler Microsoft Word® belgesi olarak hazırlanmalıdır.
- Sayfa kenarlarında 2,5 cm boşluk bırakılmalıdır.
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ANAHTAR KELİMELER
- Anahtar kelime sayısı en az 2 olmalı, kelimeler birbirlerinden noktalı virgül (;) ile ayrılmalıdır.
- Türkçe anahtar kelimeler Türkiye Bilim Terimleri (TBT)'ne (http://www.bilimterimleri.com), İngilizce anahtar kelimeler Medical Subject Headings (MESH)'e (http://www.nlm.nih.gov/mesh/MBrowser.html) uygun olarak verilmelidir.

İSTATİSTİKSEL YÖNTEMLER
- Tüm araştırma makaleleri biyoistatistik açıdan değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir. Bu makalelerde, GEREÇ VE YÖNTEMLER bölümünün son alt başlığı "İstatistiksel Analiz" olmalıdır.
- Bu bölümde çalışmada kullanılan istatistiksel yöntemler ne amaçla kullanıldığı belirtilerek yazılmalı, istatistiksel analiz için kullanılan paket programlar ve sürümleri belirtilmelidir.
- p değerleri ondalık üç basamaklı (p=0,038; p=0,810 vb.) olarak verilmelidir.
- Makalelerin biyoistatistik açıdan uygunluğunun kontrolü için ek bilgi www.icmje.org adresinden temin edilebilir.

KISALTMALAR
- Terim ilk kullanıldığında parantez içinde kısaltmayla birlikte açık olarak yazılmalı ve tüm metin boyunca aynı kısaltma kullanılmalıdır.
- Uluslararası kullanılan kısaltmalar Bilimsel Yazım Kurallarına uygun şekilde kullanılmalıdır.

TABLOLAR VE ŞEKİLLER
- Metinde ilgili cümlenin sonunda (Tablo 1) ve/veya (Şekil 1) şeklinde belirtilmelidir.
- Tablolar (başlıklarıyla birlikte) ve şekiller (açıklamalarıyla birlikte) kaynaklardan sonra ve her biri ayrı bir sayfada olacak şekilde metnin sonuna eklenmelidir.
- Tablo başlıkları tablo üstünde (Tablo 1. Tablo başlığı), şekil açıklamaları ise şeklin altında (Şekil 1. Şekil açıklaması), ilk harfleri büyük olacak şekilde yazılmalıdır.
- Tablolarda ve şekillerde kısaltma veya sembol kullanılmış ise altında dipnot olarak açıklanmalıdır.
- Şekiller ve fotoğraflar, .png, .jpg vb. formatta ve en az 300 dpi çözünürlükte ayrı dosyalar halinde yüklenmelidir.
- Şekil ve fotoğraf alt yazıları, son tablonun olduğu sayfadan sonra, ayrı bir sayfada sırasıyla verilmelidir.
- Daha önce basılmış şekil, resim, tablo, grafik vb. kullanılmış ise yazılı izin alınmalı ve açıklama olarak belirtilmelidir. Bu konudaki hukuki sorumluluk yazarlara aittir.

TEŞEKKÜR
- Eğer çıkar çatışması/çakışması, finansal destek, bağış ve diğer bütün editöryel (İngilizce/Türkçe değerlendirme) ve/veya teknik yardım varsa, bu bölümde, KAYNAKLAR bölümünden önce belirtilmelidir.

KAYNAKLAR
- Kaynaklar, kullanım sırasına göre numaralandırılmalı ve metin içinde ilgili cümlenin sonunda parantez içinde numaralarla (1) veya (1,2) veya (3-5) şeklinde verilmelidir.
- Kaynaklar dizini, metin içinde kaynakların kullanıldığı sıraya göre oluşturulmalıdır.
- Yazar sayısı 6 veya daha az ise tüm yazarlar belirtilmeli, 7 veya daha fazla ise ilk 6 yazar belirtildikten sonra "et al." eklenmelidir.
- Kongre bildirileri, kişisel deneyimler, basılmamış yayınlar, tezler ve internet adresleri kaynak olarak gösterilmemelidir.
- DOI tek kabul edilebilir online referanstır.

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