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A Case of COVID-19 in a Patient with Pemphigus Successfully Managed with Favipiravir

ABSTRACT

COVID-19 is not only a respiratory disease, but a multisystem disease that can cause organ dysfunction and coagulation disorder associated with high mortality and morbidity, particularly in vulnerable populations. Severe complications can be seen especially in elderly patients with systemic disease and immunosuppressive patients. We present the case of COVID-19 that developed in a 38-year-old female patient with pemphigus successfully managed with favipiravir.

Keywords: COVID-19, Pemphigus, Favipiravir

Favipiravir ile Başarılı Şekilde Tedavi Edilen Pemfiguslu bir COVID-19 Vakası

ÖZET

COVID-19 sadece bir solunum hastalığı değil, aynı zamanda özellikle hassas popülasyonda yüksek mortalite ve morbidite ile ilişkili organ disfonksiyonuna ve pıhtılaşma bozukluğuna neden olabilen multisistemik bir hastalıktır. Özellikle sistemik hastalığı olan yaşlı hastalarda ve immünsüpresif hastalarda ciddi komplikasyonlar görülebilmektedir. Favipiravir ile başarılı bir şekilde tedavi edilen pemfiguslu 38 yaşındaki bir kadın hastada gelişen COVID-19 vakasını sunuyoruz.

Anahtar Kelimeler: COVID-19, Pemfigus, Favipiravir

Dear Editor,

Coronavirus disease 2019 (COVID-19) is a multisystemic infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1,2). COVID-19 has caused many social, cultural, and economic problems since declared as a pandemic by the World Health Organization and caused disruptions in health activities. The management of cutaneous diseases, including pemphigus, has also been affected from the difficulties and disruptions caused by the pandemic (2,3). A 38-year-old female presented with cough and loss of taste and smell. She was followed up with the diagnosis of pemphigus vulgaris that confirmed by histomorphologic and immunofluorescence findings three years before (Fig. 1). She had no further disease.

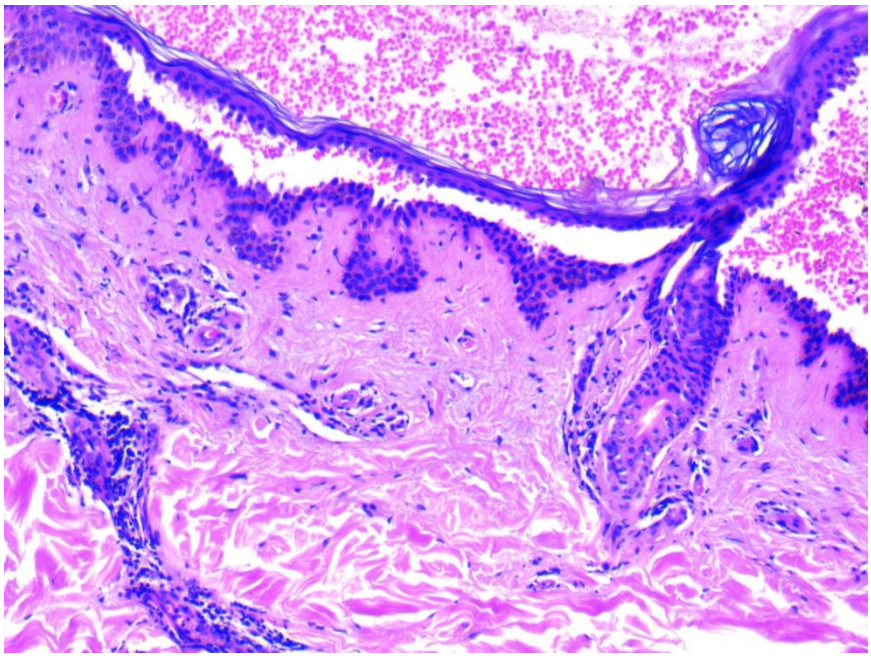

Figure 1. Cutaneous biopsy specimen showed suprabasal intraepidermal acantholysis (H&E, ×100).

She was in remission with 1500 mg/day mycophenolate mofetile and 2 mg oral methylprednisolone. The nasopharyngeal swab test for SARS-CoV-2 turned out to be positive while laboratory investigation including complete blood count, ferritin, acute phase reactants, d-dimer, fibrinogen, liver and renal function tests were within normal limits. Mycophenolate mofetil treatment was discontinued immediately and favipiravir was started (1st day at loading dose 2x800 mg; 2-5th day at maintaining dose 2x300 mg). In addition, the dose of oral methylprednisolone treatment was increased to 10 mg/day. Oral methylprednisolone dose was increased to 18 mg after 1 week following the diagnosis of COVID-19 due to few superficial erosive foci appeared in the oral mucosa. Symptoms related to COVID-19 were completely disappeared after 15 days following the diagnosis. The dose of methylprednisolone was gradually reduced to 2 mg within four week and mycophenolate mofetil treatment was restarted. No recurrence was observed in the following 3 months.

COVID-19 is considered not only a respiratory disease but a multisystemic disorder associated with a significant mortality and morbidity rates, particularly in vulnerable population. The main risk factors for mortality and morbidity includes advanced age, comorbidities and immunosuppressive conditions. Pemphigus vulgaris is a life-threatening autoimmune bullous disease with mucocutaneous involvement that usually requires immunosuppressive therapy (4,5,6).

Some authors suggested that, in patients with pemphigus immunosuppressive treatment should be suspended until sign and symptoms related to COVID-19 is regressed, while others recommended that immunosuppressive medications should only be discontinued in confirmed cases of SARS-CoV-2 infections (3).

Systemic corticosteroids are generally considered the mainstay therapy in pemphigus. Although corticosteroids have positively changed the course of pemphigus, their adverse effects including susceptibility to serious infections, has become more pronounced with the COVID-19 pandemic. It has been recently suggested that COVID-19 causes excessive production of pro-inflamatory mediators causing exaggerated inflammatory tissue response, which is considered to be associated with increased mortality and morbidity. Despite the concerns that corticosteroids may vitiate viral clearance, a low to medium dose of systemic corticosteroids seem to have a significant role in the management of severe COVID-19 cases. In their expert consensus,

Kasperkiewicz et al suggested that 10 mg or lower daily doses of prednisolone can be maintained in patients with pemphigus, while doses higher than 10 mg/day should be decreased considering the activity of the disease, accompanying systemic diseases, and severity of the infection (7).

The relevant guide published by the European Academy of Dermatology and Venereology Task Force Autoimmune Blistering Diseases also recommended to discuss reducing the dose of systemic corticosteroids for pemphigus patients with COVID-19 (8).

Favipiravir, a purine nucleoside analogue, was identified to have in vitro antiviral activity against SARS-CoV-2 (9,10). It is one of the proposed antiviral drugs for COVID-19 but no study focused on the efficacy of favipiravir alone for the treatment of COVID-19. Although there was no robust evidence, some studies showed positive effects on disease progression and viral clearance in patients with COVID-19. The side effects reported were mainly mild and manageable (11).

To conclude, low-dose methylprednisolone and favipiravir combination may offer a safe and successful management for COVID-19 in patients with pemphigus. It is clear that, however, more reports are needed to demonstrate the efficacy and safety of this combination.

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RESEARCH ARTICLE

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Evaluation of Turkish Validity and Reliability of Knowledge, Attitude, Practice and Perceived Barriers in Infection Control Questionnaire among Emergency Healthcare Professionals regarding COVID-19

ABSTRACT

Objective: Determination of deficiencies in knowledge, attitude, practice (KAP) and perceived barriers in infection control among healthcare professionals (HCP) is important for fighting against epidemics. This study aims to conduct Turkish validity and reliability of the "KAP and Perceived Barriers in Infection Control" among HCP and to evaluate the study group.

Methods: This is a methodological, cross-sectional study conducted among emergency HCP during the 12-24th week of the pandemic. The questionnaire was applied online and consisted of sociodemographic characteristics, COVID-19 KAP and perceived barriers in infection control questionnaire. In first stage of the study, to evaluate the Turkish reliability-validity of the questionnaire, this study was conducted among 177 HCP. In the second stage, it was aimed to reach the whole group which was consisted of 307 (73.1%) HCP.

Results: The Cronbach's alpha values of the sub-dimensions were calculated as 0.68-0.90 and factor loads as 0.38-0.88. Knowledge level of those with associate and higher degree was found to be superior. Those who had university or higher education degree, paramedics indicated more positive attitude. It was observed that female compared to male, emergency medical technicians compared to other occupational groups had better practice level. Moreover, those who had an associate or higher degree; those who had 6-10 years working experience; those who did not experience COVID-19 symptoms had better practice level ($p<0.05$).

Conclusions: The questionnaire is a valid-reliable measurement tool. In Turkey, it was observed that HCP had better knowledge and practice than average however deficiencies were found in all sub-dimensions.

Keywords: COVID-19, Knowledge, Attitude, Practice, Healthcare Professionals.

Acil Sağlık Çalışanlarında COVID-19 Hakkında Bilgi, Tutum, Beceri ve Enfeksiyon Kontrolünde Algılanan Engeller Düzeyinin Belirlenmesi

ÖZET

Amaç: Sağlık çalışanlarında bilgi, tutum, beceri ve enfeksiyon kontrolünde algılanan engeller konusunda eksikliklerin belirlenmesi salgınlarla mücadelede önem taşımaktadır. Çalışmada acil sağlık çalışanlarında "COVID-19 Hakkında Bilgi, Tutum ve Beceri ve Enfeksiyon kontrolünde algılanan engel" anketinin Türkçe geçerlik-güvenirlik çalışmasının yapılması ve çalışma grubunun ankete göre değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışma, COVID-19 pandemisinin 12-24.haftasında acil sağlık çalışanlarında gerçekleştirilen metadolojik ve kesitsel tipte bir araştırmadır. Anket form, kişilerin sosyodemografik özellikleri, COVID-19 bilgi, tutum, beceri ve enfeksiyon kontrolünde algılanan engeller anketinden oluşmakta olup online uygulandı. Çalışmanın ilk aşaması, anket formun Türkçe geçerlik-güvenirliğini değerlendirmek için anket madde sayısı dikkate alınarak 177 sağlık çalışanında gerçekleştirildi. İkinci aşamada ise çalışma grubunun tümüne ulaşılması hedeflenmiş olup 307(%73.1) sağlık çalışanına ulaşıldı.

Bulgular: Anketin güvenirlik geçerlilik analizleri sonuçlarına göre alt boyutların Cronbach alfa değerleri 0.68-0.90 ve faktör yükleri 0.38-0.88 olarak hesaplandı. COVID-19 bilgi düzeyi yüksekokul ve üzeri öğrenime sahip olanlarda daha yüksekti. Üniversite ve üzeri öğrenim derecesine sahip olanlar ve paramedikler daha olumlu bir tutum sergiledi. Kadınlar erkeklere göre, acil tıp teknisyenleri diğer meslek gruplarına göre daha iyi uygulama düzeyine sahipti. Ayrıca, yüksek okul ve üzeri öğrenime sahip olanlar; 6-10 yıl iş tecrübesi olanlar; COVID-19 semptomlarını yaşamayanlar daha iyi beceri düzeyine sahipti ($p<0.05$).

Sonuç: Sonuç olarak anket geçerli ve güvenilir bir ölçme aracıdır. Türkiye'de sağlık çalışanları ortalamaya göre iyi bilgi ve beceri düzeyine sahip olmakla birlikte bilgi, tutum ve beceri ve enfeksiyon kontrolünde algılanan engeller açısından eksiklikler bulundu.

Anahtar Kelimeler: COVID-19, Bilgi, Tutum, Beceri, Sağlık Çalışanları.

INTRODUCTION

Similar to previous epidemics in the world, it had been observed that healthcare professionals (HCP) were in serious danger during COVID-19 pandemic (1). It was reported that COVID-19 positivity among HCP during the pandemic had varied between 3.5-38% (2-5). In Turkey in December 2020; out of 1,9 million COVID-19 cases 120.000 of them were HCP and 375 of them lost their lives (6,7). One of the most important problems faced by HCP during the pandemic was the risk of getting infection and causing the infection to spread unconsciously (8). The risk of infection in HCP increased due to reasons such as the need to stay together with infected patients for a long time and provide care, lack of knowledge about infection prevention and control, long working hours and excessive fatigue.

Emergency HCP had a higher risk of outbreaks compared to other HCP (9). The emergency HCP are responsible for providing emergency care from the notification of the emergency to the delivery of the definitive treatment. Delivery of emergency health services requires intervention in the patient's environment, and then patient transfer by ambulance if necessary. The risk of emergency HCP increases in terms of COVID-19 since they need to conduct rapid intervention to the patient in their own location and to stay in ambulance which is a closed and narrow environment. During COVID-19 and similar epidemics, in order to ensure continuous emergency reception and care; knowledge level, attitude and practice of emergency HCP at the front line should also be high (10). At this point, HCP who had the first contact with the patient should have sufficient knowledge and practices about disease characteristics, mode of transmission and risks, protective measures, compliance with guidelines, and risk controls (11, 12).

Examining the knowledge, attitude and practice of HCP and perceived barriers to infection control help to reveal the situation; to understand the deficiencies and possible risk factors and determine the effective interventions in the fight against future epidemic (13). Although, there are questionnaire form development studies in determining the knowledge, attitude and practice of HCP about the pandemic, there is no accepted questionnaire form yet. It was aimed to adapt the questionnaire named "Knowledge, attitude, practice and perceived barriers among healthcare professionals regarding COVID-19", which was first published in the international literature on April 17, 2020,to Turkish; then to conduct a reliability and validity study and to evaluate the group in terms of these characteristics.

MATERIAL AND METHODS

This study is a methodological and cross-sectional research conducted among pre-hospital emergency HCP during the 12-24th week of the COVID-19 pandemic (when the first wave started to decline), in Eskişehir which is a city of middle Anatolia region.

Working Group and Design: Eskişehir 112 Provincial Ambulance Service consisted of total of 36 Emergency Health Services Stations; 21 of which were in the city center and 15 of them were in peripheral districts. In addition, it comprised of a Command Control Center and 420 health personnel. The study was executed in two stages. In the first stage of the study, considering item number in the questionnaire, it was aimed to reach 177 people in order to evaluate the Turkish reliability and validity of the questionnaire (14). In the second stage, it was objected to reach the whole study group and 307 (73.1%) HCP were reached in order to determine the knowledge, attitude, practice and perceived barriers in infection control among emergency healthcare professionals regarding COVID-19. There was no difference between the two groups in terms of age and gender distribution.

Permissions: Permission was obtained from the author to translate the questionnaire into Turkish. Necessary permissions and ethical committee approval were obtained from official institutions in order to conduct the study.

Data Collection Tools: In the study, a questionnaire form was prepared by benefiting from the literature in order to collect data. The questionnaire consisted of socio-demographic characteristics (age, gender, marital status, etc.) and COVID-19 related factors, COVID-19 knowledge, attitudes, practices and perceived barriers in infection control. The questionnaire named "Knowledge, attitude, practice and perceived barriers among healthcare professionals regarding COVID-19" had four subdimensions as 'Knowledge of HCP regarding COVID -19', Attitude of HCP regarding COVID-19" and "Practice among HCP regarding COVID-19"and "Barriers in infection control practice perceived by healthcare professionals regarding COVID-19". In the original form of the questionnaire consisted of 14 questions of knowledge, 7 questions of attitude, 6 questions of practice, and 8 questions of perceived barriers in infection control and the Cronbach alpha value was reported as 0.77 (14). Due to the pandemic, data in the study group were collected online. The questionnaire was sent to the working group three times and was encouraged by verbal warnings.

Turkish Validity and Reliability of Knowledge, Attitude and Practice and Perceived Barriers Questionnaire among healthcare professionals regarding COVID-19: The

questionnaire was translated into Turkish by two independent foreign language experts in accordance with the translation-back translation method due to the adaptation of the questionnaire from different languages and cultures, and it was translated back into English by another linguist. The Turkish form, which was created by comparing all forms, was evaluated with expert opinion for content validity. The content validity rate of the questionnaire, which was evaluated by eight experts to determine its suitability and comprehensibility, ranged from 0.8 to 1.0, and the content validity index was found to be 0.95. Exploratory factor analysis (EFA) was used to determine the construct validity. Kaiser Meyer Olkin and Barlett test values were determined accordingly. Internal consistency (Cronbach alpha) and Interclass Correlation (ICC) analyzes were used to evaluate the reliability of the questionnaire. Items with a factor load greater than 0.30 and total item correlations greater than 0.20 were accepted as reliable (15). Cronbach alpha coefficient above 0.60 was considered reliable (16).

Knowledge questions consisted of 8 items and each question was answered as "Yes, No and I don't know". One question (Eighth question) was reverse coded. Correct answer was scored as "2", I don't know as "1", wrong answer as "0". The score that could be obtained from the knowledge sub-dimension varied between 0 and 16. The higher the score, the higher the knowledge level was accepted.

Attitude questions consisted of 7 items and the answer of each item was scored in a 5-point Likert format ranging from “1 point” to “I strongly agree” and “5 points to absolutely disagree”. The total score ranged from 7-35, with an overall lower score indicating a positive attitude towards COVID-19.

Practice Questions of Healthcare Professionals on COVID-19 consisted of 5 items and each item would be answered as yes "2 points", sometimes "1 point" and no "0 points". The total score ranged from 0 to 10, the higher the score was, the better the practice level was considered.

The perceived barriers sub-dimension in the infection control application consisted of 8 questions and the answer of each item was scored in a 5-point Likert format ranging from "strongly agree" "5 points" to "strongly disagree" "1 point". For the sub-dimension of perceived barriers in infection control, it ranged between 8 and 40 points, indicating that the perceived barriers increased as the score increased.

Data Analyzes: The data obtained were transferred to the computer environment and evaluated in the SPSS (Version 15.0) statistical package program, and $p<0.05$ was accepted as the statistical significance value. Number, percentage, mean and standard deviation values were used in the evaluation of descriptive data. The compliance of the data to normal distribution was evaluated with the Kolmogrov-Smirnov and Shapiro-Wilk tests. Mann-Whitney U and Kruskal Wallis tests were used in the evaluation of knowledge, attitude and practices, since the data did not indicate a normal distribution.

RESULTS

62.5% (n=199) of the 307 HCP reached in the cross-sectional phase of the study were women and the mean age±SD (min-max) was 32.1±6.9 (20-60) years. 54.4% of the individuals in the study group were emergency medical technicians, 33.2% were paramedic, 12.4% were in the other profession groups. (midwife, medical secretary…).

Evaluation of Turkish Validity and Reliability of Knowledge, Attitude, Practice and Perceived Barriers in Infection Control Questionnaire: It was determined that the item to which the participants in the study group gave the most correct answer in the knowledge sub-dimension was "Coronavirus infection could be fatal" with 99.3% correct answers. It was determined that the attitude question that the people in study group most participated was ‘COVID-19 patients should be kept in isolation" with 80.8%". It was observed that the question ‘Do you use soap or hand sanitizer to wash your hands continuously’ was the question which was most answered ‘Yes’ with 99.7% by the participants in the study group. It was monitored that ‘Overcrowding in the emergency department is an obstacle in infection control practice." was the perceived barriers in infection control subdimension question to which the participant individuals in the study group agreed more with 59.3%. Explatory factor analysis results and percentage of participation for items of "COVID-19 KAP and perceived barriers in infection control questionnaire" was indicated in Table 1.

The scores the participants obtained from the knowledge sub-dimension ranged from 5 to 16, with an average of 14.7 ± 1.8, and a median of 16.0. Their scores from the attitude sub-dimension ranged from 7 to 33, with a mean of 11.9 ± 3.6, and a median of 12. The scores they got from the practice sub-dimension ranged from 1 to 10, with an average of 9.5 ± 1.1 and a median of 10. The scores obtained from the subscale of perceived barriers in infection control practices in HCP ranged from 8 to 40, with an average of 34.8 ± 5.2 and a median value of 36.

The median score obtained from the COVID-19 knowledge level sub-dimension was higher in those with associate or higher education than those with high school level ($p = 0.001$). Those with university and higher education level indicated more positive attitude than those with high school and college education ($p=0.009$). In addition, paramedics showed more positive attitude than EMT and other professions ($p=0.019$). Female compared to male ($p=0.013$), those with college and higher education compared with high school graduates ($p=0.001$); EMT compared with people

Table 1. Explatory factor analysis results and percentage of participation for items of "COVID-19 KAP and perceived barriers in infection control questionnaire"

Knowledge among Healthcare Professionals About COVID-19	**Factor load**	**Item total correlation value**	**Cronbach alfa if deleted item**	**Percentage of correct answers (%)**
1.COVID-19 is a viral infection. COVID-19 viral bir enfeksiyondur.	0.562	0.348	0.652	92.1
2.Coronavirus infection could be fatal. Koronavirüs enfeksiyonu ölümcül seyredebilir.	0.378	0.259	0.682	99.3
3.Incubation period for virüs is 2-14 days. İnkübasyon periyodu 2-14 gündür.	0.501	0.323	0.659	95.8
4.Polymerase chin reaction (PCR) can be used to diagnose COVID-19. Polimeraz zincir reaksiyonu (PCR) COVID-19 tespiti için kullanılabilir.	0.584	0.443	0.632	82.4
5.People with comorbidity like diabetes and hypertension are more likely to be infected. Diyabet ve hipertansiyon gibi komorbiditesi olan kişiler için daha risklidir.	0.517	0.369	0.651	95.8
6.COVID-19 spreads through close contact like caring and/or living with infected people. COVID-19, enfekte kişilere bakım verme ve/veya onlarla yakın temasta bulunma yoluyla yayılır.	0.706	0.514	0.609	82.1
7.COVID-19 patients develop severe acute respiratory illness. COVID-19 hastalarında ciddi akut solunum yolu hastalığı gelişir.	0.568	0.391	0.640	88.6
8. Influenza vaccine also gives protection from COVID-19. İnfluenza aşısı COVID-19 için de koruyucudur.	0.660	0.456	0.622	70.7
				Cronbach alpha value: 0.68 **Total variance explained: 32.2%**
Attitude among Healthcare Professionals About COVID-19	**Factor load**	**Item total correlation value**	**Cronbach alfa if deleted item**	**Percentage of "Strongly agree" answers (%)**
1. Gowns, gloves, mask and goggles must be used when dealing with COVID-19 patients? COVID-19 hastalarıyla uğraşırken önlük, eldiven, maske ve gözlük kullanılmalıdır.	0.684	0.516	0.791	80.1
2. COVID-19 patients should be kept in isolation? COVID-19 hastaları izolasyonda tutulmalıdır.	0.823	0.669	0.766	80.8
3. Intensive and Emergency treatment should be given to diagnosed patients. Tanı konulan hastalara yoğun ve acil tedavi uygulanmalıdır.	0.588	0.461	0.805	40.1
4. Prevalence of COVID-19 can be reduced by active participation of healthcare workers in the hospital infection control program? COVID-19 sıklığı, sağlık çalışanlarının enfeksiyon hastalıklarından korunma ve kontrol programına aktif katılımı ile azaltılabilir.	0.508	0.401	0.820	21.2
5. Any related information about COVID-19 should be disseminated among healthcare workers? COVID-19 ile ilgili her türlü bilgi sağlık çalışanları arasında yaygınlaştırılmalıdır.	0.802	0.675	0.766	50.8
6. Transmission of COVID-19 infection can be prevented by using universal precautions given by WHO, CDC? COVID-19 enfeksiyonunun bulaşması, Dünya Sağlık Örgütü (WHO), Hastalık Önleme ve Kontrol Merkezi (CDC) tarafından verilen evrensel önlemler kullanılarak önlenebilir.	0.637	0.523	0.789	28.3
7. Healthcare workers must acknowledge themselves with all the information about COVID-19? Sağlık çalışanları COVID-19 hakkındaki tüm bilgileri edindiklerinden emin olmalıdır.	0.859	0.727	0.758	50.8
				Cronbach alpha value: 0.81 **Total variance explained: 50.5%**

Practice of healthcare professionals toward COVID-19	Factor load	Item total correlation value	Cronbach alfa if deleted item	Percentage of "Yes" answers (%)
1. Do you use soap or hand sanitizer to wash your hands continuously? Ellerinizi sürekli yıkamak için sabun veya el dezenfektanı kullanıyor musunuz?	0.586	0.384	0.752	99.7
2. Do you cover your nose and mouth with a tissue during sneezing or coughing? Hapşırma veya öksürme sırasında burnunuzu ve ağzınızı bir mendille kapatıyor musunuz?	0.623	0.466	0.717	87.9
3. Do you throw the used tissue in the trash? Kullanılmış peçeteleri çöp kutusuna atıyor musunuz?	0.850	0.649	0.645	96.4
4. Do you avoid touching your eyes, nose or mouth as far as you can? Gözlerinize, burnunuza veya ağzınıza dokunmaktan olabildiğince kaçınır mısınız?	0.660	0.489	0.822	81.1
5. Do you use face mask in crowds? Kalabalık içinde yüz maskesi kullanıyor musunuz?	0.877	0.704	0.624	96.1
				Cronbach alpha value: 0.74 **Total variance explained: 53.2%**
Perceived barriers to infection control practice	**Factor load**	**Item total correlation value**	**Cronbach alfa if deleted item**	**Percentage of "Strongly agree" answers**
1. Lack of knowledge about the mode of transmission of the disease COVID19? COVID-19 bulaşma şekli hakkında bilgi eksikliğimin olması enfeksiyon kontrolünde engeldir.	0.608	0.525	0.901	38.8
2. Not wearing mask while examine or contact with the patient? Hastayı muayene ederken veya hastayla temas halindeyken maske takmamak enfeksiyon kontrolünde engeldir.	0.681	0.617	0.896	57.7
3. Limitation of infection control material? Enfeksiyon kontrol materyallerinin sınırlı olması enfeksiyon kontrolünde engeldir.	0.859	0.776	0.876	52.1
4. No hand washing after examine or contact with the patient? Muayene veya hastayla temas ettikten sonra el yıkamama enfeksiyon kontrolünde engeldir.	0.768	0.691	0.884	57.3
5. Lack of policy and Procedures of infection control Practice? Enfeksiyon kontrol uygulamasında politika ve prosedür eksikliği enfeksiyon kontrolünde engeldir.	0.865	0.797	0.874	47.9
6. Insufficient training in infection control measurements? Enfeksiyon kontrol önlemlerinde yetersiz eğitim enfeksiyon kontrolünde engeldir.	0.839	0.752	0.879	51.8
7. Less commitment of health care workers to the policies and procedures? Sağlık çalışanlarının politika ve prosedürlere daha az bağlılığı enfeksiyon kontrolünde engeldir.	0.782	0.699	0.883	45.6
8. Overcrowding in Emergency room is also a barrier in infection control practice? Acil serviste aşırı kalabalıklaşmanın enfeksiyon kontrol uygulamasında bir engeldir.	0.841	0.752	0.882	59.3
				Cronbach alpha value: 0.90 **Total variance explained: 61.6%**

Table 2. The distribution of the points that healthcare professionals obtained from knowledge, attitude, practice and perceived barriers in infection control questionnaire about COVID-19

Sociodemographic characteristics and related factors	Knowledge		Attitude		Practice		Perceived barriers in infection control	
	Median (Min-Max)	Test Degree (p)	Median (Min-Max)	Test Degree (p)	Median (Min-Max)	Test Degree (p)	Median (Min-Max)	Test Degree (p)
Age group								
20-24	15(8-16)	0.455	12(7-16)	0.663	10(1-10)	0.696	37(26-40)	0.281
25-44	16(5-16)		12(7-33)		10(2-10)		36(8-40)	
45-60	16(6-16)		11(7-17)		10(7-10)		36(19-40)	
Gender								
Female	16(7-16)	0.313	12(7-33)	0.995	10(3-10)	**0.013**	35(8-40)	0.287
Male	16(5-16)		12(7-16)		10(1-10)		37(10-40)	
Education level								
Highschool	14(5-16)	**0.001**	13(7-33)	**0.009**	9(1-10)	**0.001**	32(10-40)	**0.002**
Associate degree	16(11-16)		12(7-33)		10(6-10)		34(8-40)	
University and above	16(10-16)		11(7-19)		10(6-10)		38(19-40)	
Occupation								
Paramedic	15(10-16)	0.334	11(7-33)	**0.019**	10(6-10)	**0.027**	36(20-40)	0.138
Emergency Medical Technician	15(5-16)		12(7-33)		10(1-10)		34(8-40)	
Others	16(6-16)		12(7-17)		10.0(7.0-10.0)		38(19-40)	
Working time (year)								
0-5	15(6-16)	0.428	12(7-19)	0.623	10(1-10)	**0.019**	38(19-40)	0.101
6-10	16(7-16)		12(7-31)		10(3-10)		38(19-40)	
11 and above	16(5-16)		12(7-33)		10(2-10)		36(8-40)	
Experiencing symptoms of COVID-19								
No	15(5-16)	0.255	12(7-33)	0.187	10(1-10)	**0.015**	36(8-40)	0.814
Yes	16(5-16)		14(7-17)		9(7-10)		38(28-40)	
Have COVID-19 test								
No	15(6-16)	0.796	12(7-33)	0.720	10(2-10)	0.520	34(10-40)	0.596
Yes	16(5-16)		12(7-33)		10(1-10)		36(8-40)	
If a relative has been diagnosed with COVID-19								
No	15(5-16)	0.135	12(7-17)	0.656	10(1-10)	0.336	35(7-40)	0.099
Yes	15(5-16)		12(7-33)		10(7-10)		39(29-40)	
Total	16(5-16)		12(7-33)		10(1-10)		36(8-40)	

from other professions (p=0.027), those with 6-10 years working experience compared with people with 11 and higher experience (p=0.019), people who did not live COVID-19 symptoms compared with people who lived (p=0.015) were observed to have better practice level. The distribution of the points that HCP obtained from the knowledge, attitude and practice and perceived barriers in infection control questionnaire about COVID-19 were indicated in Table 2. The most preferred source of information was the Ministry of Health (84.6%), followed by expert and colleague opinions (61.8%) and radio and television (58.3%) in the third place. The distribution of information sources preferred by the individuals in the study group was demonstrated in Figure 1.

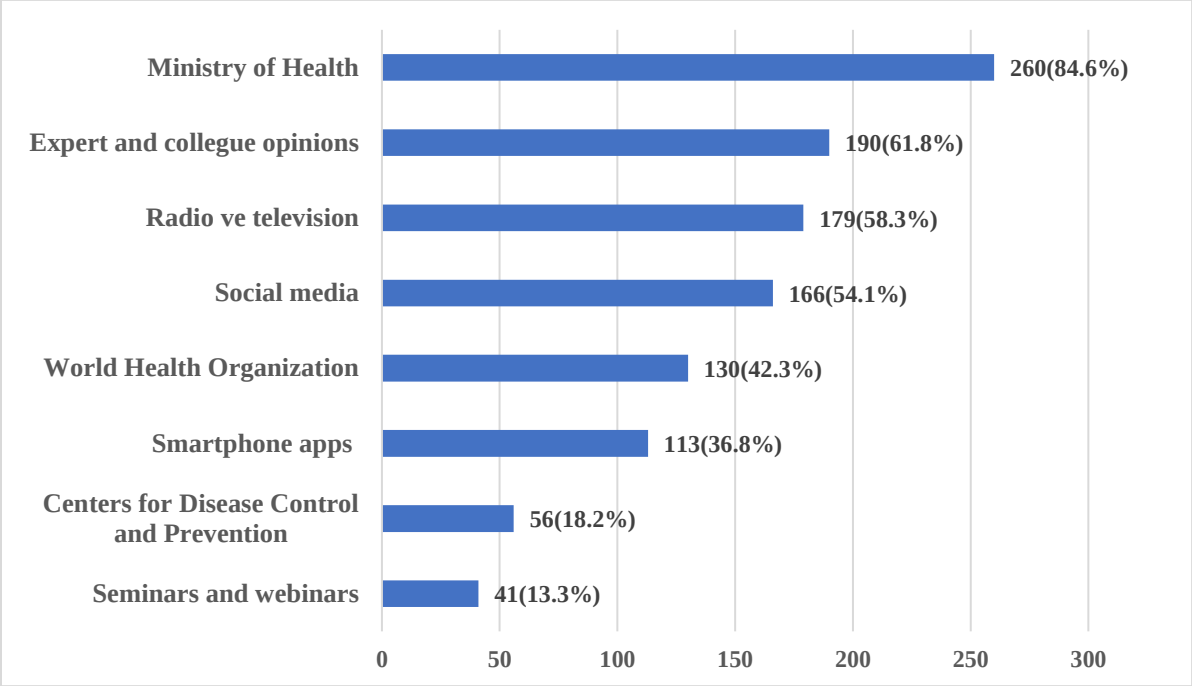

Figure 1. The distribution of information sources preferred by the individuals in the study group(* Percentages are based on the number of people.)

DISCUSSION

In the study knowledge, attitude, practice, and perceived barriers to infection control regarding COVID-19 for HCP Turkey was conducted in a comprehensive way to evaluate the reliability and validity of an internationally recognized questionnaire. Improving the level of knowledge, attitudes and practices about COVID-19 in the working processes of the COVID-19 pandemic among HCP is imperative to protect both their own health and the health of patients. Moreover, in the ongoing pandemic and possible future pandemic situations, HCP should carefully follow the infection control measures and follow up-to-date information in implementing the diagnosis and treatment processes and put this information into practice. Healthcare professionals, whose awareness has increased, will significantly affect the society and contribute to the protection and development of health (15).

In the study, the Cronbach's alpha coefficient was determined as 0.68 for knowledge, 0.81 for attitude, 0.73 for practice, and 0.91 for perceived barriers in infection control, and it was sufficient (16). The Cronbach alpha value of the original questionnaire was reported as 0.77. The total Cronbach alpha value in the study was determined as 0.70. Relative differences may have been observed due to the difference in sample size and the extracted items. The fact that the total correlation values of the items in the questionnaire form were greater than 0.20 indicated that the items were reliable (16).

In the validity analysis, a structure consisting of four different dimensions including knowledge, attitude, practice and perceived barriers in infection control was revealed in EFA. The total variance was 32.2% for knowledge, 50.5% for attitude, 53.2% for skills, and 61.6% for perceived barriers in infection control. In the studies conducted, it was known that the total variance over 30% was an adequate criterion (17). In questionnaire adaptation studies, if the factor loadings were not below 0.30 after EFA was performed, it indicated that the questionnaire form had sufficient factor load (18).

As a result of the factor analysis, six items were removed from the knowledge sub-dimension and one item from the practice sub-dimension. As a result, knowledge was composed of 8 items, attitude 7, skill 5, and perceived barriers in infection control 8 items and were evaluated as sufficient. In the extraction of the items, it was

effective to bring new information about COVID-19 related to the original questionnaire developed in April to the literature. "Vaccination of coronavirus disease is available", "Special caution must be taken if a person presents with symptoms of COVID-19 travelled from infected area?" the accuracy of the items had changed during the course of the pandemic. This may have played a role in the removal of these items.

Approximately 70% of the participants in the study group obtained points above average from the knowledge sub-dimension of the questionnaire. In the original study, it was reported that 93.2% of the HCP had a good level of knowledge (19). In a study conducted by Nemati et al. in Iran it was reported that 89,5% of HCP had sufficient level of knowledge. In addition, the study executed by Giao et al. and Zhang et al. in China indicated this ratio as 89,0% (20-22). In a study conducted in Indonesia, it was reported that 51.7% of HCP had good knowledge about COVID-19 (23). In a study realized by Kadoya et al. in Japan, it was reported that especially non-physician HCP had insufficient knowledge (24). Another study conducted in Uganda; it was reported that 69% of the HCP had sufficient knowledge level (25). In a study executed with HCP in Nepal, it was reported that good knowledge level was found with a frequency of 82.2% (26, 27). The study conducted by Ayinde et al. among HCP in Nigeria the frequency of good knowledge was reported as 78.6% (28). As expected in the study, the median score obtained from the COVID-19 knowledge level sub-dimension was found to be higher in those with associate degree and university degrees than those with high school education.

In this study, it was determined that 58.6% of the HCP indicated a more positive attitude than the average. The average score of the individuals in the study group (11.9) was higher than the original study (8.43) (19). Olum et al. reported that 21% of HCP had a positive attitude towards COVID-19 (25). Moreover, Nepal et al. reported that 90.9% of HCP had a positive attitude (27). The frequency of positive attitudes among HCP in Nigeria had been reported as 64% (26). In this study, those with university and higher education level demonstrated more positive attitude than those with high school and associate education level. In addition, paramedics indicated more positive attitude than EMT and other professions. Differences in attitude among HCP might have been affected by many different variables such as their sociodemographic characteristics, professions, personal experiences, the unit they work in, and the responsibilities of the administrative unit.

It was found that 73% of the HCP had a better practice level than the average. In the original study, 88.7% of the HCP were reported to have a good practice level (19). In Uganda, it had been reported that 74.0% of HCP had good practice level (25). In the study conducted by Nepal et al., the frequency of good practice was reported as 83.6% (27). Gender, education level, occupation, duration of work and COVID-19 symptoms are considered as the factors that affected the practice level. Guidelines and algorithms prepared by the Ministry of Health could have positive impact in applying practices.

53.1% of the HCP had a higher perception of barrier in infection control practices compared to the average. Similar to the original study, crowding in the emergency room, not washing hands after examination and contact with the patient, and inadequate education were identified as the most perceived obstacles in infection control (19). Similarly, studies reported that crowding in the emergency room was perceived as a barrier in infection control (19, 29).

Although the most frequently used information source by HCP is the Ministry of Health, the least preferred information source was declared as seminars and webinars. In a study conducted with university students, it was reported that the most preferred information source was the internet and social media, and the least preferred information source was scientific websites and articles (30). Many studies reported that the most frequently used information source for HCP was social media and the website of the Ministry of Health (19-21). Since The Ministry of Health was actively tracking the process and publishing guides, it became the information source firstly preferred. It is crucial for HCP to follow the scientific information published by the Ministry of Health in order to prevent malicious and false information epidemic.

Limitations

By virtue of being an online study involved in pre-hospital emergency healthcare professionals in a city, it cannot be generalized. Further research is needed.

CONCLUSION

In the light of the analysis, it was found that the Knowledge, Attitudes and Practice and Perceived Barriers in Infection Control About COVID-19 in Healthcare Professionals questionnaire was a valid and reliable measurement tool. According to the average, HCP in Turkey had good knowledge and practice levels. However, deficiencies were found in terms of knowledge, attitude, practices and perceived barriers in infection control. In this context, it should be ensured that all preventive and control practices related to COVID-19 are promoted by raising awareness about the importance of HCP. Well-structured, up-to-date training programs for each HCP should be planned and implemented completely in order to effectively control the spread of the infection and to increase existing knowledge, to gain positive attitudes and practices, and to improve perceived barriers in infection control.

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RESEARCH ARTICLE

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Comparison of the Number and Reasons of Death in the First Five Months of 2020 in Kayseri with the Previous Year

ABSTRACT

Objective: The spread of a new contagious disease across the world is called a pandemic. COVID-19 was declared as a pandemic by WHO on 11th March 2020. Although treatment modalities and vaccines are being developed against COVID-19 disease, COVID-19 related deaths continue and the rate of infectious diseases among all causes of death increases. In this study, we aimed to determine the effect of COVID-19 infection on mortality statistics by comparing mortality statistics in the first five months of 2020 with mortality statistics in the same period of 2019.

Methods: This study was conducted by evaluating the death notification system data records using the ICD 10 diagnostic coding system for the first five months of 2019-2020 of the Kayseri Provincial Health Directorate, between 1 June 2020 and 1 July 2020. It is a retrospective study. In the study, data on dates (months) of deaths, ages, genders, marital statuses, causes of death and manners of death (infectious disease, forensic, natural death) in Kayseri were evaluated. Data were evaluated in SPSS (version 21.0) statistical package program.

Results: There were 3349 deaths in the first 5 months of 2019, and 3491 deaths in the first five months of 2020. Of these, 54.6% were male and 45.4% were female. The monthly average numbers of death in 2019 and 2020 were similar. The rates of disease diagnoses differed in 2019 and 2020. In 2020, all-cause death numbers, including COVID-19, were higher among men. The total mortality rate of infectious diseases was 20.2% in 2019, and the mortality rate due to infectious diseases including COVID-19 was 20.1% in 2020.

Conclusions: During the COVID-19 outbreak, there were significant changes in the rates of some specific causes of death. However, there was no significant change in the total number of deaths during the first five months in Kayseri province.

Keywords: COVID-19, Pandemic, Cause of Death.

Kayseri'de 2020 Yılı İlk Beş Ayının Ölüm Sayı Ve Nedenlerinin Bir Önceki Yıl İle Karşılaştırılması

ÖZET

Amaç: Yeni ve bulaşıcı bir hastalığın tüm dünyaya yayılmasına pandemi denir. Dünya Sağlık Örgütü (DSÖ) tarafından 11 Mart 2020 tarihinde COVID-19 pandemisi ilan edilmiştir. COVID-19 hastalığına karşı tedavi modaliteleri ve aşı geliştirilmeye çalışılsa da COVID-19'a bağlı ölümler devam etmektedir ve tüm ölüm nedenleri arasında enfeksiyon hastalıklarının oranı artmaktadır. Biz de bu çalışmamızda COVID-19 enfeksiyonunun ölüm istatistiklerine etkisini 2020 yılının ilk beş ayındaki ölüm istatistiklerini 2019 yılının aynı dönemindeki ölüm istatistikleri ile karşılaştırarak ortaya koymayı amaçladık.

Gereç ve Yöntem: Bu çalışma, 1 Haziran 2020-1 Temmuz 2020 tarihleri arasında KAYSERİ İl Sağlık Müdürlüğü'nün 2019- 2020 yılı ilk beş ayına ait ICD 10 tanı kodlama sistemi kullanan ölüm bildirim sistemi verileri kayıtları değerlendirilerek yapılmıştır. Retrospektif bir çalışmadır. Çalışmada Kayseri'de meydana gelen ölümlerin tarihleri (ay), ölenlerin yaşı, cinsiyeti, medeni hali, ölüm nedenleri ve ölüm şekilleri (bulaşıcı hastalık, adli, doğal ölüm) ile ilgili veriler değerlendirilmiştir. Veriler, SPSS (versiyon 21.0) istatistik Paket Programında değerlendirilmiştir.

Bulgular: 2019 yılı ilk beş ayında 3349, 2020 yılı ilk beş ayında ise 3491 ölüm gerçekleşmiştir. Bunların %54,6'sı erkek, %45,4'ü kadındı. 2019 ve 2020 yıllarında aylık ölen kişi sayısı ortalamaları benzerdi. 2019 ve 2020 yıllarında hastalık tanılarının oranları farklılık gösterdi. 2020 yılında COVID-19 da dâhil olmak üzere tüm nedenlere bağlı ölüm oranları erkeklerde daha fazla görülmekteydi. 2019 yılında enfeksiyon hastalıklarının toplam ölüm oranı %20,2, 2020 yılında COVID-19 dahil enfeksiyon hastalıkları nedeniyle ölüm oranı toplam %20,1 idi.

Sonuç: COVID-19 salgını sırasında bazı spesifik ölüm nedenlerinin oranlarında anlamlı değişimler olmuş ancak Kayseri ili özelinde ilk beş aylık toplam ölüm sayısında anlamlı bir değişiklik gerçekleşmemiştir.

Anahtar Kelimeler: COVID-19, Pandemi, Ölüm Nedeni.

INTRODUCTION

Death is the irreversible loss of basic bodily functions; in other words, it is the arrest of the vital functions of a person. According to 2019 data from Turkish Statistical Institute (TURKSTAT), analysed within the context of death causes, the first three diseases to cause death are circulatory system diseases, malignancies and respiratory system diseases, followed by infective and contagious diseases such as pneumonia, diarrhea and tuberculosis (1). Cardiovascular diseases come first, as well, among the death causes across the world. However, infectious diseases such as diarrhea, pneumonia and tuberculosis are more common causes of deaths worldwide than in our country (2). As it can be seen from these data on death causes, infective and contagious diseases are among significant death causes.

Spread of a new and contagious disease across the world is called a pandemic (3). Pandemics are circumstances in which infective diseases are seen in masses and cause deaths of millions of people.

According to the definition of World Health Organization (WHO), for a disease to be recognized as a pandemic, it must be originated by an agent that is encountered for the first time (4). Many pandemics have occurred till this day and millions of people have died in these pandemics. The most well-known and the deadliest of them was the "Spanish Flu (H1N1)" outbreak in 1918. It is estimated that nearly 500 million people was infected by Spanish Flu and 40-100 million people died for this reason (5). In addition, two other pandemics were also occurred; Asian Flu (H2N2) in 1957-1958 and Hong Kong Flu (H3N2) in 1968, and around one million people died in each (6).

The first pandemic of the 21st century was the Swine Flu (H1N1) pandemic, which was first seen in North America in 2009, and around 100-400 thousand people died (7).

In 20th and 21st centuries, regional epidemics that affected millions of people have also occurred, such as Ebola, yellow fever, cholera, SARS, MERS and Zika virus. Nevertheless, the most important pandemic in these days is the COVID-19 pandemic, which was declared as one on 11th March 2020 by WHO. This new isolated virus was called as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease was named by WHO as COVID-19 (8).

COVID-19 pandemic was first began as cases of pneumonia of unknown etiology, in Wuhan city of Hubei province in China (8-10). According to July 2020 data of WHO, there were nearly 15 million confirmed cases and more than 600 thousand confirmed deaths caused by COVID-19, in 215 countries and regions across the world (11). Although treatment modalities and vaccines are being tried to develop against COVID-19 disease, deaths linked to COVID-19 still continue to happen and the proportion of infectious diseases is rising among all causes of death.

Since it is a new epidemic, we aimed to investigate the effect of the COVID-19 pandemic on the number and causes of deaths in our province by comparing the death data of 2020, when the pandemic started, and the first five months of the previous year

MATERIAL AND METHODS

Workgroup Planning: This study was carried out between 1 June 2020 and 1 July 2020 by evaluating the death notification system data of the first five months of 2019-2020 of the Kayseri Provincial Health Directorate. The death notification system is a data system in which the responsible physician uses the International Classification of Diseases (ICD) 10 diagnostic coding system while specifying the causes of death. The completed form is checked and approved by a responsible physician. The study was conducted as a retrospective file review. The total population of Kayseri province, which is located in the Central Anatolian Region, has a metropolitan status and is a semi-rural settlement, is 1,407,409 in 2019, and its population in 2020 is 1,421,455. A total of 6840 people, who were 3349 in the first five months of 2019 and 3491 in the first five months of 2020, were included in our study.

Data Scanning Process: In the study, various data on deaths in Kayseri was evaluated, such as dates (months, seasons), ages, genders and marital statuses of dead persons, death causes and manners of death (contagious disease, forensic, natural death).

ICD which was defined by WHO, is a coding system, used for writing down disease diagnoses, as well as indicating death causes, with certain international rules and reminders on disease and mortality coding it introduced (12). In our study, ICD diagnosis system was used for classification of death causes. Our study was planned in accordance to Helsinki Declaration decisions and by-law on patient rights; and obtained ethics committee approval dated 14.05.2020 and numbered 70, from Clinical Research Ethics Committee of Kayseri City Training and Research Hospital.

Statistical Analysis: Data was evaluated with SPSS (version 21.0) statistical package software. Descriptive statistics; mean, standard deviation, minimum and maximum values were calculated for continuous variables, and categorical variables were expressed as numbers and percentages. One-sample Kolmogorov Smirnov test was used for determining whether numerical values of variables were concordant with normal distribution. Chi-square test was used for determining the relationship between groups and categorical variables. P-value was assumed as $p<0.05$ for statistical significance.

RESULTS

There were 3349 deaths in the first five months of 2019 and 3491 deaths in the first five months of 2020, with a total of 6840 deaths. In the first five months of the years of 2019 and 2020, a total of 6.840 deaths have occurred. 54.6% of these were males and 45.4% were females. Age median of the dead persons was 73 (0-103) in 2019 and it was 73 (0-102) in 2020. The top three most common causes of death in 2019 are cardiovascular diseases, infectious diseases and malignant diseases. In 2020, the ranking is as malignant diseases, infectious diseases and cardiovascular diseases (Table 1).

Table 1. Distribution of Diseases Causing Death by Gender

	2019			2020		
	Male n (%)	Female n (%)	Total n (%)	Male n (%)	Female n (%)	Total n (%)
Cardiovascular Diseases - Hypertension	393 (55.1)	320 (44.9)	713 (100)	356 (57)	269 (43)	625 (100)
Malignancy	397 (66.2)	203 (33.8)	600 (100)	382 (57.8)	279 (42.2)	661 (100)
Infection	344 (50.9)	332 (49.1)	676 (100)	350 (54.1)	297 (45.9)	647 (100)
Respiratory System	141 (51.8)	131 (48.2)	272 (100)	176 (55.7)	140 (44.3)	316 (100)
Neurology	160 (45.3)	193 (54.7)	353 (100)	233 (52.8)	208 (47.2)	441 (100)
Infant Mortality	80 (46.8)	91 (53.2)	171 (100)	83 (55.3)	67 (44.7)	150 (100)
Nephrology	51 (44)	65 (56)	116 (100)	72 (52.6)	65 (47.4)	137 (100)
Gastrointestinal System - Endocrine	72 (40.9)	104 (59.1)	176 (100)	72 (50)	72 (50)	144 (100)
Trauma-Intoxication-Suicide	85 (65.9)	44 (34.1)	129 (100)	55 (61.1)	35 (38.9)	90 (100)
Other	74 (51.7)	69 (48.3)	143 (100)	125 (56.1)	98 (43.9)	223 (100)
COVID-19	0	0	0	37 (64.9)	20 (35.1)	57 (100)
Total	1797 (53.7)	1552 (46.3)	3349 (100)	1941 (55.6)	1550 (44.4)	3491 (100)

52.3% of the dead persons in 2019 were married, 36.1% were widowed/divorced and 11.6% were single. 51.4% of the dead persons in 2020 were married, 37.1% were widowed/divorced and 11.5% were single. Marital statuses of the dead persons were similar in both years (p: 0.064). 13.9% percent of the dead persons in 2019 were graduated from primary school and 13.3% were illiterate. 11.6% of the dead persons in 2020 were graduated from primary school and 11.1% was illiterate.

While the mean of death numbers in the first five months of 2019 was 669.8 ± 128.22, the mean of death numbers in the first five months of 2020 was 698.2 ± 126.63. Monthly death numbers in 2019 and 2020 was similar (p: 0.734), (Table 2).

Table 2. Comparison of Monthly Death Numbers in 2019-2020

Monthly Death Number in 2019	Monthly Death Number in 2020	*p*
Mean±Std	Mean±Std	**0.734**
669.8±128.2291	698.2±126.6381	

*Student t test was used, p-value was assumed as $p<0.05$.

In terms of age groups of dead persons, there was no significant difference between 2019 and 2020 (p: 0.68). There was difference between age groups of dead persons in terms of genders in 2019 (p<0.001); death numbers of male patients aged 18-65 was higher than its female counterpart. Age groups of dead persons were similar in terms of genders in 2020 (p: 0.784), but death numbers of male patients over 65 was higher than females (Table 3).

Table 3. Evaluation of Death Numbers By Age Groups

		2019	Male	Female	2020	Male	Female
0-1	**(n)**	228	105	123	251	146	105
	(%)	6.80%	5.80%	7.90%	7.20%	7.50%	6.80%
Age 1-18	**(n)**	53	31	22	56	29	27
	(%)	1.60%	1.70%	1.40%	1.60%	1.50%	1.70%
Age 18-65	**(n)**	824	540	284	893	498	395
	(%)	24.60%	30.10%	18.30%	25.60%	25.70%	25.50%
Age 65 and over	**(n)**	2244	1121	1123	2291	1268	1023
	(%)	67.00%	62.40%	72.40%	65.60%	65.30%	66.00%

In terms of death causes by genders in 2019, cardiovascular diseases, malignancies and deaths caused by trauma, suicide and intoxication were more common in males, while neurological, nephrological, gastrointestinal system-endocrine associated deaths were more common in females (p<0.001). In 2020, all-cause death numbers, including COVID-19, were higher among males (p:0.514), (Table 1). 21.3% of deaths in the first five months of 2019 were associated with

cardiovascular diseases and hypertension; this rate was 17.9% in 2020. Deaths caused by malignancies were 17.9% of total in 2019, and it was 18.9% in 2020. Deaths associated with infectious diseases occurred in rates of 20.2% in 2019 and 18.5% in 2020. In 2020, 163,000 cases were seen in Turkey in the first five months, while 944 people had COVID-19 infections in Kayseri in the same period. Again, 1.6% of deaths in the same period were due to COVID-19 infection. 1.6% of deaths in 2020 were caused by COVID-19 infection (Table 4).

Table 4. Yearly Comparison of Diagnoses of Death

	2019		2020		
	Number	**Percentage**	**Number**	**Percentage**	***p* value**
Cardiovascular Diseases - Hypertension	713	21.3	625	17.9	**<0.001**
Malign Diseases	600	17.9	661	18.9	0.146
Infection	676	20.2	647	18.5	0.092
Respiratory System	272	8.1	316	9.1	0.092
Neurological Diseases	353	10.5	441	12.6	0.004
Infant Mortality	171	5.1	150	4.3	0.064
Nephrology	116	3.5	137	3.9	0.172
Gastrointestinal System - Endocrine	176	5.3	144	4.1	0.016
Trauma - Intoxication -Suicide	129	3.9	90	2.6	0.002
COVID-19	0	0	57	1.6	**<0.001**
Other	143	4.3	223	6.4	**<0.001**

***** Chi-Square test was done, p-value was assumed as $P<0.05$.

Total mortality rate caused by infectious diseases in 2019 were 20.2%, while in 2020 total mortality rate from infectious diseases, including COVID-19, was 20.1%.

DISCUSSION

Many studies that analyse death causes were conducted in Turkey and worldwide. Utilizing the results of these studies, preventable death causes, such as tuberculosis, maternal and infant mortalities and infectious diseases, were reduced (13, 14). However, from time to time, newly occurred infections also spread across the world, caused pandemics and resulted in deaths of millions of people (15). Significance of infectious diseases among death causes was understood during these pandemics.

For these reasons, in our study, where we evaluated how the COVID-19 pandemic affected the number of deaths in our province, the death data of the first five months of 2019-2020 were examined. It was observed that there was no significant difference in monthly death numbers. Death numbers in 2019 and 2020 were similar, while there were changes in diagnoses of death causes.

In a study conducted in Adnan Menderes University, it was seen that 45.8% of people that died in 2008 were female and 54.2% of them were male, while in 2009 it was 46.2% female and 53.8% male (16). In another study that analysed mortality statistics in Turkey between 2009 and 2016, it was seen that male and female mortality percentages did not differ from year to year (17). In our study, gender-based death number distribution was also observed to be similar to the literature. Evaluating the marital statuses of the dead persons in both years, no significant difference was found in our study and obtained data was seen to be comparable with the literature (18).

In many studies that analyse death causes worldwide and by country, mortality rates of males of adult age groups were observed to be higher than females in same age group (19, 20). Deaths associated with cardiovascular system diseases being more common in males of this age group is indicated to be the reason for this situation (14). In our study, similar to the literature, death numbers of males in adult age group in the first five months of 2019 was found to be significantly higher than females of same age group. Distribution of age-linked death numbers in other age groups was also similar to the literature and it was the highest for males and females over 65 (13, 17, 20). In the first five months of 2020, death numbers of males of adult age group were similar to females of same age group. We consider that the decrease of male death numbers in adult age group in 2020 could be linked to decisions taken in order to fight COVID-19 disease, such as lockdowns and quarantine measures, culminating a decrease in deaths caused by trauma like traffic accidents and murders, which is an important cause of death for males in this age group.

An important analysis conducted between 1990 and 2013 found that trauma-related deaths were significantly higher in males in all age groups, except for those aged 80 and over, where the gender gap disappeared (21). In “Final Report on Disease Burden”, which was published in December 2004 within the scope of National Project on Disease Burden and Cost Effectiveness conducted in our country, it was emphasized that deaths caused by trauma in males aged 15-25 were much higher than females of same age group, while age-based distribution of deaths caused by trauma was similar

in both genders (13). Significant decrease in crime rates and traffic accidents as a result of decisions and measures taken in order to fight COVID-19 disease, supports our opinion about the decrease of male mortality rates in adult age group (22).

In our study, non-contagious diseases, like cardiovascular system, hypertension, malignancies, gastrointestinal-endocrine system, nephrology and respiratory system diseases such as chronic obstructive pulmonary disease (COPD), were more common than contagious diseases in the first five months of 2019 and 2020, similar to the literature. In many studies that analyse yearly changes in death causes and mortality rates in Turkey and in the world, death causes and mortality rates were analysed under main titles of deaths caused by traumas, non-contagious diseases and contagious diseases, such as pneumonia, enteritis, tuberculosis and malaria; and it was observed that mortality rates linked with non-contagious diseases were much higher than of contagious diseases (13, 18, 20, 23).

In our study, as well, total rate of deaths linked to non-contagious diseases was higher than the rate of deaths linked to infectious diseases, including contagious diseases like pneumonia, enteritis and tuberculosis. Also the rate of deaths caused by traumas, intoxication and suicide among all-cause deaths turned out to be similar with the studies in the literature (17, 24).

In our study, respiratory tract diseases increased proportionally compared to the previous year. However, there is no statistically significant difference and this increase did not affect death numbers.

There are differences between death causes of the first five months of 2019 and 2020. While cardiovascular diseases and hypertension were the most fatal diseases with a rate of 21.3% in the first five months of 2019, this rate has decreased to 17.3% and cardiovascular diseases and hypertension have fallen to third rank among fatal diseases in 2020.

Diseases of cardiovascular system and hypertension are the most common causes of death across the world and in Turkey; their risk factors are quite well-defined (25, 26). Male gender, advanced age, obesity and dietary habits, diabetes, sedentary life, emotional stress and some other factors constitute the risk factors of cardiovascular diseases. Home isolation and quarantine practices were implemented for a long time by the government for individuals over 65, due to them being at high risk regarding to COVID-19. Although sedentary lifestyle is a risk factor for cardiovascular system diseases, and individuals over 65 constitute the riskiest age group for cardiovascular diseases; we consider that stays of these persons at their homes within the context of isolation and quarantine measures, may have resulted in cautiously applying to hospitals earlier by themselves or other family members living in the same house, for the slightest changes in their medical conditions, thereby reaching early diagnosis and treatment opportunities, and consequently leading to a decrease in mortalities. Moreover, we also consider that, having been in administrative leave for a long period during COVID-19 pandemic, persons with chronic diseases, such as cardiovascular system diseases and hypertension, were kept away from emotional stress, which is a serious risk factor regarding cardiovascular system diseases and hypertension; resulting them to be protected from fatal and unwanted acute incidents of these diseases like sudden cardiac death (27).

We also observe that, another change in the rates of fatal diseases, directly or indirectly linked to COVID-19 pandemic and measures taken during the pandemic, has happened in deaths linked to neurological diseases. It is seen that the death numbers linked to neurological diseases in 2019 increased significantly in the first five months of 2020.

Diseases of nervous system and sense organs, which were the fourth most common cause of death in Turkey regarding to 2018 data of the Turkish Statistical Institute, have also been seen as the fourth most common cause in our study (1). In some other studies conducted in our country, stroke was the third most common death cause (14, 28).

The title of neurological diseases is a wide spectrum of diseases. This complicates the evaluation of the effects of COVID-19 pandemic and pandemic-related measures, like isolation and quarantine, on the course of diseases under the title of neurological diseases.

In line with all these information, we consider that already extended hospital application periods of neurological patients, who had developed disabilities caused by previous neurological incidents and have comorbidities, were even more prolonged as a result of the knowledge of COVID-19 disease to progress more fatal in persons over 65 and the fear of the risk of getting this disease in hospitals; resulting newly-emerged neurological incidents to show a more fatal course.

Another case, in which change of death numbers can be seen clearly as a result of COVID-19 pandemic and the implementation of pandemic-related measures and prohibitions, is the significant decrease of deaths caused by traumas such as traffic accidents, intoxication and suicides in the first five months of 2020, in comparison with the same period of 2019. We consider this situation to be linked with the decline of trauma rates in especially males of adult age group, as a result of isolation measures, such as lockdowns and quarantines, which were implemented in 2020 in the context of fight against COVID-19 pandemic since the detection of first case in Turkey.

Coercive factors occurring during pandemics have led to an increase in suicide cases (29,30). However, the reason for the decrease in suicide cases in our study may be that family support, which is a preventive factor for suicide (31), was felt more during isolation, quarantine and lockdown measures.

In addition, the loyalty support services, which provide the needs of people in quarantine during the pandemic and can be easily reached with a fixed number, have made a significant contribution to reducing the negative psychological impact.

Since December of 2019, when COVID-19 disease was understood to be a new pandemic, studies have begun on diagnosis, treatment and vaccines against this disease. Many studies also have been launched in order to find a cure for COVID-19 disease, definitive treatment yet to be found. Several modalities were tried in treatment, such as mesenchymal stem cell treatment and many agent and plasma treatments, including the one used for the treatment of SARS, because of the resemblance with the agent of SARS outbreak; however the definitive treatment of COVID-19 disease could not been discovered yet (32, 33, 34).

Because a definitive treatment has not yet been discovered and the vaccination endeavours do not seem to be completed in short term, isolation still appears to be the most effective way to control COVID-19 pandemic. Indeed, isolation measures had worked in the fight against the 1918 "Spanish Flu" pandemic, when not any antiviral and antibacterial treatments had been discovered yet. For example, during the 1918 "Spanish Flu" pandemic, no cases was detected in American Samoa, where isolation rules could be implemented; while in Western Samoa, which is just a few kilometres away but could not implement isolation from the world, 22-23% of the population have died from the flu (5).

We too, in our study, have observed the effects on causes of death, directly, and by secondary factors indirectly, resulted from decisions such as lockdowns and quarantines, as a part of measures taken by the government in the context of isolative-preventive health services.

Limitations

Our study was conducted in a specific province and in a limited region. In addition, cases were first seen in March in our country, and this study includes only the first two months of cases. Because it includes the first period of the pandemic and the population is narrow, the number of cases and deaths may not reflect the overall. These situations constitute the limitations of our study. Future studies that would be conducted within a longer period may pose sufficient data.

CONCLUSION

Pandemics are important occasions, which can cause serious results on sociodemographical data of related countries during their span, with effects enduring for years. In these days, COVID-19 pandemic is globally the most important health problem. Without a doubt, COVID-19 pandemic has already caused serious changes in every domain of life. More clear effects of the pandemic on yearly death causes and rates will be seen in the upcoming years, with more studies in this area. Our study showed that there was no significant change in the number of deaths in our province in the early days of the pandemic, but the causes of death changed. For this reason, we think that it will be a source for new studies to be done in the future.

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RESEARCH ARTICLE

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COVID-19 Course in Patients Receiving Pneumococcal Vaccine

ABSTRACT

Objective: The coronavirus pandemic emerged at the end of 2019 and still affects the whole world, causing severe deaths. The COVID-19 vaccine is highly anticipated, but the emphasis is also given to other vaccines. In this study, the data of 16 cases known having received a pneumococcal vaccine during the COVID-19 period were examined.

Methods: Of the 200 COVID-19 cases aged over 65, data of 16 patients who have had pneumococcal vaccination were accessed using the hospital health registry and the national health system records (https://enabiz.gov.tr/). Prognostic factors and COVID-19-related findings of these patients were given in frequency tables. In addition, all raw data were presented in a detailed table.

Results: Most of the cases were PCR positive (68.75%), and in 68.75% of the persons, the CT was compatible with COVID-19. Fourteen of the cases were treated by hospitalization. One patient was followed as an outpatient, and one case had already died when brought to the emergency room.

Conclusions: Data on cases known to have received the pneumococcal vaccine, which became important during the COVID-19 outbreak, were presented. This work will motivate researchers to conduct large-scale studies.

Keywords: Vaccine, Pneumococcal Vaccine, Covid-19, Coronavirus, Pandemic.

Pnömokok Aşısı Olduğu Bilinen Hastalarda Covid 19 Seyri

ÖZET

Amaç: 2019 yılı sonlarında ortaya çıkan ve halen tüm dünyayı etkileyen coronavirüs pandemisi ciddi sayıda vaka ve ölümlere neden olmaktadır. Covid-19 aşılarının dünyada hızla yapılmaya başlandığı bu dönemde diğer aşılar da önemsenmektedir. Özellikle pnömokok aşısının etkileri bu dönemde merak edilmektedir. Bu çalışmada pnömokok aşısı olduğu bilinen 16 vakanın covid 19 dönemindeki verileri incelendi.

Gereç ve Yöntem: 65 yaş üstü 200 kişilik covid 19 pozitif hastanın içinden pnömokok aşısı olduğu bilinen 16 vakanın verilerine hastane sistemleri ile ulusal sağlık sisteminden yararlanılarak ulaşıldı. Bu vakalara ait kronik hastalık ile covid dönemi prognostik faktörleri frekans tabloları ile verildi. Ayrıca tüm vakalar detaylı bir tablo ile çözümlendi.

Bulgular: 16 vakanın hepsinde kronik hastalık tanısı vardı. Hastalardan dördünün durumu ölümle sonuçlandı. Vakaların çoğu PCR pozitifti (%68.75) ve yine %68.75 kişide BT Covid ile uyumluydu. Vakalardan 14 tanesi hastaneye yatırılarak tedavi edildi. 1 tanesi ayaktan takip edildi. Bir vaka ise ölü olarak acil servise getirilmişti.

Sonuç: Son derece önemli olan ve covid 19 döneminde önemi gittikçe artan pnömokok aşısının önceden yapıldığı bilinen 16 vakaya ait veriler verildi. Bu çalışmanın büyük ölçekli çalışmalara kaynak niteliğinde olacağı öngörülmektedir.

Anahtar Kelimeler: Aşı, Pnömokok Aşısı, Covid-19, Koronavirüs, Pandemi.

INTRODUCTION

In December 2019, a new coronavirus caused multiple cases of severe pneumonia in Wuhan, China (1, 2). Afterward, it was named by the World Health Organization (WHO) "Coronavirus disease 2019" (COVID-19), and its etiological agent was determined as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) (3). The human-to-human transmission was first confirmed in January 2020, and the WHO declared COVID-19 a Public Health Emergency. Later, the WHO announced that the COVID-19 is a global pandemic, with 400,000 thousand cases being recorded worldwide (3, 4). More than 90 million cases and over two million deaths were reported by January 2021 (5).

Currently, no approved specific drug or method is available to treat COVID-19, other than palliative and preventive medicine. Authorities all over the world recommend hand washing, wearing masks, and social distancing to their citizens. As a result of various studies conducted in many countries around the world, many vaccines have now been approved to prevent COVID-19 (6). However, immunological and clinical evidence of the benefits of influenza, pneumococcal and tuberculosis vaccines related to COVID-19 continues to be discussed (7, 8). These vaccines can have a direct or indirect effect on COVID-19 with different types of immune responses.

Additionally, these vaccines may have indirect effects by reducing the burden of viral and bacterial respiratory diseases on patients and countries during the pandemic period (9). In this respect, a limited number of studies showing the effects of these vaccines on COVID-19 are seen in the literature. This study aimed to present the results of 16 people who had COVID-19 disease and were known to have the pneumococcal vaccine before the pandemic as registered in the national health system.

MATERIAL AND METHODS

Research Type: Our study is a retrospective descriptive and observational study.

Case Selection: Sixteen of the 200 patients over the age of 65 with positive COVID-19 PCR results detected until June 2020 in the Kocaeli province were included in the study. Patients over the age of 65 were selected because the pneumococcal vaccine was free for this group.

Information on chronic diseases, such as diabetes mellitus, hypertension, heart disease, chronic lung diseases, and kidney disease, was derived from data systems and recorded to control additional factors that could affect the clinical course.

Data Collection Tools: COVID-19 Polymerase Chain Reaction (PCR) test result, computed tomography (CT) result, sex, age, presence of chronic disease, intensive care stay, intubation status, mortality status, and hospitalization information were obtained through the data system provided by the provincial health directorate. Additionally, the pneumococcal vaccination status of the patients within the last 1 year was obtained from the national health record system and E-health (https://enabiz.gov.tr/) data system.

Permissions: Necessary permissions for the study were obtained first from the Turkish Ministry of Health and then from the Kocaeli Provincial Health Directorate. Besides, an ethics committee approval was obtained from the Health Sciences University Kocaeli Derince Training and Research Hospital Clinical Research Ethics Committee (28.05.2020; 2020/67).

Statistical Analysis: Descriptive statistics were presented as means and standard deviations for numerical data and as numbers and percentages for categorical data. The Statistical Package for the Social Sciences (SPSS, version 23X, IBM, Armonk, New York 10504, NY, USA) was used in the analyzes.

RESULTS

Data were presented for 16 patients who were COVID-19 (PCR and/or CT) positive and who had a pneumococcal vaccine within the last year. All cases were of domestic origin. The patients were diagnosed during March, April, May, and June 2020. Furthermore, one patient had an influenza vaccine before developing COVID-19. The mean age of these patients was 73.44±5.69. Half of the patients were male, and half were female. All patients had at least one chronic disease. Most of the patients were married. The sociodemographic data of the patients and their chronic conditions are given in detail in Table 1.

Table 1. Descriptive data and chronic disease status of the patients.

	Features	**n**	**%**
Age (mean ± SD)		73.44±5.69	
Gender	Male	8	50.0
	Female	8	50.0
Marital status	Married	10	62.5
	Widowed	5	31.3
	Single	1	6.3
Presence of Hypertension and/or Heart Disease	Present	13	81.3
	Absent	3	18.8
Diabetes Mellitus	Present	8	50.0
	Absent	8	50.0
Chronic Renal Failure	Present	4	25.0
	Absent	12	75.0
COPD and/or Asthma	Present	3	18.3
	Absent	13	81.3

COVID-19 PCR results, CT results, admission status to the hospital and intensive care unit, the presence of pneumonia, mortality, and intubation were examined. While 68.8% (n=11) of the patients were PCR positive, 31.3% (n=5) were PCR negative. While no CT findings were found in 3 (18.8%) patients, significant findings concerning COVID-19 were observed in the CT of the remaining patients. The disease ended up with death in four (25.0%) patients, while the others recovered. PCR, CT results, and other prognostic data of all patients are given in Table 2.

Table 2. Distribution of some prognostic data, PCR, and CT results

	Features	**n**	**%**
PCR	Positive	11	68.75
	Negative	5	31.25
CT	COVID-19 compatible	11	68.75
	Viral pneumonia compatible	2	12.50
	No CT available	3	18.75
Hospitalization	Yes	14	87.50
	No	2	12.50
Pneumonia	Yes	7	43.75
	No	9	56.25
Follow-up in Intensive Care	Yes	5	31.25
	No	11	68.75
Intubation Status	Yes	4	25.00
	No	12	75.00
Result	Admitted with symptoms and died	4	25.00
	Admitted with symptoms, improved after admission	3	18.75
	Applied for screening or due to contact without symptoms	9	56.25

Table 3 shows raw COVID-19 data of all cases. It is seen here that a patient with mortality was not hospitalized. Records indicated that this case arrived in the emergency room with cardiac arrest. As the table suggests, those diagnosed with chronic obstructive pulmonary disease and asthma recovered, while all patients who died had hypertension or heart disease. In addition, the antiaggregant and anticoagulant treatment status of the patients before COVID-19 was also examined (Table 3).

Table 3. Descriptive and prognostic data of all cases

Patients	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16
Age	85	76	66	69	73	76	82	69	72	76	71	67	82	68	73	70
Gender (F: female, M: male)	F	M	M	F	M	F	M	F	M	M	M	F	F	F	M	F
Marital status (M: married, S: single, W: widow)	W	M	M	M	M	M	W	W	M	M	M	W	W	M	S	M
Month (Ap: April)	May	Ap	March	June	May	May	May	May	Ap	Ap	Ap	Ap	Ap	Ap	May	Ap
Presence of symptoms		√		√	√	√			√				√		√	
PCR +	√	√	√	√		√	√	√		√		√			√	√
CT (N: Normal, C: COVID, V: Viral)	N	N	N	C	C	C	C	C	C	C	C	C	C	C	V	V
HT or HD	√	√	√	√		√	√	√	√			√	√	√	√	√
DM	√	√					√	√		√		√	√	√		
CRF							√			√					√	√
COPD or Asthma					√				√		√					
Hospitalization	√			√	√	√	√	√	√	√	√	√	√	√	√	√
Pneumonia				√		√			√		√	√	√		√	
Intensive Care		√				√	√						√		√	
Intubation		√				√							√		√	
Taking AA or AC Drugs			√			√	√		√						√	
Flu vaccine		√														
Death		√				√							√		√	

Yes (√), Chronic Obstructive Pulmonary Disease (COPD), Chronic Renal Failure (CRF), Hypertension (HT), Heart Disease (HD), Computed Tomography (CT), Antiaggregant (AA), Anticoagulant (AC).

DISCUSSION

In this retrospective study, the COVID-19 infection process of 16 cases known to have been immunized against pneumococci before getting COVID-19 was detailed. Pneumococcal vaccine is recommended for routine use in elderly adults in Turkey as well as in many countries and is provided free of charge in primary health care institutions (10-13). Still, it was seen that very few patients preferred to receive the pneumococcal vaccine before COVID-19. However, it is known that after the COVID-19 pandemic, there is a raised interest in pneumococci and other vaccines (7, 8).

Studies show that immunocompromised people have low pneumococcal vaccination rates (14). This situation demonstrates that it will be challenging to prevent pneumococcal deaths during the COVID-19 period. As a matter of fact, it was seen in our study that only 16 out of 200 COVID-19 positive patients over the age of 65 were vaccinated against pneumococci. However, the most blamed source of infection during the pandemic and seasonal infections is known as pneumococci (15, 16). In some studies, it was reported that pneumococcal bacteria were isolated from a small number of patients from COVID-19 patients (17). This may be related to the early initiation of antibiotherapy.

Nevertheless, pneumococcal vaccination rates should be increased, especially in people over 65 and people with chronic diagnoses. However, there is a risk of COVID-19 transmission during the vaccination of these people. Despite these handicaps, the health systems of countries should take measures to reduce the risk of transmission of patients and find ways to reach and vaccinate a large number of people not affected by the epidemics. Besides, it is known that people's interest in this issue is increasing (7).

In our study, deaths occurred despite the pneumococcal vaccine. This condition may be related to the fact that all patients had at least one chronic disease and were elderly. It has been shown in many studies that death proportions increase with age and the presence of chronic diseases (2, 18). On the other hand, hypertension or heart disease, diabetes mellitus, chronic obstructive pulmonary diseases, and chronic kidney diseases were present in most of our cases; the possible reason being our selection of patients over the age of 65. The outcome of all intubated cases resulted in death. This is similar to published data and is usually associated with the intubation of worsening patients.

The primary limitation of the study is the insufficient number of cases. Furthermore, since there was no control group, a comparison with COVID-19 positive patients without pneumococcal vaccine could not be made. Another limitation is that we could not present other laboratory data of the studied cases.

CONCLUSION

It is known that in the COVID-19 pandemic affecting the whole world, vaccines are more crucial than during other times. Today as well as in different eras, vaccines have always been the most essential factor in preventing diseases. In our study, it is seen that the pneumococcal vaccine is less preferred in people over 65 years of age. That the interest in vaccines should increase all over the world after the COVID-19 outbreak is over.

Declaration of Competing Interest: The authors declare no conflict of interest.

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RESEARCH ARTICLE

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Teachers' Approaches to Strengthening Their Immune Systems during the COVID-19 Pandemic

ABSTRACT

Objective: Strengthening the immune system constitutes an important part of struggling with COVID-19. The aim of this study was to evaluate the approaches of the teachers to strengthen their immunity during COVID-19 pandemic in Turkey.

Methods: This descriptive study was conducted between 15 June - 15 July 2020 in teachers using social media. The 31-questioned online survey included multiple-choice questions about sociodemographic characteristics, health conditions before and after the onset of the COVID-19 pandemic, lifestyle changes such as nutrition, sleep, stress and exercise, information about the immune system, methods used to strengthen immunity, and training needs of the participants.

Results: The median age of all 500 participants was 37 (min: 22, max: 69) years and 76.8% were women. Of the teachers, 47.4% stated that they gained weight during COVID-19 pandemic period. Fruit and vegetable consuming (52.8%), praying (36.2%) and sunbathing (26.0%) were the most common methods to strengthen immunity. Of the teachers, 45.2% (n:226) were using supplementary products. The most commonly used supplements are; Vitamin D (17%), vitamin C (14.2%) and multi-vitamin (10.8%). While there was no statistically significant difference between supplementary product usage and income levels (p = 0.839), there was a significant difference with allotting of money for their health (p = 0.001). Of the teachers, 46.2% were confident about their knowledge on immunity strengthening methods and 61.2% stated that they would like to be trained.

Conclusions: In this study, more than half of the teachers stated that their stress increased during the pandemic period and almost half of them gained weight during this period. Teachers are eager to learn how to improve their health. Informing the teachers, who are good role models for the society, about the methods that strengthen the immune system, may cause permanent behavioral changes in the society.

Keywords: COVID-19, Immune System, Nutrition, Healthy Lifestyle, Complementary Therapies.

Öğretmenlerin COVID-19 Pandemisi Döneminde Bağışıklık Sistemini Güçlendirme ile İlgili Yaklaşımları

ÖZET

Amaç: Bağışıklık sistemini güçlendirmek, COVID-19 ile mücadelenin önemli bir bölümünü oluşturur. Bu çalışmanın amacı, öğretmenlerin COVID-19 pandemisinden nasıl etkilendiklerini ve bağışıklıklarını güçlendirmeye yönelik yaklaşımlarını değerlendirmektir.

Gereç ve Yöntem: Tanımlayıcı tipteki bu çalışma, sosyal medya kullanan öğretmenlere 15 Haziran - 15 Temmuz 2020 tarihleri arasında anket uygulanarak gerçekleştirilmiştir. Otuzbir soruluk online ankette sosyodemografik özellikler, COVID-19 pandemisinin başlamasından önceki ve sonraki sağlık koşulları, beslenme, uyku, stres ve egzersiz gibi yaşam tarzı değişiklikleri, bağışıklık sistemi hakkındaki bilgileri, bağışıklığı güçlendirmek için kullanılan yöntemler ve eğitim ihtiyaçları hakkında çoktan seçmeli sorular yer aldı.

Bulgular: 500 katılımcının medyan yaşı 37 (min: 22, max: 69) yıl ve %76.8'i kadındı. Öğretmenlerin %47.4'ü COVID-19 pandemi döneminde kilo aldıklarını belirtti. Bağışıklığı güçlendirmek için kullandıları en yaygın yöntemler, meyve ve sebze tüketimi (%52.8), dua etmek (%36.2) ve güneşlenmek (%26.0) olarak tespit edildi. Öğretmenlerin %45.2'si (n: 226) takviye ürün kullanıyordu. Takviye preparatlardan en sık kullanılanlar; vitamin D (%17) , vitamin C (%14.2) ve multi vitamin (%10.8) idi. Takviye ürün kullanımı ile gelir seviyeleri arasında istatistiksel olarak anlamlı bir fark yok iken (p=0.839), sağlıklarına para ayırma ile (p = 0.001) anlamlı farklılık vardı. Öğretmenlerin %46.2'si bağışıklığı güçlendirme yöntemleri konusundaki bilgilerine güvenirken, %61.2'si bu konuda eğitim almak istediğini belirtti..

Sonuç: Çalışmamızda, öğretmenlerin yarıdan fazlası pandemi döneminde streslerinin arttığını ve bu dönemde neredeyse yarısı kilo aldığını belirtti. Öğretmenler sağlıklarını nasıl iyileştireceklerini öğrenmeye isteklidir. Toplum için iyi bir rol model olan öğretmenlere, bağışıklık sistemini güçlendiren yöntemler hakkında bilgi verilmesi, toplumda kalıcı davranış değişikliğine sebep olabileceğini düşünmekteyiz.

Anahtar Kelimeler: COVID-19, Bağışıklık Sistemi, Beslenme, Sağlıklı Yaşam, Tamamlayıcı Tedaviler.

INTRODUCTION

In December 2019, a disease emerged in Wuhan, China, with clinical symptoms of acute upper respiratory tract infection (1). COVID-19 is a new type of corona virus quickly spreading among humans through droplets, and the World Health Organization declared it is a controllable pandemic on March 10, 2020 (2). That same day, it was declared that the virus was also detected officially in Turkey (3).

Besides many negative consequences in terms of health, economic and social aspects, COVID-19 pandemic also has negative consequences in the field of education (4). This study is important as it was carried out at the early months of the pandemic, when schools were closed and distance education was initiated. Because, it has been observed that individuals perceive an increased level of fear, anxiety and stress, especially during the emergence of the epidemic and the increase in the number of cases (5).

As pandemic termination time cannot be assumed, strengthening the immune system is important. Since the Spanish influenza pandemic in 1918, both insufficient and excessive nutrition have been found to negatively affect viral infection prognosis (6). Obesity, additional chronic diseases, and an unhealthy lifestyle interact to impair immune function and increase the risk of serious infectious diseases (7). Physical exercise is the strongest non-pharmacological and most positive immunomodulatory intervention. A moderate degree of aerobic exercise (fit-walking, cycling, swimming and running) has a anti-inflammatory effect, decreasing alpha-TNF, MCP-1 and IL-6 and increasing IL-10 (6).

In pandemics whose influence has expanded so much, the issue must be dealt with in a very comprehensive way in order to cope with the disease and overcome it with the least damage. Such an approach is to exhibit the many stakeholders (media, health care organizations, educators, general ducation services, public institutions, all academic fields, etc.) is extremely important to act together (8).

Teachers and health workers are two important occupational groups that interact with each other and set role models for the society. At the Ottawa First Health Promotion Conference (1986), while discussing health promotion at a universal level, it was stated that health promotion activities are not only the responsibility of the health sector, but a multisectoral working environment is needed (9).

The students are spending more time with their teachers than their parents and other relatives. Teachers adopting a healthy life will also have a lasting impact on students.

The aim of this study was to evaluate how teachers are affected by the COVID-19 pandemic and their approaches to strengthening their immunity.

MATERIAL AND METHODS

This descriptive study was approved by the Ministry of Health and ethical board of the xxx University (2019/2619) and conducted according to the ethical principles of Helsinki Declaration.

The study group was consisted of teachers who had social health insurance, and were using social media accounts. A literature review with words “immune system, nutrition, healthy lifestyle” was made in PubMed, Clinical Key and Google Scholar databases and an online survey with 31 questions was prepared according to the previous studies. Participants were reached through national ‘Turkish teacher’s Facebook group’. Ten pilot survey were fulfilled and the questions were arranged according to the feedback of the participants. The survey could be completed in about 15 minutes. It contained multiple-choice questions on socio-demographic characteristics, health conditions before and after the initiation of the COVID-19 pandemic, lifestyle changes, such as nutrition, sleep, stress and exercise, knowledge on the immune system, methods used to strengthen immunity and training needs of the participants. The survey was performed online between June 15 and July 15, 2020, in three months after the schools were closed due to the COVID-19 pandemic in Turkey. All volunteers (n = 513) approved to join the online study. Thirteen participants did not complete the survey, so they were excluded during data analysis.

Statistical Analysis: Data coding and statistical analyses were done using SPSS 13.0. Minimum and maximum values, means, standard deviations, medians, percentage values and chi-square, Mann Whitney U, Kruskal-Wallis and paired sample T tests were used. The significance level was accepted as $p < 0.05$.

RESULTS

The median age of all 500 participants was 37 (min: 22, max: 69) years old. Socio-demographic characteristics of the participants are given in Table 1.

Table 1. Socio-demographic characteristics of participants

	n	%
Gender		
Female	384	76.8
Male	116	23.2
Working status		
Unemployed	19	3.8
Works in a public institution	411	82.2
Works in a private institution	55	11.0
Retired	7	11.4
Other	8	1.6
Income Level		
Income lower than the expenses	68	13.6
Income is equal to the expenses	300	60.0
Income is higher than the expenses	132	26.4

About 59% of the participants (n = 295) allotted a small share of their budget for their health needs, 23.2% (n = 116) allotted a high share and 19.4% (n = 97) allotted no money for their health. Income levels were correlated with the allowance for health (p < 0.001). Median body mass index (BMI) of the participants was 25.14 (min:16.53 - max:43.55) kg/m^2 (Table 2).

Table 2. BMI values according to gender

BMI classification	Gender		Total	χ^2	P
	Female n (%)	Male n (%)	n (%)		
Thin (<18.5 kg/m^2)	9 (2.3)	0 (0.0)	9 (1.8)	53.709	<0.001
Normal (18.5-24.9 kg/m^2)	236 (61.5)	32 (27.6)	268 (53.6)		
Overweight (25-29.9 kg/m^2)	97 (25.3)	58 (58.6)	165 (33.0)		
Fat (≥30 kg/m^2)	42 (10.9)	16 (13.8)	58 (11.6)		

BMI: Body mass index

While 47.4% (n:237) gained weight during COVID-19 pandemic, 41.4% (n: 207) stated that their weight were stable and 11.2% (n:56) lost weight. There was not any significant difference between the genders (p=0.318). Weight change and BMI changes were significantly related (p=0.007).

Of the participants, 23.8% (n:119) had chronic diseases. Gender was not related with chronic disease presence (p=0.252) whereas age and chronic disease presence were significantly related (p<0.001).

Of the teachers, 21.8% (n:109) had regular medical screening even though they did not have complaints. There was no significant difference between the genders (p:0.061).

Of participants, 46.2% (n:231) believed that they knew immune system strengthening methods very well, 49.4% (n:247) had few information while 4.4% (n:22) had no idea. A significant relationship was present between their knowledge and caring about healthy nutrition (p<0.001).

Of the teachers, 64.4% (n:322) stated that they never smoked while 27.6% (n:138) were still smoking and 8% (n:40) quitted. Among smokers, 62 (44.9%) smoked the same amount, 50 (36.2%) smoked less and 26 (18.8%) stated that they increased number of cigarettes during COVID-19 pandemic. Smoking rate was significantly higher in males (p<0.001).

According to the participants, there was no difference in their health condition before and during COVID-19 (p:0.294).

Of the participants, 3.8% (n:19) were using anti-depressants and two (0.4%) of them initiated during COVID period.

The participants' stress levels, exercising condition, sleep duration and quality changes with COVID-19 pandemic are listed in Table 3.

Table 3. Evaluation of lifestyle changes during COVID-19 pandemic based on genders

	How would you evaluate your lifestyle changes in COVID-19 compared to the past?									p
	Increased			Decreased			Didn't change			
	Female n (%)	Male n (%)	Total n (%)	Female n (%)	Male n (%)	Total n (%)	Female n (%)	Male n (%)	Total n (%)	
Stress level	230 (59.9)	44 (37.9)	274 (54.8)	56 (14.6)	22 (19.0)	78 (15.6)	98 (25.5)	50 (43.1)	148 (29.6)	p<0.001
Exercising Condition	86 (22.4)	17 (14.7)	103 (20.6)	132 (34.4)	56 (48.3)	188 (37.6)	166 (43.2)	43 (37.1)	209 (41.8)	p=0.019
Total sleep duration per day	231 (60.2)	82 (70.7)	313 (62.6)	59 (15.4)	14 (12.1)	73 (14.6)	94 (24.5)	20 (17.2)	114 (22.8)	p=0.844
Sleep Quality	72 (18.8)	20 (17.2)	92 (18.4)	173 (45.1)	50 (43.1)	223 (44.6)	139 (36.2)	46 (39.7)	185 (37.0)	p=0.789
Spending time for one's self	231 (60.2)	82 (70.7)	313 (62.6)	59 (15.4)	14 (12.1)	73 (14.6)	94 (24.5)	20 (17.2)	114 (22.4)	p=0.117
Caring about healthy nutrition	128 (33.3)	34 (29.4)	152 (30.4)	94 (24.5)	26 (22.4)	120 (24.0)	162 (42.2)	56 (48.3)	218 (43.6)	p=0.506

Seven (1.4%) participants had positive COVID-19 test while 98.4% (n:492) did not performed any test.

Of the participants, 79.0% (n:395) were afraid of being infected by COVID-19 and fear was significantly higher in women (p:0.003).

Methods and treatments applied by the participants to strengthen their immunity during COVID-19 pandemic are listed in Table 4. Of the teachers, 54.8% (n:274) were not using any supplementary products. Among 226 individuals using supplementary products, 121 (53.53%) said quality/certificate of the product is important, 97 (42.92%) used a product recommended by their doctor, 77 (34.07%) preferred the ones sold at pharmacy and 17 (7.52%) cared the price of the product.

Income levels didn't affect supplementary product usage (p=0.839) but it was correlated with allotting money to their health (p=0.001).

Table 4. Methods and treatments to strengthen immunity during COVID-19 pandemic

Methods	n	%	Treatments	n	%
Vegetable and fruit-based nutrition	264	52.8	Using multi vitamin reinforcement	54	10.8
Praying	181	36.2	Traditional and Complementary Medicine	9	1.8
Sunbathing	130	26.0	Taking vitamin D supplement	85	17.0
Probiotics rich nutrition	126	25.2	Taking probiotic supplement	16	3.2
Consuming honey	113	22.6	Using Propolis supplements	37	7.4
Eating fish for 1-2 times a week	70	14.0	Taking Omega 3 supplement	40	8.0
Exercising regularly	85	17.0	Taking zinc supplement	27	5.4
Consuming blackseed	59	11.8	Using blackseed or blackseed oil supplement	23	4.6
Meditation, yoga	16	3.2	Using Vitamin C supplement	71	14.2

When the side effects were questioned, 7 participants (1.4%) stated that they had gastrointestinal system side effects related with iron, magnesium, omega-3 and B12 supplements and 4 (0.8%) had skin rashes or allergy related to the use of aloe vera containing products, fish oil, zinc and multi-vitamin use. One person (0.2%) reported decreased kidney functions due to vitamin D supplementation while another participant reported impaired liver functions due to omega-3 supplement.

Of the teachers, 61.2% (n:306) stated that they wanted to be trained on immunity strengthening methods. Willingness to take training were not related with gender (p:0.068) but it was significantly related to age (p:0.006).

Of the teachers, 84.8% (n:424) agreed that they would suggest the methods they experienced and benefited, to their relatives, neighbors, friends or students.

DISCUSSION

Infectious diseases not only affect the physical health of individuals, but also the psychological health and well-being of the entire population, whether infected or not. Even after the epidemic ends, the psychological effects will likely last for months or even years when we return to our normal lives (10). Our study is important because it reveals how teachers, who are an exemplary role model for the society, are affected by the COVID-19 pandemic and what they do to improve their immunity. Actually, no similar study was found in the literature.

In our study, more than half of the teachers stated that their stress increased during the pandemic and one out of five participants stated that they were afraid of contracting the COVID-19 disease. Chronic stress now appears consistently in the literature as factors that often have a weakening effect on the immune system (11). Their stress levels increased, and this could be attributed to the increased time spent at home, news about the pandemic, worries about health, etc.

Increased stress levels resulted in an increased amount of fat, carbohydrate and protein consumption. Sleep disorders also increase nutrient intake, and this leads to a dangerous and vicious cycle (12). Nearly half of the participants gained weight during pandemic, and the quality of their sleep was also impaired despite increased sleep durations. Physical activity is advantageous for health and lowers anxiety levels (13), and regular mild and heavy exercise strengthens the immune system (14). Less than one fifth of the participants stated that they perform regular exercise. This may be related to the fact that they live and work at home, but nearly half of the participants were not performing regular exercise before the start of the pandemic. Regular exercising habits in teachers are not only healthy but these habits also position them as good role models for their students.

Noncontagious diseases constitute 70% of all global deaths (15), and underlying systemic inflammation may exacerbate COVID-19 infections (16). In our study, nearly one fourth of the teachers had a chronic disease and one third were smokers. Healthy lifestyle changes are highly important for both the prevention and treatment of noncontagious diseases (15).

Interestingly, activities, such as the consumption of fruits and vegetables, praying and sunbathing were among the main methods applied by the teachers to strengthen their immune systems. Nutrition can have a substantial impact on fighting infections (17). Evidence-based therapeutics or treatment strategies to reduce the prevalence or severity of COVID-19 have not yet been identified (17). A high consumption of a western diet, which is rich in saturated fats, sugar and refined carbohydrates, contributes to obesity and type-2 diabetes and may expose individuals to the high risk of COVID-19. However, adequate diet and nutrition fortify the immune system (17).

As pandemic termination time cannot be estimated, strengthening the immune system is important. Immunity is divided into innate and adaptive immunity. Innate immunity comprises of the elements of the immune system that provide immediate defense. Adaptive immunity deals with the reactions of T and B lymphocytes, which form the antigen-specific response (18). Antioxidants increase the lymphocyte response to mitogens, interleukin-2 production, natural killer cell activity

and the number of subsets of T cells (12). Different vitamins, including vitamins A, B6, B12, C, D and E and folate and trace elements, such as zinc, iron, selenium, magnesium and copper, play important and complementary roles in strengthening both innate and adaptive immune systems (19). In our study, about half of the teachers were using supplementary products. About half of those who used vitamin and mineral supplements preferred to use the product recommended by their doctor. Only 14 participants mentioned the side effect of the supplement they used. Health professionals should search for evidence-based studies on supplements and inform patients about their positive and negative effects.

Religions provide an optimistic philosophy on life and may propose the presence of an individual transcendental force that loves and cares about people and responds to their needs. This cognition gives individuals a subjective feeling of control over events (if God controls, he can influence the situation, and prayers may be effective in changing conditions positively) (20). Immunity has been found to increase in studies examining the relationship between religion and immune function. There is also qualitative and quantitative research showing that religion/spirituality can help people to cope better with difficulties (20). In our study, more than one third of the participants prayed to strengthen their immunity.

Approximately one-fourth of the teachers had a chronic disease and approximately one-fifth of them went to regular health check-ups even though they had no complaints. The fact that primary health care services are the first place of application and provide continuous, person-centered care is also the main reason for contact with teachers. Informing teachers about healthy life during periodic health examinations is also of great importance in terms of public health.

In a study conducted in Turkey, it was concluded that teachers had positive attitudes toward in-service training (21). Although nearly half the teachers participating in our study believed they had very good knowledge of immunity-strengthening methods, more than half wanted to take in-service training on this subject. A majority of the teachers also reported that they would share the immunity strengthening methods they tried and benefited from, with their social environment and students. Teachers are willing to learn how to improve their health.

Limitation: The teachers who participated in this study are interested in this subject and actively use the internet to acquire information about it, which may have affected our results. Another limitation was that the sample did not contain sufficient number of individuals who were at high risk of mortality or hospitalization in case of being infected by COVID-19.

CONCLUSION

In our study, more than half of the teachers stated that their stress increased during the pandemic period and almost half of them gained weight during this period. Teachers are eager to learn how to improve their health. We think that informing the teachers, who have an important impact on and are good role models for the society, about the methods that strengthen the immune system, may cause permanent behavioral changes in the society.

We hope that this study, having been carried out in the midst of the current global health crisis, will inspire future studies in seeking solutions to global health problems.

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RESEARCH ARTICLE

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Features on ECG During Admission May Predict In-hospital Events for COVID-19 Patients

ABSTRACT

Objective: To evaluate the association of electrocardiography (ECG) features obtained on admission with treating units and in-hospital all-cause mortality in coronavirus disease (COVID-19) patients.

Methods: A total of 172 hospitalized COVID-19 patients who were diagnosed by detecting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with real-time reverse-transcription polymerase chain reactionmethod between 15 May and 17 June 2020 were consecutively enrolled in the study. Laboratory parameters and findings on ECG obtained during admission were recorded. Criteria for hospitalization and intensive care unit (ICU) admission were determined in accordance with the interim guidance of the Republic of Turkey Ministry of Health. Patients were divided according to their in-hospital mortality status and units where patients were treated.

Results: The median age was significantly higher in the non-survivors group and in patients treated in the ICU ($p < 0.05$, for both). PR duration, P dispersion, QRS duration (QRSd), corrected QT duration (QTc), and QT dispersion (QTd) were significantly longer in patients treated in the ICU ($p < 0.001$, for all), whilst PR duration, P dispersion, QRSd, QTd, and QTc were significantly longer in the non-survivors group ($p < 0.05$, for all). QTd predicted admission to ICU, whereas QRSd predicted in-hospital all-cause mortality in patients with COVID-19.

Conclusions: Findings on ECG during admission may be independently associated with treating units and in-hospital all-cause mortality in COVID-19 patients.

Keywords: ECG, QRS Duration, QT Dispersion, COVID-19, ICU Admission.

COVİD-19 Hastalarında Başvuru Esnasında EKG'deki Özellikler Hastane İçi Olayları Öngörebilir

ÖZET

Amaç: COVID-19 hastalarında başvuru esnasındaki elektrokardiyografi (EKG) özellikleri ile tüm nedenlere bağlı hastane-içi mortalite ile tedavi üniteleri arasındaki ilişkiyi değerlendirmektir.

Gereç ve Yöntem: 15 Mart ile 17 Haziran 2020 tarihleri arasında gerçek zamanlı ters transkripsiyon polimeraz zincir reaksiyonu metodu ile şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) tespit edilerek COVID-19 tanısı konulan ve hastaneye yatırılan toplam 172 ardışık hasta bu çalışmaya dahil edildi. Laboratuar parametleri ve EKG bulguları başvuru sırasında kaydedildi. Hastaneye ve yoğun bakım ünitesine (YBÜ) yatış kriterleri Türkiye Cumhuriyeti Sağlık Bakanlığı'nın geçici kılavuzuna göre belirlendi. Hastalar hastane içi mortalite durumlarına ve tedavi gördükleri birime göre gruplandırıldı.

Bulgular: Ortanca yaş mortalite grubunda ve YBÜ'de tedavi edilen hastalarda önemli ölçüde daha yüksekti (her ikisi için, $p < 0.05$). P dispersiyonu, QRS süresi, QTc süresi ve QT dispersiyonu YBÜ'de tedavi edilen hastalarda önemli ölçüde daha uzundu (hepsi için, $p < 0.001$). PR süresi, P dispersiyonu, QRS süresi, QT dispersiyonu ve QTc süresi mortalite grubunda önemli ölçüde daha uzundu (hepsi için $p < 0.05$). QT dispersiyonu YBÜ başvurularını öngörürken QRS süresi COVID-19 hastalarında tüm nedenlere bağlı hastane-içi mortaliteyi öngördü.

Sonuç: Başvuru esnasındaki EKG bulguları, COVID-19 hastalarında tedavi birimleri ve tüm nedenlere bağlı hastane-içi mortalite ile bağımsız olarak ilişkilendirilebilir.

Anahtar Kelimeler: EKG, QRS Süresi, QT Dispersiyonu, COVID-19, YBÜ Başvuru.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory coronavirus-2 (SARS-CoV-2). Most hospitalized individuals are over 65-year-old, male, and those with multi-comorbidities (1). Patients could have a variety of clinical courses ranging from an asymptomatic stage to pneumonia, acute respiratory distress syndrome, and multi-organ failure (2-5). SARS-CoV-2 enters the cell by binding to angiotensin-converting enzyme-2 which is found in many organs, especially lungs, cardiovascular system, kidneys, gastrointestinal system, and testicles (6), and may lead to myocarditis, arrhythmias, and cardiac death (7-9). Thus, COVID-19 appears to be a multi-systemic infectious disease. Hospitalized patients with COVID-19 are treated in emergency rooms, inpatient rooms, and intensive care units (ICU). Additionaly, in-hospital mortality rates may vary depending on the unit where patients are treated (10).

Electrocardiography (ECG), a simple and easily accessible tool, is utilized to define arrhythmias, abnormal findings in acute and chronic heart diseases, ST-T changes as well as electrical conduction disorders (11). Changes in QRS duration (QRSd) that indicates ventricular depolarization or QT dispersion (QTd) associated with ventricular repolarization could give rise to ventricular arrhythmias and thus cardiac deaths (12-16). Not enough data in the literature is available regarding the relationship between ECG findings and poor outcomes in infectious diseases. Therefore, the purpose of the present study is to examine the association of ECG features on admission with treating units and in-hospital all-cause mortality in COVID-19 patients.

MATERIAL AND METHODS

Study Population and Design: This is a single-center (Adana City Training and Research Hospital) and retrospective observational cohort study that includes a total of 172 consecutively hospitalized COVID-19 patients diagnosed by detecting SARS-CoV-2 RNA with real-time reverse-transcription polymerase chain reaction method from 15 May to 17 June 2020. Subjects were grouped according to their in-hospital mortality status, as survivors (n=155) and non-survivors (n=17), and units where patients are treated, as ICU (n=23) and inpatient room (n=149). ECG parameters of the study population were obtained only based on ECG taken during admission. Age, gender, and comorbidities were achieved from their anamnesis during hospitalization or from the medical record system. Laboratory parameters including complete blood cell count, white blood cell count, urea, creatinine, glomerular filtration rate (GFR), alanine transaminase (ALT), aspartate transaminase (AST), and lactate dehydrogenase (LDH) were analyzed from the blood samples taken on admission. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count from a complete blood count. GFR was calculated with the Modification of Diet in Renal Disease formula (17). The study was conducted according to the Declaration of Helsinki and was approved by an institutional ethics committee (No: 99, May 15, 2020), as well as the Ministry of Health. The need for written informed consent was waived due to the retrospective nature of the study.

Hospitalization was planned according to the following criteria determined by the Republic of Turkey Ministry of Health (18);

- Confusion or tachycardia (>125/ bpm)
- Dyspnea or tachypnea (>22/ bpm)
- Hypotension (<90/60 mmHg or mean blood pressure <65 mmHg)
- >50 year-old and presence of co-morbidity (immunosuppressive conditions, especially cardiovascular diseases, Diabetes mellitus, hypertension, cancer, chronic lung diseases)
- Mild-moderate pneumonia and blood lymphocyte count <800 / µl or serum CRP> 40 mg/l or ferritin> 500ng / ml or D-dimer > 1000 ng / ml, etc.
- Presence of bilateral diffuse (> 50%) involvement in lung imaging

Criteria for ICU admission are described as follows; a) Dyspnea and respiratory distress despite oxygen therapy; respiratory rate > 30 / min or PaO2 / FiO2 <300 mmHg or SPO2 <90 or PaO2 <70 mmHg, b) Hypotension (systolic blood pressure <90 mmHg and a decrease of systolic blood pressure higher than 40 mmHg or mean arterial pressure <65 mmHg, c) Acute kidney injury, acute liver dysfunction, development of acute organ dysfunction such as confusion, acute bleeding diathesis, and immunosuppression, d) Elevated troponin and arrhythmia, e) Lactate > 2 mmol, f) Presence of skin findings such as prolonged capillary filling time and cutis marmorata (18). Patients with chronic kidney disease (GFR <30 ml/min / 1.73 m2), chronic liver failure, immunosuppression, atrial fibrillation, those using heart rate-reducing agents, or those under 16 years of age were excluded from the study.

ECG Analysis and Definitions: 12-lead ECG data taken on admission were recorded. 300% magnification was applied to all ECGs obtained from individuals using Adobe Photoshop Software. ECG recordings (filter range 0.05–150 Hz, AC filter 60 Hz, 25 mm/s, 10 mm/mV, CardioFax S; Nihon Kohden, Tokyo, Japan) were manually analyzed by two independent cardiologists who were blinded to the present study for the following parameters: Heart rate, P-wave dispersion, PR duration, QRSd, fragmented QRS complex, QT duration corrected by the Bazzett-formula(QTc)

(19), QTd, premature atrial contraction, premature ventricular contraction, ST depression, and T inversion. QTd was identified as the difference between the longest (QTmax) and the shortest (QTmin) QT intervals within a 12-lead ECG (20). Similarly, P-wave dispersion was described as the difference between the longest and the shortest P wave duration recorded from 12-lead surface ECG (21).

Statistical Analysis: An analytical (Kolmogorov–Smirnov test) method and visual methods (histograms and probability plots) were used to test the normality of distribution. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) and categorical variables were expressed as numbers and percentages (%). The Student t-test and the Mann-Whitney U test were used to compare continuous variables. The Chi-square and Fisher's exact test were used to compare categorical variables as appropriate. All of the significant parameters in the univariate analysis with p <0.1 were selected for the multivariable model and backward stepwise logistic regression analysis was used to determine the independent predictors of ICU admission and all-cause in-hospital mortality of COVID-19 patients. The odds ratio (OR) and 95% confidence interval (CI) of each independent variable were calculated. Receiver operating characteristic curve analysis was used to determine the cut-off value of independent predictors in predicting ICU admission based on the Youden index. A 2-tailed p-value of <0.05 was considered significant. In all statistical analyses; SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc statistical software v19.5.6 (Ostend, Belgium) were utilized.

RESULTS

There was no significant difference across the two groups by the treating units in terms of gender and comorbidities including hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, chronic obstructive pulmonary disease, heart failure, and current smoker. The median age of the patients treated in ICU was older than that of the patients treated in the inpatient room [68,7 (16,0-88,0) vs 44,9 (16,0-90,0) p <0,001]. Detailed demographic characteristics and laboratory parameters of the study population according to the treating units are shown in Table 1.

Table 1. Demographic and laboratory findings of the study population by the treating unit

	Inpatient room (n:149)	**ICU (n:23)**	**Overall (n:172)**	**p-value**
Age, years	44 (31-57)	68 (62-77)	48 (34-62)	<**0.001**
Sex, male, n (%)	71 (47.6)	13 (56.5)	84 (48.8)	0.428
Hypertension, n (%)	93 (62.4)	18 (78.2)	111 (64.5)	0.139
Diabetes mellitus, n (%)	48 (32.2)	9 (39.1)	57 (33.1)	0.512
Coronary artery disease, n (%)	28 (18.7)	7 (30.4)	35 (20.3)	0.263
Hyperlipidemia, n (%)	55 (36.9)	9 (39.1)	64 (37.2)	0.838
COPD, n (%)	35 (23.4)	8 (34.7)	43 (25.0)	0.244
Current smoker, n (%)	17 (11.4)	3 (13.0)	20 (11.6)	0.737
Heart failure, n (%)	1 (0.6)	1 (4.3)	2 (1.1)	0.250
Body mass index, kg/m^2	28.3±4.9	29.4±5.2	28.4±4.9	0.294
Systolic blood pressure, mmHg	122.5±13.0	126.6±21.0	118.6±13.6	0.387
Diastolic blood pressure, mmHg	70.7±7.5	74.1±11.3	71.2±8.1	0.190
Heart rate, bpm	82.5±10.1	86.0±10.2	82.9±10.2	0.127
Glucose, mg/dL	135 (108-145)	114 (92-259)	133 (105-145)	0.866
Hemoglobin, g/dL	14.3±1.6	13.2±1.6	14.1±1.6	**0.004**
WBC, 10^3/uL	5.5 (4.6-7.2)	5.9 (5.1-9.7)	5.7 (4.7-7.2)	0.171
Platelet count, 10^3/uL	214.0 (180.0-254.5)	178.0 (158.0-211.0)	209.0 (176.0-249.8)	**0.003**
NLR	1.8 (1.2-2.6)	5.6 (2.9-8.1)	1.9 (1.3-3.2)	<**0.001**
Neutrophil, 10^3/uL	3.2 (2.5-4.2)	4.7 (3.5-7.7)	3.4 (2.6-4.7)	<**0.001**
Lymphocyte, 10^3/uL	1.8 (1.4-2.4)	0.9 (0.7-0.9)	1.7 (1.2-2.3)	<**0.001**
MPV, fL	9.0±0.9	9.0±0.9	9.0±0.9	0.950
Urea, mg/dL	27.5 (22.7-34.5)	47.6 (32.3-68.7)	29.7 (23.3-36.6)	<**0.001**
Creatinine, mg/dL	0.78 (0.66-0.91)	1.06 (0.73-1.41)	0.80 (0.67-0.97)	<**0.001**
GFR, ml/min/1.73 m^2	101.04±24.1	70.7±27.7	96.9±26.6	<**0.001**
AST, U/L	23.0 (18.0-30.5)	37.0 (29.0-57.0)	23.5 (18.3-32.0)	<**0.001**
ALT, U/L	21.0 (13.5-31.5)	21.0 (14.0-26.0)	21.0 (14.0-30.0)	0.850
LDH, U/L	190.0 (151.5-229.0)	353.0 (279.0-514.0)	201.0 (155.0-254.0)	<**0.001**
ALP, U/L	75.0 (62.0-93.5)	67.0 (53.5-83.5)	74.0 (61.0-92.3)	0.199
Time from onset of symptom to hospitalization	2.00 (1.00-6.00)	4.00 (1.00-8.00)	2.00 (1.00-8.00)	<**0.001**
Length of stay, day	12 (10-14)	14 (12-22)	12 (10-15)	<**0.004**
In-hospital mortality, n (%)	5 (3.4)	12 (52.2)	17 (9.9)	<**0.001**

COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase.

Hemoglobin, platelet count, lymphocyte count, GFR, ALT were significantly lower in patients treated in the ICU; whereas white blood cell, neutrophil count, NLR, urea, creatinine, AST, and LDH values were significantly higher (p <0.05). The in-hospital all-cause mortality rate of patients treated in the ICU was statistically higher than in patients treated in the ward (p <0.001). When ECG parameters obtained on admission were compared; PR duration, P dispersion, QRSd, QTc, and QTd were significantly longer in patients treated in the ICU (p <0.001, for all) (Table 2).

Table 2. ECG findings of the study population by the treating unit

	Inpatient room (n: 149)	**ICU (n:23)**	**Overall (n: 172)**	**p-value**
PR interval, ms	148.9±23.8	171.2±31.2	151.8±25.9	**0.004**
P-wave dispersion, ms	56.41±13.73	71.19±13.40	58.32±14.52	**<0.001**
QRS duration, ms	91.5±14.7	107.6±20.5	93.6±16.4	**0.002**
QTc interval, ms	415.2±26.3	446.6±33.5	419.3±29.2	**<0.001**
QT dispersion, ms	51.2±10.4	65.9±12.5	53.1±11.7	**<0.001**
fQRS, n (%)	3 (2.1)	2 (9.5)	5 (3.1)	0.126
RBBB, n (%)	11 (7.3)	1 (4.3)	12 (6.9)	1.000
Premature atrial contraction, n (%)	15 (10.0)	5 (21.7)	20 (11.6)	0.153
Premature ventricular contraction, n (%)	24 (16.1)	7 (30.4)	31 (18.0)	0.140
ST-segment depression, n (%)	38 (25.5)	9 (39.1)	47 (27.3)	0.172
ST-segment elevation, n (%)	4 (2.6)	1 (4.3)	5 (2.9)	0.517
T-wave inversion, n (%)	31 (20.8)	8 (34.7)	39 (22.6)	0.136

fQRS: fragmente QRS, RBBB: Right bundle branch block.

When we analyzed the predictors of ICU admission (Table 3); in backward stepwise logistic regression analysis, NLR (OR: 1.550, 95% Cl: 1.037-2.316, p=0.032), QTd (OR: 1.093, 95% Cl: 1.018 + 1.174, p=0.014), GFR (OR: 0.959, 95% Cl: 0.924-0.996, p=0.030), and LDH (OR: 1.013, 95% Cl: 1.005-1.022, p=0.003) predicted ICU admission.

Table 3. Independent risk factors of ICU admission

Variable	**Univariate Analysis**		**Multivariate Analysis**	
	OR (95 % CI)	**p-value**	**OR (95 % CI)**	**p-value**
Age, years	1.090 (1.052-1.130)	**<0.001**	-	-
Gender, male	1.428 (0.590-3.460)	0.430	-	-
NLR	2.120 (1.567-2869)	**<0.001**	1.550 (1.037-2.316)	**0.032**
PR interval, ms	1.030 (1.013-1.048)	**0.001**	-	-
P-wave dispersion, ms	1.069 (1.034-1.105)	**<0.001**	-	-
QRS duration, ms	1.054 (1.025-1.083)	**<0.001**	-	-
QT_c interval, ms	1.041 (1.021-1.061)	**<0.001**	-	-
QT dispersion, ms	1.103 (1.058-1.150)	**<0.001**	1.093 (1.018-1.174)	**0.014**
GFR, ml/min/1.73 m^2	0.948 (0.927-0.970)	**<0.001**	0.959 (0.924-0.996)	**0.030**
Hemoglobin, g/dL	0.664 (0.497-0.887)	**0.006**	-	-
Platelet count, x $10^3/\mu L$	0.993 (0.985-1.002)	0.133	-	-
LDH, U/L	1.019 (1.011-1.026)	**<0.001**	1.013 (1.005-1.022)	0.003
AST, U/L	1.056 (1.028-1.085)	**<0.001**	-	-

p-value < 0.05 was considered significant. Nagelkerke R^2: 0.739, p< 0.001
NLR: Neutrophil to lymphocyte ratio, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase.

In ROC analyses for predicting ICU admission; a cut-off value of > 269 U/L for LDH had an 82.6 % sensitivity and 88.4 % specificity [AUC: 0.910, 95 % CI 0.856-0.949, p <0.001] and a cut-off value of > 3.83 for NLR had a 69.6 % sensitivity and 91.9 % specificity [AUC: 0.898, 95 % CI 0.843-0.939, p <0.001] and a cut-off value of > 54 ms for QTd had a 90.5 % sensitivity and 65.9 % specificity [AUC: 0.824, 95 % CI 0.757-0.879, p <0.001], and a cut-off value of ≤ 82 ml/min/1.73 m2 for GFR had a 69.6 % sensitivity and 77.9 % specificity [AUC: 0.791, 95 % CI 0.722-0.849, p <0.001]. In the pairwise comparison of ROC curves; There was no significant difference (p >0.05, for all) (Fig 1).

The demographic characteristics, laboratory data, and ECG findings of the patients with and without in-hospital mortality are shown in Table 4.

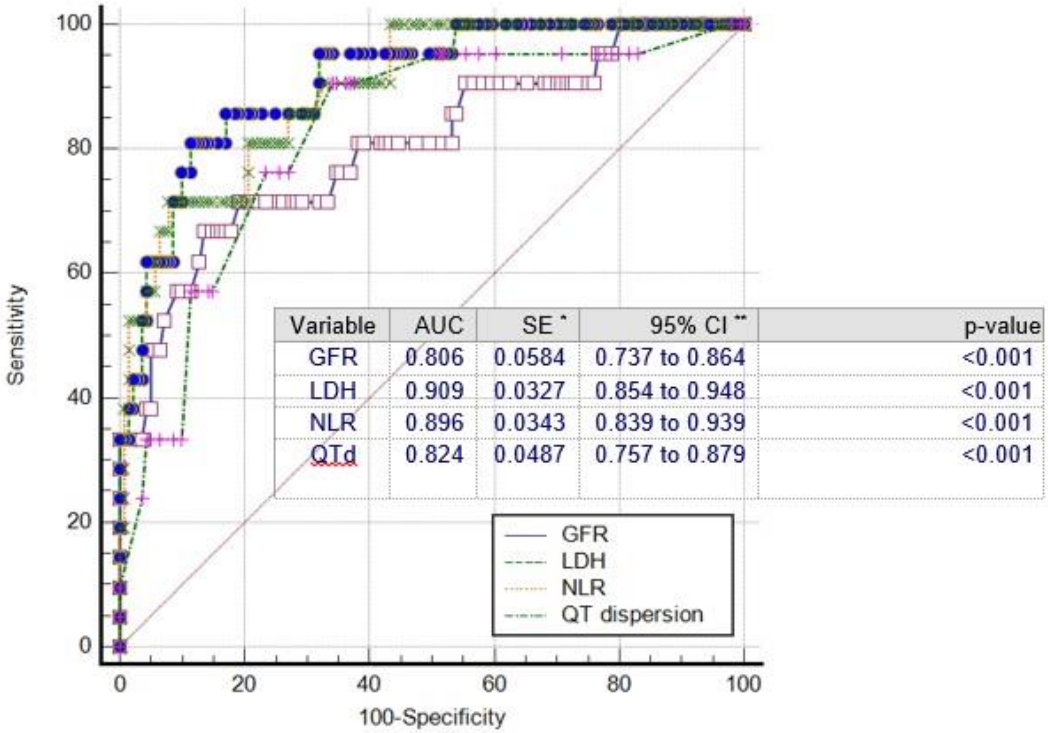

Figure 1. Receiver operating characteristic (ROC) curves of predictors for ICU admission in patients with COVID-19. SE: standart Error. CI: confidence interval.

Table 4. Demographic and laboratory findings of the study population by in-hospital mortality status

	Survivors (n: 155)	**Non-survivors (n: 17)**	**Overall (n: 172)**	**p-value**
Age, years	44 (32-59)	65 (61-73)	48 (34-62)	**<0.001**
Sex, male n (%)	74 (47.7)	10 (58.8)	84 (48.8)	0.386
Hypertension, n (%)	99 (63.8)	12 (70.5)	111 (64.5)	0.583
Diabetes mellitus, n (%)	49 (31.6)	8 (47.0)	57 (33.1)	0.199
Coronary artery disease, n (%)	31 (20.0)	4 (23.5)	35 (20.3)	0.753
Hyperlipidemia, n (%)	55 (35.4)	9 (52.9)	64 (37.2)	0.157
COPD, n (%)	39 (25.1)	4 (23.5)	43 (25.0)	1.000
Current smokers, n (%)	17 (10.9)	3 (17.6)	20 (11.6)	0.391
Heart failure, n (%)	1 (0.6)	1 (5.9)	2 (1.1)	0.188
Body mass index, kg/m2	28.2±4.9	30.8±4.9	28.4±4.9	0.054
Systolic blood pressure, mmHg	122.6±13.8	128.4±20.3	123.0±14.3	0.400
Diastolic blood pressure, mmHg	70.9±8.0	74.2±9.9	71.2±8.1	0.224
Heart rate, bpm	83.1±10.2	81.8±10.6	82.9±10.2	0.605
Hemoglobin, g/dL	14.3±1.7	13.1±1.1	14.1±1.6	**0.004**
WBC, 10^3/uL	5.5 (4.6-7.2)	6.1 (5.2-6.6)	5.7 (4.7-7.2)	0.292
Platelet count, 10^3/uL	212.0 (180.0-251.0)	178.0 (154.5-229.5)	209.0 (176.0-249.8)	0.069
NLR	1.8 (1.2-2.9)	4.0 (2.2-7.6)	1.9 (1.3-3.2)	**<0.001**
MPV, fL	9.0±0.8	9.2±1.2	9.0±0.9	0.360
Glucose, mg/dL	135 (107-145)	120 (93-268)	133 (105-145)	0.780
Urea, mg/dL	28.0 (23.2-35.6)	41.5 (31.5-59.4)	29.7 (23.3-36.6)	**0.001**
Creatinine, mg/dL	0.78 (0.66-0.94)	0.99 (0.83-1.35)	0.80 (0.67-0.97)	**0.002**
GFR, ml/min/1.73 m^2	100.3±24.9	66.6±23.1	96.9±26.6	**<0.001**
AST, U/L	23.0 (18.0-31.0)	36.0 (23.5-51.0)	23.5 (18.3-32.0)	**0.006**
ALT, U/L	20.0 (14.0-30.0)	25.0 (12.5-29.5)	21.0 (14.0-30.0)	0.797
LDH, U/L	191.5 (152.0-240.0)	338.0 (275.0-514.0)	201.0 (155.0-254.0)	**<0.001**
ALP, U/L	74.5 (61.8-93.3)	66.5 (50.8-82.5)	74.0 (61.0-92.3)	0.279
Time to onset of symptom to hospitalization, day	2.00 (1.00-6.00)	5.00 (2.00-8.00)	2.00 (1.00-8.00)	**<0.001**

COPD: Chronic obstructive pulmonary disease, WBC: White blood cell, NLR: Neutrophil to lymphocyte ratio, MPV: Mean platelet volume, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase LDH: Lactate dehydrogenase, ALP: Alkaline phosphatase.

There was no significant difference in gender and comorbid diseases between survivors and non-survivors. The median age was significantly higher in the non-survivor group [67,41 (46,0-88,0) vs. 45,99 (16,0-90,0); p <0.001]. Hemoglobin, lymphocyte count, and GFR were lower in the non-survivor group, whereas neutrophil, NLR, urea, creatinine, and LDH were significantly higher (p <0.05). PR duration, P dispersion, QRSd, QTd, and QTc were significantly longer in the non-survivor group compared with survivors (p <0.05, for all) (Table 5).

Table 5. ECG findings of the patients by in-hospital mortality status

	Survivors (n:155)	**Non-survivors (n:17)**	**Overall (n:172)**	**p-value**
PR interval, ms	149.9±24.6	179.7±29.6	151.8±25.9	**<0.001**
P-wave dispersion, ms	57.3±14.1	74.0±12.6	58.3±14.5	**<0.001**
QRS duration, ms	92.3±15.0	113.5±23.3	93.6±16.4	**0.018**
QTc interval, ms	417.8±28.4	441.1±34.1	419.3±29.2	**0.014**
QT dispersion, ms	52.4±11.5	64.0±11.0	53.1±11.7	**0.002**
fQRS, n(%)	4 (2.6)	1 (5.8)	5 (3.1)	0.276
RBBB, n(%)	10 (0.6)	2 (11.7)	12 (6.9)	0.337
Premature atrial contraction, n (%)	16 (10.3)	4 (23.5)	20 (11.6)	0.116
Premature ventricular contraction, n (%)	28 (18.0)	3 (17.6)	31 (18.0)	1.000
ST-segment depression, n(%)	42 (27.0)	5 (29.4)	47 (27.3)	0.782
ST-segment elevation, n(%)	4 (2.5)	1 (5.8)	5 (2.9)	0.410
T-wave inversion, n(%)	33 (21.2)	6 (35.2)	39 (22.6)	0.223

fQRS: fragmente QRS, RBBB: Right bundle branch block.

There was no difference in terms of fragmented QRS between the groups. In multivariate regression analysis with backward selection, QRSd (OR: 1.045, 95% Cl: 1.000-1.091, p=0.049), GFR (OR: 0.922, 95% Cl: 0.875-0.972, p=0.003) and LDH (OR: 1.009, 95% Cl: 1.003 - 1.015, p=0.003) predicted in-hospital all-cause mortality (Table 6).

Table 6. Independent risk factors of all-cause in-hospital mortality of patients with COVID-19

Variable	**Univariate Analysis**		**Multivariate Analysis**	
	OR (95 % CI)	**p-value**	**OR (95 % CI)**	**p-value**
Age, years	1.074 (1.037-1.113)	**<0.001**	-	-
Gender, male	1.564 (0.566-4.319)	0.388	-	-
Body mass index, kg/m^2	1.101 (0.996-1.217)	0.059	-	-
QRS duration, ms	1.061 (1.026-1.098)	**0.001**	1.045 (1.000-1.091)	**0.049**
QT_c interval, ms	1.026 (1.004-1.049)	**0.019**	-	-
QT dispersion, ms	1.072 (1.021-1.125)	**0.005**	-	-
PR interval, ms	1.037 (1.014-1.061)	**0.001**	-	-
P-wave dispersion, ms	1.074 (1.027-1.123)	**0.002**	-	-
NLR	1.221 (1.064-1.401)	**0.004**	-	-
Hemoglobin, g/dL	0.626 (0.450-0.871)	**0.005**	-	-
GFR, ml/min/1.73 m^2	0.942 (0.918-0.968)	**<0.001**	0.922 (0.875-0.972)	**0.003**
AST, U/L	1.045 (1.018-1.073)	**0.001**	-	-
LDH, U/L	1.009 (1.004-1.013)	**<0.001**	1.009 (1.003-1.015)	**0.003**

p-value < 0.05 was considered significant. Nagelkerke R^2: 0.662, p< 0.001
NLR: Neutrophil to lymphocyte ratio, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, LDH: Lactate dehydrogenase.

DISCUSSION

Few reports have been published regarding the relationship between ECG findings and ICU admission and all-cause in-hospital mortality in infectious diseases, especially in COVID-19 patients. Consequently, convincing evidence has been yet to found. In the present study, according to ECGs obtained during admission to the hospital; we found an independent association between ICU admission and QTd, and between QRSd and in-hospital all-cause mortality.

The increased risk of myocardial involvement in COVID-19 patients explains the conduction disturbance and thus the change in QRSd. Although this was not the aim of our study, the increased in-hospital mortality and post-discharge sudden cardiac death in COVID-19 patients with myocardial involvement may be partially attributable to the prolonged QRSd (22). In our study, the relationship between QRSd and in-hospital all-cause mortality, and prolonged QRSd in

the ICU admission group seem to support this theory. In addition, comparing COVID-19 and other acute respiratory infectious diseases, Antonio et al. revealed that increased QRSd is associated with mortality. Similarly, another investigation of 324 COVID-19 patients compared the ECG findings and reported that an increase in QRSd predicted mortality (23). The mechanisms underlying the association between prolonged QRSd and mortality may also be explained by left ventricular dysfunction, repolarization abnormalities, and malignant arrhythmias.

Increasing dispersion of repolarization that indicates heterogeneity of repolarization is a marker of crucial ventricular arrhythmias (24-27). QTd contributes to the heterogeneities of repolarization time in the three-dimensional structure of the ventricular myocardium, which is secondary to regional differences in action potential duration and activation time (28,29). The association of QTd with cardiac arrhythmia is thought to be related to the sympathetic innervation of the left ventricle (30). Increased sympathetic innervation in COVID-19 patients also strengthens this relationship (31). Even though the relationship between QTd and arrhythmias is relatively clear, there are conflicting results regarding its relationship with mortality. For instance, In a meta-analysis (32); prolonged QTd in myocardial infarction has been reported to be associated with an increase in arrhythmic events, but not with all-cause mortality. These conflicting results may be attributed to the various reasons stated as follows: (i) QTd may rather describe T wave morphology than ventricular repolarization (33), (ii) The reproducibility of QTd measurement is low and inter-observer error might be >20% (33), (iii) Difficulty in identifying T wave-end when measuring the QT interval, and differences of opinion about whether it is calculated according to heart rate could indicate the subjectivity of QTd. In the present study, we found that QTd predicted ICU admission but not in-hospital all-cause mortality. This discordance may be associated with several plausible reasons such as the selection of in-hospital all-cause mortality over cardiovascular mortality as an endpoint, insufficient number of in-hospital mortality for the model fit of statistical analysis.

In our results, GFR, LDH, and NLR were associated with poor outcomes, compatible with the literature. However, those with co-morbidities such as coronary artery disease or chronic obstructive pulmonary disease did not seem to have a worse prognosis during hospitalization. This could be attributed to the inclusion of only hospitalized patients with COVID-19 and the criteria for hospitalization. Therefore, this methodological approach may be causing an equal distribution of comorbidities across the groups.

Limitations

The present study has the following notable limitations. The main limitations are the sample size of the population and study design without long-term follow-up. Since only the ECGs on admission were evaluated, we did not examine ECG changes during hospitalization and their relationship with in-hospital all-cause mortality. The results can not be generalized to other segments of the population, as the study was conducted at a single center. Another substantial limitation is that the low number of patients in the non-survivors group may affect the reliability of statistical analysis on in-hospital mortality. Finally, since the criteria for admission to ICU are determined according to the interim guidance of the Turkish Ministry of Health, alterations in these criteria may give rise to changes in the results of the study. Further comprehensive prospective investigations with long-term follow-up and a large sample size are needed to better clarify the association of findings on ECG with morbidity and mortality in COVID-19 patients.

CONCLUSION

We found that ECG findings on admission were independently associated with in-hospital all-cause mortality and ICU admission in patients with COVID-19. Consequently, these results suggest that ECGs on admission might enable clinicians to determine the treatment priority of patients as well as to predict prognosis.

Conflicts of interest: No

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RESEARCH ARTICLE

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An Examination of the Factors, Which May Affect the Duration of Admission to the Hospital of Panic Diagnosed Patient in Surgical Pathology during and Pre-COVID-19 Pandemic

ABSTRACT

Objective: This study aimed to determine the duration of hospital admission of the panic diagnosed patients in surgical pathology, examine the factors that may influence hospital admission time, and identify the impact of the COVID-19 pandemic on hospital admission time.

Methods: The panic diagnosed patients in surgical pathology between January 2018 and January 2021 were determined. These patients' demographic, clinical, and critical diagnostic form data were documented. The duration of hospital admission of patients during and pre-COVID-19 pandemic period was determined.

Results: There were 65 panic diagnosed cases in surgical pathology, of which one patient had leukocytoclastic vasculitis, 10 patients had uterine contents without villi or trophoblasts, and 54 patients had unexpected malignancy. The mean time of admission to the hospital of verbally informed and not verbally informed cases were five days and 156 days, respectively, in the pre-COVID-19 group. All cases in the COVID-19 pandemic group were verbally informed about critical diagnosis and the mean time of admission to the hospital was 18 days (1–40). Admission times were on mean about 13 days longer in verbally informed cases in the COVID-19 pandemic group compared to verbally informed cases in the pre-COVID-19 group.

Conclusions: We determined a dramatic decrease in the number of panic diagnosed cases in surgical pathology during the COVID-19 pandemic and patients who are verbally informed admitted to the hospital in a shorter time. The integration of panic diagnosis notification systems to health applications and primary responsible family physician's systems may be useful for preventing unwanted delays.

Keywords: Panic Diagnosis, Unexpected Diagnosis, Significant Diagnosis, Critical Value.

COVID-19 Pandemi Dönemi ve Öncesinde Cerrahi Patolojide Panik Tanı alan Hastaların Hastaneye Başvuru Sürelerini Etkileyebilecek Faktörlerin Değerlendirilmesi

ÖZET

Amaç: Bu çalışmada cerrahi patolojide panik tanı alan hastaların hastaneye başvuru sürleri belirlenmiş, hastaneye başvuru süresini etkileyebilecek faktörler değerlendirilmiş ve COVID-19 pandemisinin hastaneye başvuru süresi üzerine etkisi irdelenmiştir.

Gereç ve Yöntem: 2018-2021 yılları Ocak ayları arasında cerrahi patolojide panik tanı alan hastalar belirlendi. Bu hastaların demografik, klinik ve panik tanı formlarındaki bilgiler derlendi. COVID-19 pandemi dönemi ve öncesindeki hastaneye başvuru süreleri belirlendi.

Bulgular: Cerrahi patolojide panik tanı alan 65 hasta mevcuttu. Bunlardan birinde lökositoklastik vaskülit, 10'nunda villus veya trofoblast içermeyen uterin küretaj materyali ve 54'ünde beklenmeyen tümör mevcuttu. COVID-19 öncesi dönemde panik tanı hakkında sözlü olarak bilgilendirilen ve bilgilendirilmeyen vakaların hastaneye başvuru süresinin ortalaması sırası ile, beş ve 156 gündü. COVID-19 pandemi döneminde tüm hastalar sözel olarak bilgilendirilmişti ve hastaneye başvuru süreleri ortalama 18 gündü. COVID-19 pandemi döneminde sözel olarak bilgilendirilen grubun hastaneye başvuru süreleri, pandemi öncesi döneme göre 13 gün daha uzundu.

Sonuç: COVID-19 pandemi döneminde panik tanı vakalarında belirgin düşüş ve sözlü olarak bilgilendirilen hastaların hastaneye daha kısa zamanda başvurduğunu saptadık. Hastane panik tanı bildirim sistemlerinin, sağlık aplikasyonlarına ve Aile hekimliği sistemine entegre edilmesi istenmeyen gecikmelerin önüne geçmek için yararlı olabilir.

Anahtar Kelimeler: Panik Tanı, Beklenmeyen Tanı, Önemli Tanı, Kritik Değer.

INTRODUCTION

Pathology reports are crucial medical documents that contain critical information about diagnosis, prognosis, and treatment. Although all pathology reports contain valuable information, some of them contain critical information about life-threatening changes that need immediate treatment (1). These diagnoses are considered panic diagnoses in surgical pathology (2). Failure to follow up on the results of these reports or lack of appropriate communication of these reports results may lead to a delay in diagnosis that may cause severe or irreparable harm and may affect the patient outcome (3). To ensure patient safety and prevent this delay, national pathology societies recommend that each pathology department should identify potential panic diagnosis lists and draw up a communication policy (2).

The College of American Pathologists (CAP) evaluates panic diagnoses in surgical pathology under Urgent Diagnoses and Significant, Unexpected Diagnoses titles. CAP defines urgent diagnoses as an important or life-threatening medical condition that requires urgent intervention and recommends that direct verbal communication occurs on the day of diagnosis. They also define Significant, Unexpected Diagnoses as a clinically unusual or unpredictable medical condition that needs to be addressed at some point in the patient's course and recommends that communication occurs as soon as possible (2). The Federation of Turkish pathology society considers Urgent, Significant, and unexpected diagnoses under a single title as a panic diagnosis.

Several studies indicated that immediately effective verbal communication had a beneficial impact on patient's outcome and treatment management (4, 5). Although communication between the clinician and pathologist is established in a brief time, in some cases, reaching the patient may take longer. In the case of patients with an unexpected malignancy, prolonged hospital admission time may result in delayed treatment and worsening of prognosis.

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that causes coronavirus disease 2019 (COVID-19), first appeared in Wuhan (China) and the COVID-19 pandemic spread rapidly around the world (6–8). The first case in Turkey was recorded on 11 March and following this many hospitals have been turned into the COVID-19 pandemic hospitals and elective surgical procedures and non-critical healthcare services are limited. The lockdown has also made it difficult for patients to access healthcare services for non-COVID-19 conditions in addition to healthcare limitations. Many studies revealed that hospital admission for acute medical illnesses, including stroke and acute myocardial infarction, fell dramatically with the onset of the COVID-19 pandemic (9–11).

In this study, we aimed to determine the duration of hospital admission of the panic diagnosed patient in surgical pathology pre-COVID-19 and during the COVID-19 pandemic, to examine the factors that may influence hospital admission time, and to identify the impact of the COVID-19 pandemic on hospital admission time.

MATERIAL AND METHODS

This study was conducted according to the Declaration of Helsinki's principles. The medical ethics committee (Approval No. 22.09.2020/09/09/01) approved this study. We evaluated the Erzincan Mengücek Gazi Training and Research Hospital (EMGTRH), Pathology Department records and determined the panic diagnosed patient in surgical pathology between January 2018 and January 2021. Patients who had inappropriate contact information in the hospital information processing system were excluded from the study. We reviewed patients' records and documented demographic, clinical, and panic diagnosis from data. We divided the cases into two groups according to the date of their panic diagnosis. Cases diagnosed before 11 Mach 2020 were included in the pre-COVID-19 group and the cases diagnosed after 11 Mach 2020 were included in the COVID-19 pandemic group.

We determined the date of admission to the hospital of the patients after receiving panic diagnosis notification through the hospital system and then compared notification and admission date to determine the patients' admission to the hospital time.

Patients were divided into two groups according to the median of the patient's admission time. The applicants within five business days after receiving notification were assigned to a fast group (FG), whereas the later application was considered as in the slow group (SG). We evaluated the variables (age, gender, the distance of the patient home to hospital, and verbal notification status) that we considered likely to affect the hospital admission time in these groups.

Statistical analysis was performed using SPSS version 15. Descriptive statistics were presented as mean and standard deviation, median, and distribution width. Comparison of continuous variables between groups was conducted using Student's t-test and Mann –Whitney U test according to their distribution. Also, a chi-square test was used for risk estimation. The confidence level for statistical significance was defined as 95 percent (α=0.05).

Panic diagnosis lists of our department that determined according to the national pathology societies recommend, were presented in Table 1.

Table 1. Panic diagnosis List of EMG TARH pathology department

Cases with immediate clinical consequences	Leukocytoclastic vasculitis Uterine contents without villi or trophoblast Fat in an endometrial curettage specimen Fat in colonic endoscopic polypectomy specimens
Unexpected or discrepant findings	Unexpected or discrepant findings Significant disagreement between frozen section and final diagnoses Significant disagreement between immediate interpretation and final FNA diagnosis Unexpected malignancy Significant disagreement and/or change between diagnoses of primary pathologist and outside pathologist consultation (at the original or consulting institution)
Infections	Bacteria or fungi in cerebrospinal fluid cytology in immunocompromised or immunocompetent patients Pneumocystis organisms, fungi, or viral cytopathic changes in bronchoalveolar lavage, bronchial washing, or brushing cytology specimens in immunocompromised or immunocompetent patients Acid-fast bacilli in immunocompromised or immunocompetent patients Fungi in FNA specimen of immunocompromised patients Bacteria in heart valve or bone marrow Herpes in Papanicolaou smears of near-term pregnant patients Any invasive organism in surgical pathology specimens of immunocompromised patients

RESULTS

There were 74 cases reported as a panic diagnosis in EMGTRH between January 2018–2021. Nine patients who had inappropriate contact information were excluded from this study. A total of 65 patients were included in this study (Figure 1).

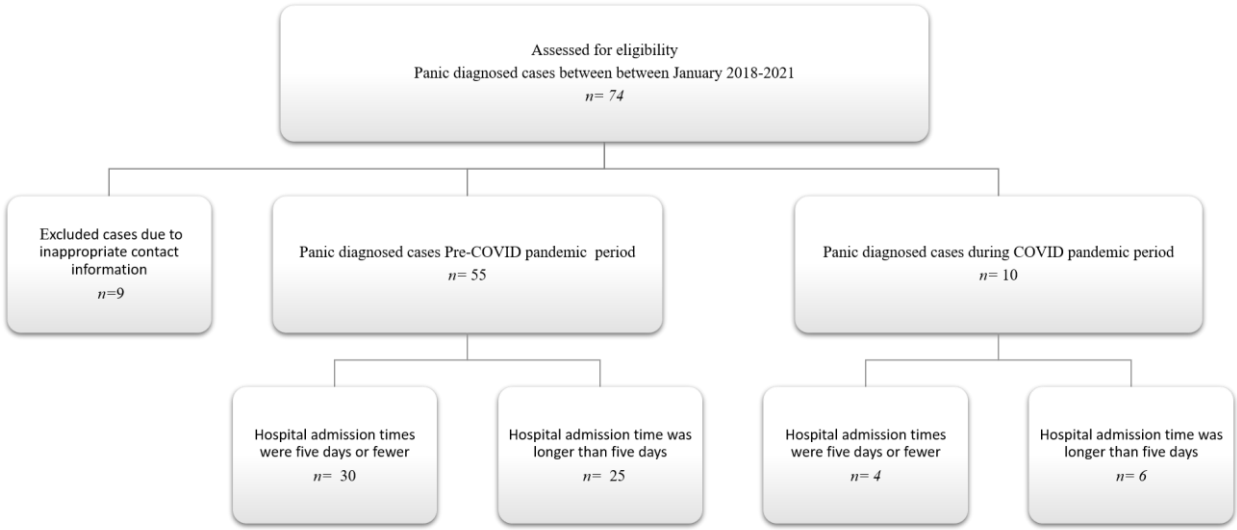

Figure 1. Flowchart demonstrating excluded cases and distribution of included cases according to hospital admission time.

The distribution of panic diagnosis of the 65 cases, demographic data, verbally notification status, and reaction time were presented in supplement data 1.

Of these 65 cases, 23 were males, and 42 were females; the median age was 52 years [range, 10–85]. One patient had leukocytoclastic vasculitis, 10 patients had uterine contents without villi or trophoblasts, and 54 patients had unexpected malignancy. The distribution of cases that had unexpected malignancy according to diagnosis was presented in Figures 2–3.

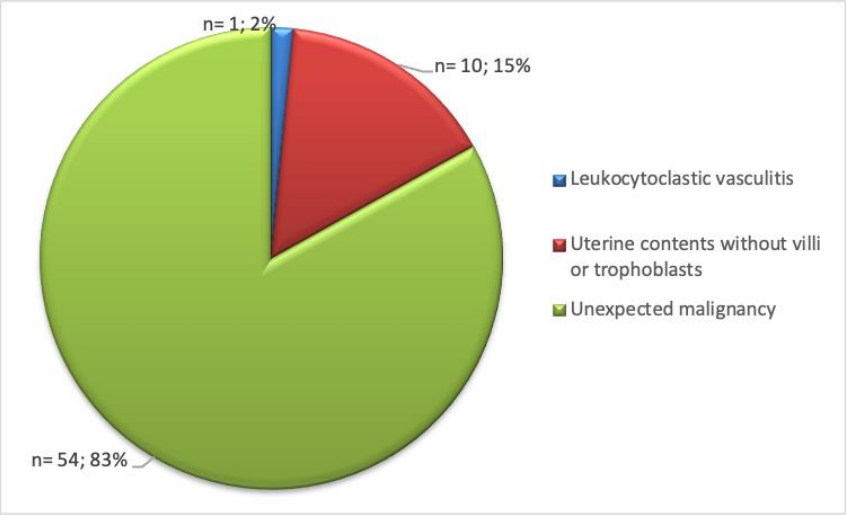

Figure 2.a. Distribution of cases according to causes of panic diagnosis

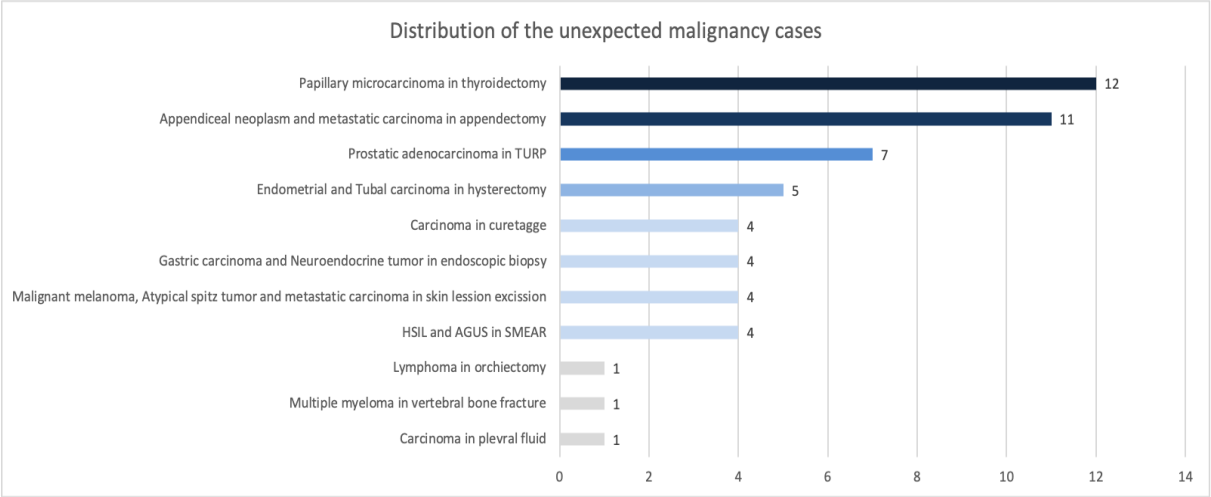

Figure 2.b. Distribution of cases with unexpected malignancy.

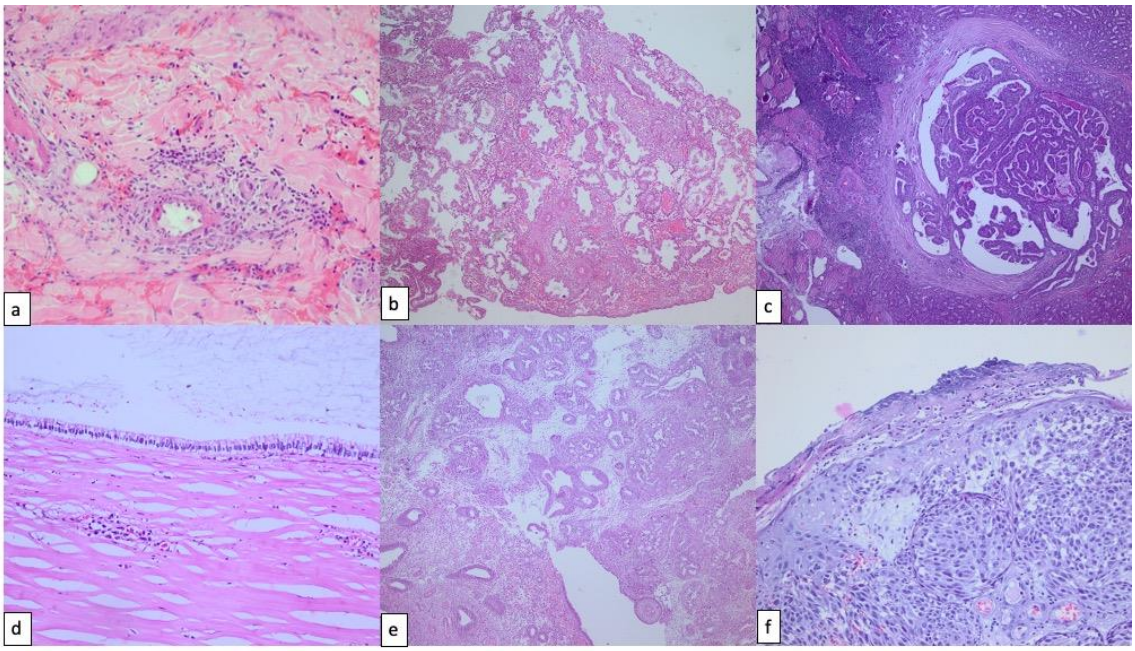

Figure 3. a; Leukocytoclastic vasculitis (H&E x100), b; Uterine contents without villi or trophoblasts (H&E x40), c; Papillary microcarcinoma (H&E x40), d; Low-grade mucinous neoplasm (H&E x200), e; Endometrial polyp and endometrial carcinoma (H&E x100), f; Malign melanoma (H&E

There were 55 cases in the pre-COVID-19 group. Thirty cases' hospital admission times were five days or fewer when cases were recruited into FG, and 25 cases' hospital admission time was longer than five days when cases were recruited into SG. The average length of admission to the hospital was 2.2 days in FG and was 99 days in SG (7–360). The average age was 47 years in FG and 59 years in SG. The average distance of the patient's living area to the hospital was 11 km (1–52) in the FG and 59 km in SG (4–390 km).

There was a statistically significant difference in the average distance of the patient's living area to the hospital, age, and notification status between FG and SG in the pre- COVID-19 group. There was no statistically significant difference in gender between FG and SG. The summary of distribution and statistical comparison of age and distance between patient home and hospital among FG and SG were presented in Table 2.

Table 2. The distribution and statistical comparison of age and distance between patient home and hospital among groups in pre- COVID period.

	Fast Admitted Group		Slow Admitted Group		
	Means ± SD	**Median (Min-Max)**	**Means ± SD**	**Median (Min-Max)**	**p**
Age	46.83±17.86	48.50 (10.00-79.00)	59±16.05	64.00 (23.00-85.00)	0.011[1]
The distance between patient home and hospital	10.03±13.02	5.00 (1.00-52.00)	59.36±80.4	55.00 (3.00-390.00)	<0.001[2]

SD: Standard deviation
[1] Student's t test, statistically significant at 0.95 confidence level
[2] Mann-Whitney U test, Statistically significant at 0.999 confidence level

Among pre-pandemic group cases, forty were verbally informed about panic diagnosis by phone call, 15 were not able to inform due to wrong phone number records. The mean time (day) of admission to the hospital of verbally informed and not verbally informed cases were five days and 156 days, respectively. Our results revealed that receiving verbal phone notification was significantly associated with patients' admission to the hospital time (Table 3). Admission times were on mean about 151 days longer in a patient in the not verbally informed cases compared to verbally informed cases in the pre- COVID-19 group.

Table 3. Chi-square test results between study groups in pre-COVID period, notification status, and gender

		FG	SG	p	OR (95%CI)
Gender	**Male/Female**	7/23	12/13	0.138*	0.431(0.140-1.326)
Notification Status	**Not Verbally informed /Verbally informed**	0/30	15/10	<0.001**	N/A

*not statistically significant (p>0.05)
**Statistically significant at 0.999 confidence level
OR: Odds ratio, FG: Fast admitted Group, SG: Slow Admitted Group

There were 10 cases in the COVID-19 pandemic group. Four cases of admission times were five days or fewer (1–5), and six cases admission time were longer than five days (16–40). We ascertained that four cases in the COVID-19 pandemic group were receiving treatment in the home due to COVID-19 infection at the time of diagnosis.

All cases in the COVID-19 pandemic group were verbally informed about panic diagnosis by phone call. The mean time (day) of admission to the hospital was 18.3 days (1–40). Admission times were on mean about 13.3 days longer in verbally informed cases in the COVID-19 pandemic group compared to verbally informed cases in the pre-COVID-19 group.

DISCUSSION

The concept of critical value in clinical pathology was first described by Lundberg in 1972 as "Pathophysiological derangements at such variance with normal as to be life-threatening if therapy is not instituted immediately." (12). The critical values in surgical pathology handled by Pereira et al. approximately thirty years from this, and they described possible surgical pathology critical value cases that need immediate communication (1). Over the years, the concept of critical diagnosis has been adopted by pathologists, and communication checklists have been added to the Laboratory Accreditation Programs by National Pathology Societies (2). National pathology societies recommend that each pathology department should identify potential panic diagnosis lists and draw up a communication policy (2).

Our panic diagnosis policy has been created according to the national pathology societies recommend; when a panic diagnosis is detected, verbal communication provides with the patient's responsible clinicians as soon as possible. The information of the clinicians and notification time are noted on the panic diagnosis form. When we

sign out a panic diagnosis, we indicate the patient as a panic diagnosed patient over the hospital information processing system (HIPS). Subsequently, the HIPS sends a notification message to the system and mobile phone of the responsible clinician. The HIPS also sends an information message to the patient's phone. We attach importance to informing the responsible clinicians as well as informing patients verbally about panic diagnosis. We only inform the patients about they had panic diagnosis and recommend that they should admit to the hospital as soon as possible. We don't give detailed information about diagnosis.

Most of the panic diagnosis cases were detected in materials sent from the surgical services department, and these clinicians devote most of their employment period to surgical procedures. If clinicians receive the panic diagnosis notification during surgical procedures, reaching a patient's contact information may take a long time. For this reason, we prefer to provide verbal information to the patient.

The annual average number of cases in our department was approximately 12000 and panic diagnosis cases accounted for approximately 0.25% of them. We recorded a significant decrease in the number of cases during the COVID-19 pandemic. Studies showed that panic diagnosis rates accounted for 0.5-20% of all cases (13, 14). This rate may differ according to the specific institutional factors, such as the bed capacity, organ transplantation unit, and case types. Informing patients verbally about the diagnosis can cause a serious increase in the daily workload in centers with a high panic diagnosis reporting rate.

Several studies indicated that well-timed effective verbal communication had a beneficial impact on patient's outcome and treatment management (5, 13). Staats et al. revealed that pathology laboratories had different approaches to time limitation, such as within 1-hour, same day, or no specific time frame, for communicating with the clinician (15). We do not have a strict time frame policy. Most of our cases had unexpected malignancy diagnosis and the information content is more important than the time of communication. Therefore, we provide communication between the clinicians and pathologists as soon as possible. Our findings showed that the duration of admission to the hospital of panic diagnosed patients in surgical pathology varied between 1 and 360 days. The prolonged admission time indicates that patients are not adequately informed about following up pathology reports, even if only indirectly.

The most important findings of our study were taking a phone notification has a beneficial impact on admission time. Admission times were on mean about 151 days longer in the patient in the not verbally informed group compared to the verbally informed group in the pre-COVID-19 period. We observed that even if the patients were verbally informed during the COVID-19 pandemic, they applied to the hospital for a longer period compared to the pre-pandemic period, five days, and 18.3 days, respectively.

We could not make a notification to fifteen patients since the contact information in HIPS belonged to different people or was not up to date. We believe that informing patients about the process of pathology reports and reminding them to keep their phone numbers in hospital records up to date to communicate in possible panic diagnosis situations may help shorten the admission time.

Many studies revealed that hospital admission for acute medical illnesses, including stroke and acute myocardial infarction, fell dramatically with the onset of the COVID-19 pandemic (9–11). The most reasonable explanation for patients' attitude is that the limitation of elective surgical procedures and non-critical healthcare services and quarantine procedure made it difficult for patients to access healthcare services for non-COVID-19 conditions or patients avoided seeking hospital care, perhaps in response to the fear of COVID-19 infection. The transportation of patients with COVID-19 to the hospital is provided only through the 112 Emergency Ambulance Service (EAS) in Turkey. EAS evaluates the patient's complaints related to infection and decides for the transportation of patients with COVID-19 to the hospital. Informing the EAS about the provision of transportation to the hospital in cases of COVID-19 positive panic diagnosed patients in surgical pathology may be effective in shortening the admission time.

In Turkey, doctors and patients can access health data collected from the health institution, regardless of where the examinations and treatments are held, via e-nabız that is an application developed by the Ministry of Health. Mobile phone applications such as e-nabız that provide communication between patients and the healthcare system, contribute positively to the country's healthcare system. In our country, primary care can also reach patients in a brief time via e-nabız. Therefore, we believe that sending automatic messages to family medicine units, which are primarily responsible for patients with applications such as e-nabız, can increase the chance of success in reaching the patient in cases of panic diagnosis. Our hospital has been integrated into this system in 2020. Due to the small sample size, the effect of this system on the application period cannot be evaluated clearly.

So far, a limited number of studies have been published on panic diagnosis. Most of the previous studies focused on the general recommendation of critical value policy, effective communication of critical diagnosis, or documentation of possible diagnostic list considered a critical diagnosis by pathologist or

clinician (13, 14, 16-20). To the best of our knowledge, this study is the first attempt at a comprehensive evaluation of factors that may affect the time of admission to the hospital who reaches a panic diagnosis. Our study has some limitations. This study has retrospective character in a single center and only provides information about the duration of hospital admission and trends of patients living around Erzincan. Therefore, our findings cannot be generalized to other population. Nevertheless, we believe that the findings of this study may be helpful to review the panic diagnosis communication policies of pathology laboratories. Further research with well-planned multi-centric studies in larger patient groups may be helpful to contribute to the development of panic diagnosis policy.

CONCLUSION

Several studies indicated that well-timed effective verbal communication had a beneficial impact on patient outcomes and treatment management. Our findings revealed that patients who were verbally informed about panic diagnosis were admitted to the hospital in a shorter time. Therefore, we believe that informing patients verbally should be included in panic diagnosis policies of surgical pathology, patients should be informed about the follow-up of the pathology report and their contact information should be kept up to date. Besides, integration of hospital panic diagnosis notification systems of the surgical pathology to health application and primary responsible family physician's systems may be useful for preventing unwanted delays.

Notes

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Supplement data-1. Demographic data, verbally notification status, admission to the hospital time and clinicopathological characteristic of the patients.

Panic Diagnosed Patients in Surgical Pathology, pre-COVID period

No	Gender	Age	Preliminary diagnosis	Procedure	Pathological diagnosis	Admission time	Study's group according to admission time	The distance between patient home and hospital	Verbally notification status
1	M	64	Vertebra fracture	Vertebral bone curettage	Multiple myeloma	2 days	FG	3 km	P
2	W	38	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	3 days	FG	4 km	P
3	M	78	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	1 days	FG	5 km	P
4	W	60	Leukoclastic vasculitis	Punch biopsy	Leukoclastic vasculitis	1 days	FG	4 km	P
5	M	61	Pangastritis	Endoscopic biopsy	Adenocarcinoma	2 days	FG	2 km	P
6	W	44	Acute appendicitis	Appendectomy	Neuroendocrine neoplasm	4 days	FG	3 km	P
7	W	40	Menorrhagia, Polyp	Curettage	Squamous cell carcinoma	2 days	FG	5 km	P
8	W	52	Screen test	SMEAR	HSIL	2 days	FG	6 km	P
9	W	55	Menorrhagia, Polyp	Curettage	Endometrial carcinoma	1 days	FG	3 km	P
10	W	59	Myoma uteri	TAH+BSO	Serous carcinoma of tuba uterine	2 days	FG	2 km	P
11	W	79	Menorrhagia, Polyp	Curettage	Squamous cell carcinoma	1 days	FG	4 km	P
12	W	10	Pyogenic granuloma	Lesion excision	Atypical spitz tumor	2 days	FG	3 km	P
13	W	22	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	2 days	FG	4 km	P
14	W	25	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	2 days	FG	5 km	P
15	M	64	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	5 days	FG	6 km	P
16	W	32	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	2 days	FG	2 km	P
17	W	28	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	3 days	FG	52 km	P

18	W	26	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	1 days	FG	10 km	P
19	W	30	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	1 days	FG	8 km	P
20	W	27	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	3 days	FG	43 km	P
21	W	29	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	4 days	FG	12 km	P
22	W	50	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	3 days	FG	39 km	P
23	W	42	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	2 days	FG	14 km	P
24	M	73	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	2 days	FG	8 km	P
25	W	66	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	3 days	FG	7 km	P
26	M	49	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	1 days	FG	6 km	P
27	W	54	Myoma uteri	TAH+BSO	Endometrial carcinoma	1 days	FG	1 km	P
28	W	48	Myoma uteri	TAH+BSO	Endometrial carcinoma	2 days	FG	5 km	P
29	M	62	Acute appendicitis	Appendectomy	Neuroendocrine neoplasm	2 days	FG	5 km	P
30	W	38	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	4 days	FG	30 km	P
31	M	67	Lipoma	Lesion excision	Metastatic Squamous cell carcinoma	32 days	SG	4 km	N
32	W	81	Vaginitis	SMEAR	HSIL	360 days	SG	70 km	N
33	W	85	Pangastritis	Endoscopic biopsy	Adenocarcinoma	180 days	SG	12 km	N
34	M	61	Pangastritis	Endoscopic biopsy	Adenocarcinoma	20 days	SG	7 km	P
35	W	64	Myoma uteri	TAH+BSO	Squamous cell carcinoma	35 days	SG	95 km	N
36	W	41	Myoma uteri	TAH+BSO	Endometrial carcinoma	90 days	SG	62 km	N
37	W	65	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	8 days	SG	101 km	P

38	W	73	Pyogenic granuloma	Lesion excision	Malign Melanoma	7 days	SG	4 km	P
39	M	65	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	18 days	SG	5 km	P
40	M	67	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	60 days	SG	5 km	N
41	M	70	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	20 days	SG	20 km	P
42	M	66	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	110 days	SG	120 km	N
43	W	58	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	360 days	SG	390 km	N
44	W	43	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	7 days	SG	8 km	P
45	M	60	Pangastritis	Endoscopic biopsy	Neuroendocrine neoplasm	16 days	SG	7 km	P
46	W	69	Multinodular goiter	Thyroidectomy	Papillary microcarcinoma	360 days	SG	72 km	N
47	M	50	Pilonidal cyst	Lesion excision	Malign Melanoma	20 days	SG	76 km	N
48	W	56	Screen test	SMEAR	HSIL	90 days	SG	77 km	N
49	M	36	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	8 days	SG	5 km	P
50	M	70	Acute appendicitis	Appendectomy	Metastatic Adenocarcinoma	10 days	SG	60 km	P
51	W	80	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	191 days	SG	100 km	N
52	M	29	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	112 days	SG	55 km	N
53	W	40	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	320 days	SG	6 km	N
54	W	23	Acute appendicitis	Appendectomy	Neuroendocrine neoplasm	19 days	SG	3 km	N
55	M	56	Acute appendicitis	Appendectomy	Mucinous Adenocarcinoma	10 days	SG	120 km	P

Panic Diagnosed Patients in Surgical Pathology, during COVID pandemic

No	Gender	Age	Preliminary diagnosis	Procedure	Pathological diagnosis	Admission time	Study's group according to admission time	The distance between patient home and hospital	Verbally notification status	COVID infection
1	W	55	Multi nodular goiter	Thyroidectomy	Papillary microcarcinoma	30 days	SG	2 km	P	COVID +
2	W	53	Vaginitis	SMEAR	Atypical glandular cells	16 days	SG	30 km	P	COVID +
3	W	29	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	3 days	FG	23 km	P	-
4	W	27	Suspicious of an ectopic pregnancy	Curettage	Uterine contents without villi	2 days	FG	19 km	P	-
5	M	71	Benign prostate hyperplasia	Transurethral resection	Prostatic adenocarcinoma	36 days	SG	45 km	P	COVID +
6	W	53	Menorrhagia, Polyp	Curettage	Squamous cell carcinoma	1 days	FG	60 km	P	-
7	M	45	Multi nodular goiter	Thyroidectomy	Papillary microcarcinoma	25 days	SG	12 km	P	-
8	W	40	Acute appendicitis	Appendectomy	Low-grade mucinous neoplasm	40 days	SG	14 km	P	COVID +
9	M	55	Viral pneumonia	Thoracentesis	Lung Adenocarcinoma	5 days	FG	40 km	P	-
10	M	70	Orchitis	Orchiectomy	Lymphoma	25 days	SG	120 km	p	-

W: Woman; M; Man; TAH+BSO: Total abdominal hysterectomy with bilateral salpingo-oophorectomy; FG: Fast Group; SG: Slow Group; P: verbally informed; N: not verbally informed.

RESEARCH ARTICLE

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Treatment Cost Analysis of COVID-19 in patients Treated at a University Hospital in Turkey

ABSTRACT

Objective: To guide both the hospital management and the health policymakers who play a role in the management process of their disease by analysing the costs of the patients receiving inpatient treatment in Düzce University Health Application and Research Center (Hospital - DUHARH) due to coronavirus disease 2019 (COVID-19) from the perspective of the Social Security Institution (SSI).

Methods: The study covers 582 patients who received inpatient treatment in intensive care and other clinics in March/2020-December/2020 due to COVID-19 disease in DUHARH. In the study, all sample unselected populations were included. Retrospectively obtained data were analysed using bottom-up, document analysis, and multivariate regression analysis.

Results: It was determined that 60% of the 582 patients studied were male (350 people), 40% female (232 people) and that the average hospitalization period was 5.7 days, 23% (134 people) in the Pandemic Intensive Care Unit and 77% (448 people) in other pandemic services. The total amount invoiced to SSI by the hospital was 7.378.695,00 TRY ($ 1,052,595). It was determined that 79% of this was the intervention cost and the average daily hospitalization cost per patient was ± 2,099.80 TRY ($ 299.54). Besides, since gender discrimination is male, elderly patients are hospitalized in intensive care. The hospitalization period is P<0.05. It was observed that medicine, material, intervention, and examination costs have increased.

Conclusions: In the study conducted, it was observed that the increase in men, age and hospitalization period, and treatment in intensive care increased the costs, and among these, the intervention costs were the highest. To reduce the cost of illness, it is necessary to use lower-cost factors to eliminate the disease rate with restrictions and ultimately to vaccinate the whole population as soon as possible.

Keywords: COVID-19, Cost of Illness, Cost of Treatment, Cost Management.

Türkiye'deki Bir Üniversite Hastanesinde Yatarak Tedavi Edilen COVID-19 Hastalarının Tedavi Maliyet Analizi

ÖZET

Amaç: Coronavirus Hastalığı-2019 (COVID-19) nedeniyle Düzce Üniversitesi Sağlık Uygulama ve Araştırma Merkezinde (Hastanesinde- DUHARH) yatarak tedavi gören hastaların Sosyal Güvenlik Kurumu (SGK) perspektifi açısından maliyet analizini yaparak hem hastane yönetimine hem de hastalığın yönetim sürecinde rol oynayan sağlık politikası yapıcılarına yol göstermektir.

Gereç ve Yöntem: Araştırma, DUHARH'da COVID-19 hastalığı nedeniyle yoğun bakım ve diğer kliniklerde Mart/2020-Aralık/2020 dönemi içerisinde yatarak tedavi edilen 582 hastayı kapsamaktadır. Araştırmada örneklem seçilmemiş evrenin tamamı çalışmaya dahil edilmiştir. Retrospektif olarak elde edilen veriler, aşağıdan yukarı, doküman analizi ve çok değişkenli regresyon analiz yönetimiyle analiz edilmiştir.

Bulgular: Araştırma yapılan 582 hastanın %60'ı erkek (350 kişi), %40 kadın (232 kişi), ortalama yatış süresi 5,7 gün, Pandemi Yoğun Bakım Ünitesinde %23 (134 kişi) diğer pandemi servislerinde %77 (448 kişi) olduğu tespit edilmiştir. Hastane tarafından SSI'ya fatura edilen toplam tutar 7.378.695,00 TL ($1,052,595) olup bunun %79'nun müdahale maliyeti olduğu ve hasta başı günlük ortalama yatış maliyetin ± 2.099,80 TL ($ 299,54) olduğu saptanmıştır. Ayrıca cinsiyet ayrımının (erkeklerin), yaşlı hastaların, yatış yerinin (yoğun bakım) ve yatış süresi P<0.05 olduğundan ilaç, malzeme, müdahale ve tetkik maliyetlerini artırdığı tespit edilmiştir.

Sonuç: Yapılan çalışmada erkeklerin, yaşın ve yatış süresinin artması ve yoğun bakımda tedavi edilmenin maliyetleri artırdığı ve bunlar içerisinde en yüksek müdahale maliyetlerinin olduğu tespit edilmiştir. Hastalık maliyetinin azaltılması için daha düşük bedelli maliyet unsurlarına başvurulması, kısıtlamalarla hastalığın bulaş hızının ortadan kaldırılması ve nihayetinde tüm halkın bir an önce aşılanması gerekir.

Anahtar Kelimeler: COVID-19, Hastalık Maliyeti, Tedavi Maliyeti, Maliyet Yönetimi.

INTRODUCTION

An unknown cause of pneumonia was detected on December 31, 2019, in Wuhan city of Hubey province of China, and it was reported to the World Health Organization (WHO). Then, on January 5, 2020, the WHO named this new disease an epidemic (1). This virus, which has spread to many countries since its first appearance, was officially reported in Turkye on March 11, 2020 (2). Of even date, the WHO announced that the new type of coronavirus is a pandemic (1). As of this date, countries worldwide have had to take a series of drastic control measures, such as travel restrictions, closure of schools, universities, and workplaces, social distancing and quarantine, city, region, and country entry restrictions. The main purpose of these measures has been to reduce the rate at which the virus spreads until a vaccine, or effective treatment is found to alleviate the pressure on limited healthcare resources (3).

The most contagious time of the coronavirus, which can be transmitted directly (close contact) and indirectly (with environmental surfaces or equipment used by COVID-19 patients), is considered to be the time when the infected person is most symptomatic (4). The first symptoms of COVID-19 are usually dry cough, fatigue, muscle pain, dyspnea, and fever (5,6). While approximately 80% of patients have mild/moderate symptoms similar to cold or mild pneumonia, severe pneumonia requiring supplemental oxygen or invasive cardiopulmonary support may develop in 20% of patients (7). It is also among the findings that some patients with mild/moderate symptoms at the beginning progressed to severe pneumonia despite drug therapy (8). In case of detection of such findings, it requires treatment of COVID-19 patients through hospitalization (9). Therefore, the simultaneous hospitalization of many patients adversely affects the staff strength and capacity of hospitals and puts them in financial difficulties.

The treatment process of COVID-19 disease varies from person to person according to age, the severity of the disease, and comorbidity (8). Considering that this disease is an “epidemic” analysing the economic impact of COVID-19 treatment on healthcare institutions is gaining importance for governments to form constructive policies on the health economy. When the literature is reviewed, few studies aim to measure the direct medical costs of COVID-19. Khan et al. was evaluated survival according to age groups, gender, use of mechanical ventilators, nationality, and admission to the intensive care unit of hospitalized COVID-19 patients in the Kingdom of Saudi Arabia and measured the direct medical costs associated with hospitalization per patient (10). Jin et al. were analysed the health and societal cost of COVID-19 in 31 state-level administrative regions in China between January and March 2020 using a bottom-up approach (11). Li et al. was evaluated the affordability of treatment costs by comparing out-of-pocket expenses of COVID-19 patients in China by per capita disposable income (12). Gedik, as for that, was determined the cost of patients aged 18 and over who were diagnosed with COVID-19 between March 17 and May 11, 2020, at Taksim Training and Research Hospital in Turkey and treated for at least 24 hours (13). Besides, there are also studies investigating the economic, social, and communal effects (14,16) and labor and productivity losses (17,18) of the COVID-19 pandemic on countries.

In this study, treatment costs were analysed in terms of the SSI perspective of hospitalized patients for COVID-19 in DUHARH in Turkey. Medicine, medical equipment, intervention, and examination expenses were calculated as cost factors. However, the effects of patients’ age, gender, length of hospitalization, and treatment in pandemic intensive care unit and pandemic ward on cost factors were examined.

MATERIAL AND METHODS

Study Design: This study was conducted retrospectively in DUHARH. DUHARH is the only tertiary education and research hospital in the province where it is located and has 316 beds. According to the COVID-19 adult treatment algorithm (19) published by the Turkey Ministry of Health between March 11 and December 31, 2020, 582 hospitalized patients constitute the study sample. All COVID-19 patients of all ages and treated for at least 24 hours in all units were included in the study's scope.

All hospitalized patients gave informed consent before enrolment. This study was conducted with the Republic of Turkey Ministry of Health and Düzce University Non-Invasive Health Research Ethics Committee's approval.

Costs: Patients treated for COVID-19 disease in Turkey benefit from free health services under the General Health Insurance (GHI). Financing expenses arising from individuals with GHI's health care services are covered by a third party, the Social Security Institution (SSI). Within this scope, hospitals' expenses are collected from SSI. Price regulation applied in the collection process is provided by the Health Application Communiqué (HAC). HAC prices are a detailed pricing practice determined based on the transaction and package that SSI determines for certain services and pays to hospitals provided that they are duly invoiced. *In the study, these prices were calculated in Turkish Lira* and the Central Bank of Turkey's average exchange rate for 20*20 in $1 = 7.01 TRY.*

Retrospective data obtained through the hospital automation system was analysed with document analysis and a bottom-up approach. The bottom-up approach, one of the disease cost analysis approaches, is used to quantify each resource used to produce a service and calculate

total costs (20). In this approach, detailed activity data is used to estimate unit costs. Since it is assumed that resources will be addressed more comprehensively in a given service provider, more accurate results are obtained (21).

The purpose of the disease cost is to guide the decisions to be taken for the future by making use of past experiences. It is important to determine the perspective to be studied in the analysis process (28).

Treatment costs include all of the costs of COVID-19 and other related illnesses in pandemic intensive care and other pandemic wards hospitalized with the hospital's emergency unit. Within this scope, the invoice amount, including direct medical costs, consists of medicines, medical supplies, interventions, and examinations.

Medications include drugs such as Favipiravir, Hydroxychloroquine, Remdesivir, Azithromycin, Corticosteroids, Tocilizumab, Enoxaparin, Aspirin, non-steroidal anti-inflammatory drugs, various antibiotics, and serum treatments.

Medical supplies include blood glucose strip, cannula, three-way tap, drip adjustment set, cannula IV no: 22 (blue), surgeon glove, urine bag, an oxygen mask, patient diaper, overalls, mask, gloves, protective glasses, disinfectant, intravenous fluids, and other medical supplies.

Intervention includes factors such as oxygen inhalation therapy (hourly), glucose test (Bedside, glucometric), IV injection, Subcutaneous injection, oral, pandemic care service, intravenous drug infusion, standard bed fee, bedside visit, and respiratory support devices (high flow oxygen device, non-invasive and invasive mechanical ventilators).

Examinations include Potassium (Serum/Plasma), Creatinine (Serum/Plasma), Sodium (Serum/Plasma), Bun, Urea (Serum/Plasma), Chloride (Serum/Plasma), AST (Serum/Plasma), ALT (Serum/Plasma), CRP (Turbidimetric), Bt, thorax, posteroanterior chest X-ray P.A (one way), Covid-19 (SARS-CoV-2) Reverse Transcriptase PCR, Procalcitonin, D-dimer, quantitative, Ferritin (Serum/Plasma), Hemogram (Whole Blood).

Statistical Analysis: The study's statistical analyses were conducted with the EViews 10.0 (Quantitative Micro Software) econometric analysis program. Multivariate regression analysis was conducted in the study. There are coefficients calculated by the maximum likelihood method (OLS). When independent variables are two or more, multiple linear regression analysis is used. This analysis was examined by correlating the cost factors of hospitalized patients for COVID-19 with gender, age, hospitalization duration, and place. Accordingly, a p-value less than 0.05 was considered significant. The econometric model of the study is given below (22).

By generalizing the bivariate population regression function (PRF), the tri-variable PRF can be written as:

$Yi = \beta1 + \beta2X2i + \beta3X3i + \ldots. + ui$

The models used in this study are as follows.

Yi: total costs, medicine costs, intervention costs, material costs, examination costs

β1: Intercept/constant

X2i: gender

X3i: age

X4i: hospitalization duration

X5i: hospitalization place

Wherein Yi is the dependent variable; X2 and X3 are explanatory (or independent) variables; u is probabilistic destructive term; i is the ith observation; if the data are time series, t will be the tth observation.

In the above equation, β_1 is the constant term. Although this, in mechanical interpretation, means the average value of Y when X_2 and X_3 equal to zero, as usual, it shows the average effect on Y of all variables not included in the model. $\beta 2$ and $\beta 3$ are called partial regression coefficients. Their meanings are described below.

The mean of u_i is zero:

- For each i, $E(u_i \mid X_{2i}, X_{3i}) = 0$

There is no autocorrelation:

- $orv\ (u_i, u_j) = 0\ (i \neq j)$

There is a constant variance:

- $var\ (u_i) = \sigma^2$

Common variables between u_i, and each variable are zero:

- $orv\ (u_i, X_{2i}) = orv\ (u_i, X_{3i}) = 0$

No modelling error was made:

- The model was set up correctly.

There is no exact multi-linearity between X variables:

There is no exact linear relationship between X_2 *and* X_3.

Limitations of the Study: Study data are limited to a tertiary University Hospital in Turkey. Similar studies should be conducted in countrywide secondary-level public hospitals and private hospitals. This study is limited to the treatment costs of COVID-19 disease borne by the SSI. The cost of a disease does not consist of only one perspective and direct medical costs and should be analysed from different perspectives, taking into account indirect non-medical costs. In our study, the determination of the disease's daily and per-patient costs is an approximately average determination. Whereas each patient hospitalized with the same disease consumes hospital resources (cost factors) in different ways. The HAC pricing policy created by SSI is not suitable for this. Besides, the treatment of comorbid diseases of each patient was not considered in the study.

RESULTS

The study contains four variables that affect the cost factors. These are gender, age, hospitalization period, and place.

Gender: The results have analysed the effect of being a male on cost with the Male 1, Female 0 hypothesis.

Hospitalization Place: The effect of being in an intensive care unit on costs was analysed with pandemic intensive care 1, pandemic services 0 hypotheses. All models have heteroscedasticity problems. This reduces the confidence in the coefficients. Nevertheless, the results can be interpreted in terms of the general trend.

The relationship between the total costs, medicine, medical equipment, intervention, and examination costs invoiced to SSI for HAC and the variables of these cost factors are shown in the tables below (Table 1).

Table 1. The Effect of gender, age, hospitalization duration and place on total cost

Variable	Coefficient	Std. Error	t-Statistic	Prob.
Gender	360.0995	545.9311	0.659606	0.5098
Age	31.56875	12.37886	2.550214	0.0110
Hospitalization Duration	1626.876	47.64136	34.14838	0.0000
Hospitalization Place	4945.501	667.8411	7.405205	0.0000
C	-7012.179	918.1144	-7.637587	0.0000
R-squared	0.677198	Prob(F-statistic)		0.000000
F-statistic	302.6186	Durbin-Watson stat		2.022019

The effect of gender on total cost (Prob>0.05) is not significant. In another saying, gender discrimination has no effect on the total cost. A one-year increase in the patient's age increases the total cost by 31.50 TRY, and a one-day increase in the hospitalization duration increases the total cost by 1.626,80 TRY. Hospitalized patients in intensive care increase the total costs. Since this is a dummy variable, the average was 4,945.00 TL, but it is a correct approach not to give figures. Regarding total invoice amounts, hospitalized patients in pandemic intensive care and hospitalization duration appears to have a greater effect on costs.

Accordingly (Table 2), it was observed that being in the intensive care unit had a negative effect on medicine cost, but this was not statistically significant (Prob=0.9479). Due to the treatment fees of intensive care patients made by SSI over the price of the package (including medicine, material, intervention, and examination), medicine costs appear to be low. A one-year increase in patient age has a weak positive effect on medicine costs, but the effect's confidence interval is significant according to 10%. It is seen that each male increases the cost of medicine use by 208.38 TRY, and each additional daily admission increases the medicine cost by 70.37 TRY compared to females.

Table 2. The effect of gender, age, hospitalization duration and place on medicine costs

Variable	Coefficient	Std. Error	t-Statistic	Prob.
Gender	208.3812	92.98429	2.241037	0.0254
Age	3.680410	2.108397	1.745596	0.0814
Hospitalization Duration	70.37376	8.114391	8.672710	0.0000
Hospitalization Place	-7.435709	113.7483	-0.065370	0.9479
C	-134.6614	156.3754	-0.861141	0.3895
R-squared	0.133563	Prob(F-statistic)		0.000000
F-statistic	22.23637	Durbin-Watson stat		2.075677

Accordingly (Table 3), it was determined that the amount of material used for males increased by 181.68 TRY, an additional yearly age increase by 4.03 TRY, and each additional patient staying in intensive care increased by 343.56 TRY. By contrast, a one-day increase in hospital stay reduces the cost of material usage by 13.48 TRY.

Table 3. The effect of gender, age, hospitalization duration and place on medical equipment costs

Variable	Coefficient	Std. Error	t-Statistic	Prob.
Gender	181.6824	69.15958	2.627003	0.0088
Age	4.035029	1.568177	2.573069	0.0103
Hospitalization Duration	-13.48266	6.035297	-2.233967	0.0259
Hospitalization Place	343.5670	84.60336	4.060915	0.0001
C	-120.1599	116.3085	-1.033114	0.3020
R-squared	0.055110	Prob(F-statistic)		0.000001
F-statistic	8.413323	Durbin-Watson stat		1.997523

Accordingly (Table 4), the effect of being male on intervention costs is not statistically significant (Prob=0.9402). All other variables have a positive and significant effect on cost. A one-year increase in patient age has a weak positive effect on intervention costs, but the effect's confidence interval is significant according to 10%. One-day increase in the hospitalization duration increases the intervention cost by 1,531.38 TRY, and the treatment in the pandemic intensive care unit increases the intervention cost by 4,842.94 TRY.

Table 4. The effect of gender, age, hospitalization duration and place on intervention costs

Variable	Coefficient	Std. Error	t-Statistic	Prob.
Gender	-41.23016	549.6374	-0.075013	0.9402
Age	22.10736	12.46290	1.773854	0.0766
Hospitalization Duration	1531.388	47.96479	31.92733	0.0000
Hospitalization Place	4842.948	672.3750	7.202749	0.0000
C	-6970.922	924.3473	-7.541453	0.0000
R-squared	0.646518	Prob(F-statistic)		0.000000
F-statistic	263.8330	Durbin-Watson stat		2.000020

Accordingly (Table 5), the effect of gender and age on examination costs is statistically insignificant (Prob>0.05). While staying in the pandemic intensive care unit reduces the examination costs by 242.31 TRY, an additional day of age increases the examination costs by 33.91 TRY. Due to the treatment fees of intensive care patients made by SGK over the package price, medicine costs appear to be low.

Table 5. The effect of gender, age, hospitalization duration and place on examination costs

Variable	Coefficient	Std. Error	t-Statistic	Prob.
Gender	-19.36029	34.37494	-0.563209	0.5735
Age	1.236443	0.779444	1.586315	0.1132
Hospitalization Duration	33.91910	2.999772	11.30722	0.0000
Hospitalization Place	-242.3170	42.05109	-5.762442	0.0000
C	192.3051	57.80973	3.326517	0.0009
R-squared	0.260315	Prob(F-statistic)		0.000000
F-statistic	50.76535	Durbin-Watson stat		1.979820

It was determined that among patients hospitalized due to COVID-19, the invoice amount per patient is the highest 222,884.30 TRY and the lowest 49.19 TRY; the highest amount of drug Immun Globulin IV (Human) (Non-specific) is 5,041.99 TRY (6 units), the lowest Pantoprazole is 14.79 TRY (5.010 units), the highest material amount Triathlon Total Stabilizer Femoral Component Cemented - (Left Size # 5) is 3.019.63 TRY (1 piece) the lowest Three-Way Faucet is 0.28 TRY (2.293 pieces), the highest intervention amount (P) Hemicolectomy (right or left) is 10,327.43 TRY (1 unit), the lowest Oxygen inhalation therapy (hourly) is 1,00 TRY (33.301 hours), the highest test amount Apheresis Immun TDP is 782.00 TRY (9 pieces), the lowest Potassium (Serum/Plasma) is 2.00 TRY (4.687 pieces) (Table 6).

Table 6. Costs and factors affecting them

	Invoice	**Medicine**	**Medical Equipment**	**Intervention**	**Examination**	**Gender**	**Age**	**Hospitalization Duration**	**Hospitalization Place**
Mean	5657.506	616.7373	235.2373	4313.395	392.6949	0.609966	59.71478	5.773196	0.237113
Median	3769.640	312.7800	10.69000	2667.210	281.4600	1.000000	66.00000	4.000000	0.000000
Maximum	222884.3	5041.99	3019.63	10327.43	782.00	1.000000	97.00000	91.00000	1.000000
Minimum	49.19	14.79	0.28	1.00	2.00	0.000000	0.000000	1.000000	0.000000
Std. Dev.	11213.59	1165.778	830.3031	10788.66	466.4374	0.488177	22.95812	5.639799	0.425678
Skewness	13.65352	6.441748	7.073323	14.92851	3.993753	-0.450903	-1.217112	6.865799	1.236205
Kurtosis	249.4517	56.69830	76.83740	286.8118	31.09212	1.203313	3.913445	93.14902	2.528202
Jarque-Bera	1490990.	73950.17	137063.2	1974935.	20684.47	98.00240	163.9259	201648.5	153.6335
Probability	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
Sum	3292669.	358941.1	136908.1	2510396.	228548.4	355.0000	34754.00	3360.000	138.0000
Sum Sq.Dev.	7.31E+10	7.90E+08	4.01E+08	6.76E+10	1.26E+08	138.4622	306230.7	18480.06	105.2784
Observations	582	582	582	582	582	582	582	582	582
Total Cost (TRY)	7.378.695,22	737.679,43	231.245,27	5.850.916,42	558.854,10				

60% of the patients are male (350 people), 40% are female (232 people), the highest age of the patients is 97, the youngest age is 0 (newborn), and the average age is 59. The longest hospitalization period is 91 days, the shortest is 1 day, and the average is 5.7 days. The rate of patients receiving treatment in the Pandemic Intensive Care Unit is 23% (134 people), and the rate in other pandemic wards is 77% (448) (Table 6). 10% (59 people) of the patients died, 90% (523 people) were discharged after recovery or their current condition.

DISCUSSION

The total amount invoiced to SSI for HAC between March/2020-December/2020 due to COVID-19 disease at the hospital where the research was conducted 7,378,695.22 TRY ($ 1,052,595). It was determined that 10% of this amount is medicine cost 737,679.43 TRY ($ 105,232), and 4% material cost is 231,245.27 TRY ($ 32,988), 79% intervention cost is 5,850,916.42 TRY ($ 834,652) and 7% examination cost is 558,854.10 TRY ($ 79,722) (Chart 1).

The intervention costs are higher than other cost factors caused by the pricing policy of the treatment fees of intensive care patients based on the package price (including medicine, material, intervention, and examination) by SSI.

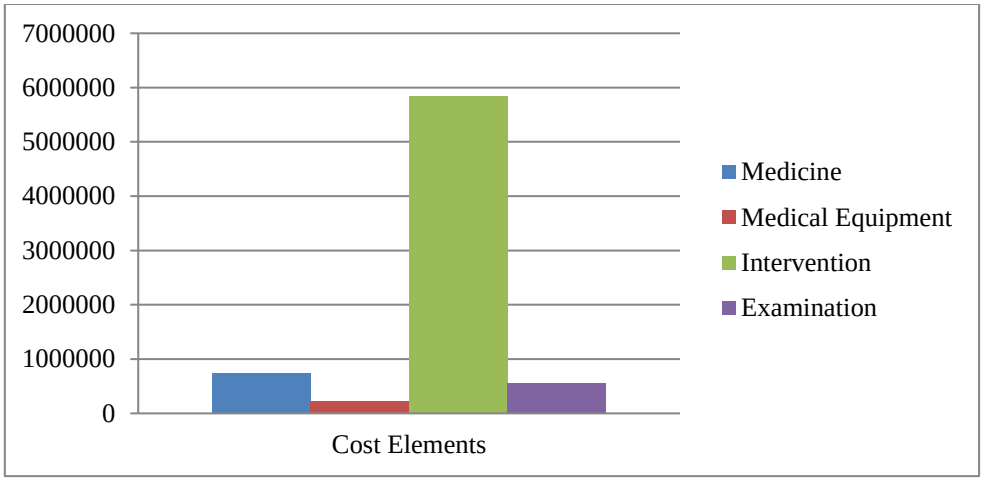

Chart 1. Invoize amount costs (TRY)

The study determined that the total cost of 582 patients treated in different units due to COVID 19 was 7,378,695.00 TRY ($ 1,052,595), and the hospitalization day was 3,514 days. According to this, the average daily cost was determined as ±2.099.80 TRY ($ 299.54), and the average cost per patient was determined as ±12,678.17 TRY (1,808 USD).

Average hospitalization costs in studies investigating medical costs per patient in other countries were reported as 3,045 USD (23) in the United States, 6,827 USD (12) in China, 12,637.42 USD in Latin America, and 2,192 USD (25) in children aged 0-19 in Korea, 12,547 USD (10) in Saudi Arabia, 4,633.43 (26) in India and 4,847 Sterling (27) in the United Kingdom. These differences in average costs between countries are thought to be due to reasons such as applying different methods in disease cost analysis, different treatment protocols, preferences in utilization rates of health personnel and health care resources, and medical equipment price levels across countries.

This study reveals that the treatment cost of COVID-19 disease is less costly in Turkey than in other countries. We can state that the most important reason for this is due to the health system in Turkey much better, the low rate of the population over the age of 65 (9%; 7.3 million), sufficient staff and bed capacity, low cost of medicine, medical equipment, intervention, examination, and other medical care.

In addition to the support provided by the Ministry of Health in the Hospital where the study was conducted, it was determined that there was no shortage of protective materials thanks to the effective material and stock management by the Hospital management. In addition, protective equipment such as masks, gloves, disinfectants, and aprons, which are vital in the epidemic, were donated by philanthropists, contributing to the uninterrupted execution of services (29).

CONCLUSION

In the study conducted, it was observed that gender discrimination did not affect the total cost. However, elderly patients slightly increased the costs. When an overall evaluation is made, it was observed that the intervention cost is the highest cost among the costs, and patients in intensive care unit and hospitalization duration appear to have a greater effect on the total cost.

The results obtained in the study were revealed that the COVID-19 epidemic caused high direct medical care costs. For this reason, to reduce the cost of the disease, it is necessary to resort to lower-cost elements, to encourage the domestic production of medical supplies, medicines, and vaccines, to review the drug price policy these days

when the vaccine is available, to take additional measures to prevent the spread of the disease, to eliminate the transmission rate of the disease with restrictions taking into account the economic balances and ultimately to vaccinate the entire population as soon as possible.

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RESEARCH ARTICLE

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An Analysis of the Attitudes of Family Physicians towards the COVID-19 Vaccine

ABSTRACT

Objective: This study has aimed to reveal the opinions of family physicians on the COVID-19 vaccine.

Methods: The data collection forms prepared for this cross-sectional study were converted into an online questionnaire form and sent to the physicians working as family physicians in different provinces of Turkey between December 2020 - January 2021 via e-mails (GoogleGroups) and communication groups (Facebook, WhatsApp, etc.). The responses of 494 family physicians in Turkey, who were accessible through this method and volunteered to participate in the study, were recorded to be analysed.

Results: Of the 494 family physicians in our study, 6.3% (n=31) appeared to have no intention of getting vaccinated against the COVID-19, whereas 13.2% (n=65) were undecided. The opinion towards which the participants in our study had the highest positive attitude was related to the necessity to provide everyone with the COVID-19 vaccine', while the most obvious negative attitude was related to the view that the efficacy of the vaccine has not yet been tested sufficiently.

Conclusions: Although a significant majority of family physicians have a positive attitude towards the need for administering the COVID-19 vaccine, more than half have expressed a negative or indecisive attitude towards relying on the statements made about the vaccine and its efficacy, which is said to have been adequately tested. For the desired levels can be reached in terms of vaccination rates, it is necessary to inform family physicians about the efficacy and benefits of the vaccine and to convey this information to individuals through family physicians.

Keywords: Family Medicine, Vaccination, COVID-19.

Aile Hekimlerinin COVID-19 Aşısına Yönelik Tutumlarının Değerlendirilmesi

ÖZET

Amaç: Bu çalışmada aile hekimlerinin COVID-19 aşısına yönelik düşüncelerinin incelenmesi amaçlanmıştır.

Gereç ve Yöntem: Kesitsel tipteki bu çalışma için hazırlanan veri toplama formları online anket formuna dönüştürülerek Aralık 2020 - Ocak 2021 tarihleri arasında Türkiye'nin farklı illerinde aile hekimi olarak çalışan hekimlere e-posta (GoogleGroups) ve iletişim grupları (Facebook, WhatsApp vb.) aracılığı ile iletildi. Bu yöntemle ulaşılan ve çalışmaya katılmaya gönüllü olan Türkiye'deki 494 aile hekiminin yanıtları analiz edilmek üzere kayıt altına alındı.

Bulgular: Çalışmamızda yer alan 494 aile hekiminin %6,3'ünün (n=31) aşı olmayı düşünmediği, %13,2'sinin (n=65) ise aşı olmak konusunda kararsız olduğu belirlendi. Çalışmadaki katılımcıların en yüksek düzeyde olumlu tutum içerisinde olduğu görüş herkese COVID-19 aşısı uygulanması gerektiği iken; en belirgin olumsuz tutum ise aşının etkinliğinin yeterince test edilmediği olarak belirlendi.

Sonuç: Aile hekimlerinin önemli bir çoğunluğu COVID-19 aşısının topluma uygulanması konusunda olumlu bir tutuma sahipken, yarıdan fazlası aşı ve etkinliği hakkında yapılan açıklamalara güvenme konusunda olumsuz veya kararsız bir tutum sergilemiştir. Aşılama oranlarının istenilen seviyelere ulaşabilmesi için aile hekimlerinin ve aile hekimleri aracılığı ile toplumun aşının güvenilirliğine ve etkililiğine dair daha fazla bilgilendirilmesine ihtiyaç vardır.

Anahtar Kelimeler: Aile Hekimliği, Aşılama, COVID-19.

INTRODUCTION

The COVID-19 virus is rapidly transmitted from person to person and can result in massive destructive consequences. The pandemic caused by the virus has, therefore, been declared as a public health problem by the World Health Organization (WHO) (1).

Since the beginning of the pandemic, scientists have been trying to develop treatments with intensive efforts in order to alleviate the evident upsurge in the number of cases and prevent negative clinical consequences around the world. Although many studies exist on the possible treatment of the virus, the consensus among experts is that only an effective COVID-19 vaccine will end the pandemic (2). For this purpose, Russia became the first country in the world to approve a vaccine developed against COVID-19 on August 11, 2020, and named it Sputnik V (3). According to the official statement of the WHO, there are 105 COVID-19 vaccine candidates in clinical development (4). A number of treatments that have been attempted in a short time with intense efforts have, unfortunately, brought some uncertainties. Despite the seemingly high efficacy of the vaccines, developed through Phase 3 trials with relatively short follow-up periods due to the race against time, it is also widely accepted that more reliable information is needed about longer-term safety and duration of vaccine protection (5).

A major concern is the administration of a weakly effective vaccine, which may lead to an erroneous interpretation among the authorities that there is a significant reduction in risk, and may negatively affect compliance with the control of the pandemic (6). Vaccination is a measure within the scope of primary protection as a preventive health service and the protective effect of vaccination depends on epidemiological criteria such as the efficacy and effectiveness of the vaccine, the effects of the vaccine program, the infectious effects of the vaccine, and the number of people needed to vaccinate (7).

In the management of the pandemic, family physicians, who are the backbone of preventive health services, are thought to have responsibilities in various areas, ranging from triage, treatment, follow-up, efficient use of resources, and providing cost-effective care (8). In Turkey, the source cases and their contacts have been identified, and the isolation of the cases and the quarantine of the contact persons have been ensured thanks to the strictly applied contract tracing under the leadership of family physicians.

In line with the latest developments in Turkey, family physicians has active duties and responsibilities in the vaccination process too.

It is believed that the COVID-19-vaccine-related attitudes and behaviours of family physicians, who deliver protective and preventive health care services to the public and are in close contact with individuals in the community, will be influential in the vaccination rates in the society. This study has aimed to reveal the opinions of family physicians on the COVID-19 vaccine.

MATERIAL AND METHODS

Sample Groups: The population of this cross-sectional survey study consisted of healthcare professionals working as family physicians in Turkey.

While calculating the sample size, the information that the number of family physicians in Turkey is 24,428 was used (9). It is aimed to reach 378 people with a 95% confidence interval and a 5% margin of error using the formula for Sample Size for Finite Universe ($n = X^2NP(1-P) \div d^2(N-1)+X^2P(1-P)$.

The data collection period started on 22 December 2020 with a group of 50 people, the majority of whom were physicians working in the Family Medicine Clinic in University of Health Sciences Antalya Training and Research Hospital. First of all, data collection forms were sent to physicians as online questionnaires via e-mail (GoogleGroups) and communication groups (Facebook, WhatsApp). After being asked sociodemographic and descriptive questions, the physicians were administered the 'COVID-19 Vaccination Attitude Scale', consisting of nine questions and two sub-dimensions (negative and positive attitude) which was developed in Turkey by Geniş et al. (10).

The data collection forms containing the scale were delivered to other family physicians in the form of an online questionnaire via e-mail and communication groups by snowball sampling. After subtracting the answers of 2 participants who declined to participate in the study, 15 participants whose questionnaires were received back more than once, and 2 participants who gave inappropriate answers (such as having more years of professional experience than their age), the answers of the remaining 494 family physicians from 53 different provinces were recorded and the data collection period ended on 08.01.2021, when Turkey had not yet started mass vaccination.

Measurement Tools

Sociodemographic Data Form: The present study includes a data form prepared by the researchers in such a way as to contain age, gender, marital status, and other sociodemographic and clinical characteristics associated with the COVID-19 pandemic.

COVID-19 Vaccination Attitude Scale: Developed by Geniş et al., consisting of nine questions and two sub-dimensions (negative and positive attitude) (10). The levels of expressions in the scale were presented as 'Definitely Disagree' 1, 'Disagree' 2, 'Undecided' 3, 'Agree' 4, and 'Strongly Agree' 5; the items in the negative attitude

sub-dimensions were scored in reverse order as follows: (1 → 5, 2 → 4, 3 → 3, 4 → 2, 5 → 1). A mean value between 1-5 was obtained by dividing the score obtained by the sum of the item scores in the scale sub-dimension by the number of items in that sub-dimension. If that mean value was for the positive attitude sub-dimension and high, the attitude towards the vaccine was deemed positive, if, on the contrary, it was for the negative attitude sub-dimension and high, the participants were considered to hold less negative attitudes towards the vaccine.

Prior to the study, the necessary permission was first obtained to use the scale, and approval was obtained from the Scientific Research Platform of the Ministry of Health and the University of Health Sciences Antalya Training and Research Hospital Clinical Research Ethics Committee with the decision number 20/13, dated 22.12.2020. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Assessment: The data obtained in the study were analysed using IBM SPSS 23.0 software (IBM Corp., Armonk, NY). Descriptive statistics were presented with n (%) and mean ± standard deviation and median (min-max) values. Fisher's Exact test was used to examine the relationships between categorical variables, and Bonferroni correction was applied in paired comparisons. Shapiro Wilks test was used to assess the assumption of normality. Mann–Whitney U test and Student's t test were used for analysis of non-normally and normally distributed numerical data, respectively. Kruskal Wallis test was used for comparison of non-parametric variables among groups and Bonferroni-Dunn test was used as a post-hoc test for significant cases. One-Way ANOVA was used for comparison of parametric variables between groups and Tukey HSD test was used as a post-hoc test for significant cases. Spearman's rank correlation test was used for relationships between ordinal variables or continuous variables, not conforming to normal distribution, while Pearson's correlation test was used for variables conforming to normal distribution. Cronbach's alpha reliability coefficient was calculated in the analysis of internal consistency of the scales. A p value less than 0.05 was considered statistically significant.

RESULTS

Of the 494 family physicians participating in our study, 55.7% were women, while 44.3% were men, with the average age of 37.1 ± 9.6 (25-63). The majority of the participants (55.7%) work in Family Health Centres (FHC) (Table 1).

According to the data based on whether the participants were infected with COVID-19 virus and documented accordingly, 427 (86.4%) physicians- the majority of the participants- were found not to have been infected with the COVID-19 virus. On the other hand, 31 (6.3%) physicians appeared that they had no intention of being vaccinated against the COVID-19 virus when asked about their relevant opinion (Table 2).

Table 1. Sociodemographic characteristics of the participants

Variables	**n:494**
Age (years)	37.1±9.6 (25-63)
25-34	249 (50.4%)
35-44	115 (23.3%)
45-54	105 (21.3%)
55-64	25 (5.1%)
Gender	
Female	275 (55.7%)
Male	219 (44.3%)
Title	
Specialist doctor	118 (23.9%)
Family medicine assistant	146 (29.6%)
Non-tenured family physician with ongoing training for specialty	54 (10.9%)
Academic	20 (4%)
Non-tenured family physician	156 (31.6%)
Place of work	
Training and research hospital	85 (17.2%)
Family health centre	275 (55.7%)
University hospital	82 (16.6%)
State hospital	25 (5.1%)
Provincial/District directorate of health	14 (2.8%)
Other	13 (2.6%)
Years of professional experience (years)	9 (1-38)
Marital status	
Single	133(26.9%)
Married	361(73.1%)
Children	
No	229 (46.4%)
Yes	265 (53.6%)
Chronic disease	
No	360 (72,9%)
Yes	134 (27.1%)

Results are shown as mean ±SD (min-max), median (min-max), or n (%).

Table 2. Participants' who were infected with the COVID-19 and opinions about getting vaccinated against the virus

Variables	**n**	**%**
Infection with COVID-19		
Not infected	427	86.4
Recovered during home follow-up	53	10.7
Recovered with inpatient/ward admission	6	1.2
Recovered with inpatient/intensive care admission	1	0.2
Currently being followed up with the diagnosis of the COVID-19	7	1.4
Intention of getting vaccinated		
No intention of getting vaccinated.	31	6.3
Undecided about getting vaccinated.	65	13.2
Intention of getting vaccinated.	392	79.4
Participated in the phase 3 trials.	6	1.2

The responses of the participants to the statements in the COVID-19 Vaccination Attitude Scale were compared with the ages, indicating a significantly higher positive attitude score in the group between the ages of 45 and 54 compared to the group between the ages of 25 and 34 (p = 0.044). According to the assessment of the attitudes of the participants as to the gender variable, positive and negative attitude scores were found to be significantly higher in men than women (p = 0.011) (Table 3).

Table 3. Participants' attitude towards vaccination according to their sociodemographic characteristics

Variables	n	Positive Attitude		Negative Attitude	
		Mean±SD	p	Mean±SD	p
Age (years)					
25-34	249	3.68±0.77[a]	**0.044**	3.51±0.51[a]	**0.044**
35-44	115	3.75±0.91[a,b]		3.55±0.65[a,b]	
45-54	105	3.95±0.88[b]		3.71±0.69[b]	
55-64	25	3.62±1.03[a,b]		3.52±0.68[a,b]	
Gender					
Female	275	3.66±0.82	**0.011**	3.51±0.56	**0.030**
Male	219	3.86±0.87		3.63±0.64	
Title					
Specialist doctor	118	3.78±0.79	0.079	3.61±0.58	0.108
Family medicine assistant	146	3.62±0.76		3.52±0.51	
Non-tenured family physician with ongoing training for specialty	54	4±0.74		3.57±0.59	
Academic	20	3.84±1.04		3.87±0.56	
Non-tenured family physician	156	3.75±0.95		3.53±0.68	
Place of work					
Training and research hospital	85	3.61±0.85[a,b]	**0.003**	3.52±0.57	0.118
Family health centre	275	3.87±0.83[a]		3.6±0.63	
University hospital	82	3.69±0.77[a,b]		3.61±0.52	
State hospital	25	3.49±0.79[a,b]		3.42±0.52	
Provincial/District directorate of health	14	3.59±0.86[a,b]		3.29±0.37	
Other	13	3.13±1.2[b]		3.32±0.66	
Marital Status					
Single	133	3.54±0.84	**0.001**	3.49±0.55	0.114
Married	361	3.83±0.83		3.59±0.61	
Children					
No	229	3.58±0.82	**<0.001**	3.46±0.54	**<0.001**
Yes	265	3.89±0.85		3.65±0.63	
Chronic Disease					
No	360	3.7±0.84	**0.032**	3.53±0.56	0.067
Yes	134	3.88±0.86		3.65±0.67	

Student's t test, ANOVA. Different lowercase letters in a column indicate statistically significant difference between groups.

While 407 (82.4%) of the participants were still actively working in COVID-19-related health care units, 39 (7.9%) never worked in such facilities during the pandemic. When the participants were evaluated according to whether they work in COVID-19-related health care facilities, positive and negative attitude scores were found to be significantly higher (p = 0.024, p = 0.029) in the group of physicians that work in a FHC, compared to the group that does not (Table 4).

Table 4. Participants' attitude to the vaccine according to the factors in relation to COVID-19

Variables	n (%)	Positive Attitude		Negative Attitude	
		Mean±SD/ Median (min-max)	p	Mean±SD/ Median (min-max)	p
Work in COVID-19-related health care facilities					
Previously working, not currently	48(9.7)	3.69±0.87	0.209	3.54±0.55	0.202
Actively working	407(82.4)	3.78±0.83		3.58±0.59	
Never worked	39(7.9)	3.53±0.98		3.41±0.69	
Work in a FHC for the follow-up of patients with COVID-19					
No	207(41.9)	3.65±0.83	**0.024**	3.5±0.54	**0.029**
Yes	287(58.1)	3.82±0.85		3.61±0.63	
Work in a contact tracing team					
No	406(82.2)	3.78±0.83	0.058	3.58±0.62	0.176
Yes	88(17.8)	3.59±0.88		3.5±0.49	
Work in a sample collection unit					
No	364(73.7)	3.77±0.86	0.302	3.58±0.63	0.180
Yes	130(26.3)	3.68±0.8		3.51±0.49	
Work in a COVID-19 triage station					
No	370(74.9)	3.77±0.88	0.370	3.56±0.62	0.785
Yes	124(25.1)	3.69±0.75		3.58±0.53	
Work in a COVID-19 unit					
No	388(78.5)	3.81±0.85	**0.003**	3.6±0.61	**0.007**
Yes	106(21.5)	3.54±0.81		3.42±0.53	
Work in a COVID-19 ICU					
No	465(94.1)	3.77±0.84	**0.032**	3.57±0.6	0.185
Yes	29(5.9)	3.42±0.83		3.42±0.51	
Work in a COVID-19 polyclinic					
No	484(98)	3.75±0.85	0.633	3.56±0.6	0.464
Yes	10(2)	3.88±0.76		3.7±0.52	

Student's t test, ANOVA, Mann-Whitney U test.; FHC: Family Health Centre; ICU: Intensive Care Unit

No statistical significance was observed between whether or not participants were infected with the COVID-19 and their positive and negative attitude scores to the vaccine.

The analysis between the sociodemographic characteristics of the participants and their intention to be vaccinated revealed a significant relationship with the years of professional experience. The years of professional experience was found to be significantly higher in the group who was considering getting vaccinated and participated in the Phase 3 Trials compared to the group who did not intend to be vaccinated and were indecisive (p <0.001) (Table 5).

Table 5. Sociodemographic characteristics of the participants according to their intention of getting vaccinated

Variables	No intention	Undecided	Have the intention	Participated in Phase 3 Trials	p
Age (years)	30(27-56)[a]	30(26-57)[a]	36(25-63)[b]	47.5(33-62)[b]	**<0.001**
25-34	21(67.7)[a,b]	48(73.8)[a]	179(45.7)[b]	1(16.7)[b]	**<0.001**
35-44	6(19.4)[a]	11(16.9)[a]	98(25)[a]	0(0)[a]	
45-54	3(9.7)[a,b]	4(6.2)[a]	94(24)[b,c]	4(66.7)[c]	
55-64	1(3.2)[a]	2(3.1)[a]	21(5.4)[a]	1(16.7)[a]	
Gender					
Female	20(64.5)[a]	43(66.2)[a]	211(53.8)[a,b]	1(16.7)[b]	**0.044**
Male	11(35.5)[a]	22(33.8)[a]	181(46.2)[a,b]	5(83.3)[b]	
Title					
Specialist doctor	5(16.1)[a]	13(20)[a]	100(25.5)[a]	0(0)[a]	**0.001**
Family medicine assistant	16(51.6)[a]	30(46.2)[a]	100(25.5)[b]	0(0)[b]	
Non-tenured family physician with ongoing training for specialty	1(3.2)[a]	7(10.8)[a]	45(11.5)[a]	1(16.7)[a]	
Academic	0(0)[a]	1(1.5)[a]	17(4.3)[a]	2(33.3)[b]	
Non-tenured family medicine specialist	9(29)[a]	14(21.5)[a]	130(33.2)[a]	3(50)[a]	
Place of Work					
Training and research hospital	13(41.9)[a]	16(24.6)[a,b]	56(14.3)[b]	0(0)[b]	**0.001**
Family health centre	9(29)[a]	26(40)[a]	237(60.5)[b]	3(50)[a,b]	
University hospital	4(12.9)[a]	16(24.6)[a]	59(15.1)[a]	3(50)[a]	
State hospital	2(6.5)[a]	4(6.2)[a]	19(4.8)[a]	0(0)[a]	
Provincial/District directorate of health	1(3.2)[a]	3(4.6)[a]	10(2.6)[a]	0(0)[a]	
Other	2(6.5)[a]	0(0)[a]	11(2.8)[a]	0(0)[a]	
Years of professional experience (years)	5(3-33)[a]	5(2-34)[a]	10(1-38)[b]	22.5(10-34)[c]	**<0.001**
Marital status					
Single	13(41.9)[a]	24(36.9)[a]	96(24.5)[a,b]	0(0)[b]	**0.016**
Married	18(58.1)[a]	41(63.1)[a]	296(75.5)[a,b]	6(100)[b]	
Children					
No	21(67.7)[a]	36(55.4)[a]	171(43.6)[a,b]	1(16.7)[b]	**0.010**
Yes	10(32.3)[a]	29(44.6)[a]	221(56.4)[a,b]	5(83.3)[b]	

The results are shown as median (min-max) or n (%). Kruskal-Wallis test, Fisher's Exact test. Different lowercase letters in a row indicate statistically significance significant difference between groups.

The mean scores corresponding to the expressions evaluating the positive and negative attitudes of the participants are shown in Table 6.

In the evaluation of the selected subgroups according to the participants' intention of being vaccinated (the group that was vaccinated upon participating in Phase 3 Trials was not included in that evaluation), positive and negative attitude sub-scores were found to be the lowest in the group who did not intend to be vaccinated (Table 7).

Table 6. Mean Scores in the Scale and Reliability Coefficients of the Participants

	Mean	SD	Min	Max	Cronbach's alpha
Positive Attitude	3.7	0.8	1	5	0.894
I want my family to have the vaccine to be developed for this disease.	3.9	0.9	1	5	-
I want to have the vaccine to be developed for this disease as much as possible.	3.9	1	1	5	-
I think everybody should have the vaccine to be developed for this disease.	3.9	1	1	5	-
I trust to explanations made for the vaccine to be developed/developed.	3.2	0.9	1	5	-
Negative Attitude	3.6	0.6	1.4	5	0.693
The vaccine to be developed/developed may cause the spread of the virus.	3.9	0.9	1	5	-
I think the vaccine to be developed/developed will not/does not have a protective effect.	3.7	0.8	1	5	-
The vaccine to be developed/developed is dangerous.	4	0.7	1	5	-
I think the effectiveness of the vaccine to be developed/developed will not be/has not been tested adequately.	2.7	1	1	5	-
I think I may survive the epidemic without a vaccine.	3.6	1	1	5	-

Table 7. Scale Scores According to Participants' Intention of Getting Vaccinated.

	No intention			Undecided			Have the intention			
Scale Scores	**Mean± SD**	**Min**	**Max**	**Mean± SD**	**Min**	**Max**	**Mean± SD**	**Min**	**Max**	**p**
Positive Attitude Score	2.8±1.1[a]	1	5	2.9±0.5[a]	1	3.8	4±0.7[b]	1.8	5	**<0.001**
I want my family to have the vaccine to be developed for this disease.	2.9±1.3[a]	1	5	3±0.6[a]	1	4	4.1±0.8[b]	1	5	**<0.001**
I want to have the vaccine to be developed for this disease as much as possible.	2.5±1.2[a]	1	5	3±0.6[b]	1	4	4.1±0.9[c]	1	5	**<0.001**
I think everybody should have the vaccine to be developed for this disease.	3±1.3[a]	1	5	3±0.7[a]	1	4	4.2±0.8[b]	1	5	**<0.001**
I trust to explanations made for the vaccine to be developed/developed.	2.6±1.1[a]	1	5	2.6±0.8[a]	1	5	3.4±0.9[b]	1	5	**<0.001**
Negative Attitude Score	2.9±0.7[a]	1.4	4.8	3.1±0.4[a]	2.4	4.2	3.7±0.5[b]	2.4	5	**<0.001**
The vaccine to be developed/developed may cause the spread of the virus.	3.5±1[a]	1	5	3.6±0.8[a]	2	5	4±0.9[b]	1	5	**0.001**
I think the vaccine to be developed/developed will not/does not have a protective effect.	3.1±1[a]	1	5	3.2±0.7[a]	2	5	3.8±0.8[b]	1	5	**<0.001**
The vaccine to be developed/developed is dangerous.	3.4±1[a]	1	5	3.5±0.6[a]	3	5	4.1±0.7[b]	2	5	**<0.001**
I think the effectiveness of the vaccine to be developed/developed will not be/has not been tested adequately.	2±0.9[a]	1	5	2.1±0.8[a]	1	4	2.8±1[b]	1	5	**<0.001**
I think I may survive the epidemic without a vaccine.	2.6±1[a]	1	5	3.3±0.9[b]	2	5	3.7±0.9[c]	1	5	**<0.001**

ANOVA. Different lowercase letters in a row indicate statistically significance significant difference between groups.

DISCUSSION

The present study conducted with family physicians in Turkey found that the necessity to provide everyone with the COVID-19 vaccine is the very statement indicating the highest positive attitude, while the statement about the reliance on explanations for the vaccine turned out the least positive attitude. The most obvious negative attitude in our study is related to the efficacy of the vaccine with the concern that it has not yet been adequately tested. An important finding in our study is the fact that 67 (13.6%) of the participants were diagnosed with COVID-19 during the pandemic, although almost all of the participants were working in COVID-19-related units with a total of 455 (92.1%) physicians. This fact indicates that family physicians are successfully practicing the duty of preventive medicine for themselves and the society. There are many studies in the literature on the COVID-19 pandemic and issues related to vaccination. The present study, however, assumed the likelihood of a direct influence that may be caused by the attitudes and behaviour of family physicians in Turkey towards a vaccine on the COVID-19 vaccine immunization rates, and study groups were limited to only family physicians, which is the strength of our study.

Various studies have shown that the vaccine adoption in the society decreases, while its opposition increases day by day (11-13). For example, a study investigating the relationship between the prevalence of vaccine rejection and demographic characteristics and underlying reasons showed that 6.57% of the participants considered vaccines useless. In the same study, the rate of those who considered vaccines useless was found to be statistically significantly higher in women than men, and in those with a higher education level than those with lower education (13).

A multi-centre study investigating the knowledge and attitudes of 250 family physicians from eight countries about COVID-19 between March and April 2020, in a period that could be considered as the beginning of the pandemic, reported that 105 (42%) participants wanted to volunteer in COVID-19 vaccine studies, and in like manner, 68 (27%) participants stated that they could encourage family members or friends to volunteer (14). In our study, the number of family physicians who voluntarily participated in the Phase 3 Trials of the COVID-19 vaccine was only 6 (1.2%), yet the mean positive attitude score of the participants in relation to their willingness for family members' getting the COVID-19 vaccine was found to be high in all participants with the score of 3.9 ± 0.9.

In a study conducted to investigate the vaccine-hesitant attitudes regarding the COVID-19 in Turkish and British societies, 31% of the participants in Turkey and 14% of them in the UK were found hesitant about getting vaccinated. Furthermore, 3% of the participants in each country refused to be vaccinated, while the vaccination rate was reported to be higher in men compared to women in Turkey with respect to agreeing to get the COVID-19. The present study has pointed out, in particular, the level of hesitance in Turkey, and suggested that sharing new virus-related scientific data more with the general public may help prevent hesitance (15). Of all the participants in our study, 31 (6.3%) stated that they had no intention of getting vaccinated, while 65 (13.2%) participants stated that they were undecided about getting

vaccinated. In parallel with the above-mentioned study, positive and negative attitude scores of men in our study were found to be significantly higher than those of women. Physicians from only 53 out of 81 provinces in Turkey participated in our study and all provinces could not be contacted for the data collection stage, which is one of the limitations of our study. Another limitation is that the density of the number of participants differed according to the provinces.

In a study conducted in a period when there was no COVID-19 vaccine yet approved in Israel, hesitations about the COVID-19 vaccine in healthcare workers and the general population were evaluated, and 78% of doctors reported that they wanted to have the COVID-19 vaccine when available (16). Similarly, in our study, 392 (79.4%) family physicians stated that they had the intention of getting vaccinated, but that the vaccine had not yet been delivered to the unit where they work. In addition, the mean score of positive attitudes of family physicians towards getting the vaccine developed against the virus as soon as possible was found to be high, with the score of 3.9 ± 1. In the same study, the biggest concern for both doctors and the general population appeared to be the fear of safety of the vaccine, while the highest concern was reported to be related to quality control (16). In our study, the negative attitude mean score of 31 (6.27%) family physicians who had no intention of getting vaccinated was 2.9 ± 0.7, while the most significant negative attitude in the same group was that the efficacy of the vaccine was not adequately tested with the given score of 2 ± 0.9.

In a study conducted with 123 family physicians and interns in Malta, Grech et al., found that 70.8% of family physicians and 29.6% of interns were willing to get the COVID-19 vaccine. The analysis of the willingness to be vaccinated according to age groups indicated that the lowest rate was between the ages of 35-44 with 41.7%, while the highest rates were found between the ages of 55-64 with 80.6% and over the age of 65 with 100%. The same study pointed out that most of the concerns about the COVID-19 vaccine were due to the inadequate information on the new vaccines and the possible, unknown long-term side effects (17). In our study, the willingness of family physicians to get vaccinated was found to be 80.6% higher than that found in the study of Grech et al, with the volunteers participating in the Phase 3 Trials. In addition, the examination of the attitudes towards COVID-19 vaccine in our study showed that the highest positive attitude appeared in the 45-54 age group, while the highest negative attitude was observed in the 25-34 age group.

CONCLUSION

It is believed that the hesitant and unsafe attitude of family physicians towards vaccination will negatively affect the vaccination rates in the society. In this regard, in order to achieve the desired protective effect, it is necessary to inform family physicians about the efficacy and benefits of the vaccine and to convey this information to individuals through family physicians so that the vaccine adoption will increase across the society, and the desired levels can be reached in terms of vaccination rates.

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RESEARCH ARTICLE

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A Computer-Assisted Diagnosis Tool for Classifying COVID-19 based on Chest X-Ray Images

ABSTRACT

Objective: Since COVID-19 is a worldwide pandemic, COVID-19 detection using a convolutional neural network (CNN) has been an extraordinary research technique. In the reported studies, many models that can predict COVID-19 based on deep learning methods using various medical images have been created; however, clinical decision support systems have been limited. The aim of this study is to develop a successful deep learning model based on X-ray images and a computer-assisted, fast, free and web-based diagnostic tool for accurate detection of COVID-19.

Methods: In this study a 15-layer CNN model was used to detect COVID-19 using X-ray images, which outperformed many previously published CNN models in terms of classification. The model performance is evaluated according to Accuracy, Matthews Correlation Coefficient (MCC), F1 Score, Specificity, Sensitivity (Recall), Youden's Index, Precision (Positive Predictive Value: PPV), Negative Predictive Value (NPV), and Confusion Matrix (Classification matrix). In the second phase of the study, the computer-aided diagnostic tool for COVID-19 disease was developed using Python Flask library, JavaScript and Html codes.

Results: The model to diagnose COVID-19 has an average accuracy of 98.68 % in the training set and 96.98 % in the testing set. Among the evaluation metrics, the minimum value is 93.4 % for MCC and Youden's index, and the maximum value is 97.8 for sensitivity and NPV. A higher sensitivity value means a lower false negative (FN) value, and a low FN value is an encouraging outcome for COVID-19 cases. This conclusion is crucial because minimizing the overlooked cases of COVID-19 (false negatives) is one of the main goals of this research.

Conclusions: In this period when COVID-19 is spreading rapidly around the world, it is thought that the free and web-based COVID-19 X-Ray clinical decision support tool can be a very effective and fast diagnostic tool. The computer-aided system can assist physicians and radiologists in making clinical decisions about the disease, as well as provide support in diagnosis, follow-up, and prognosis. The developed computer-assisted diagnosis tool can be publicly accessed at http://biostatapps.inonu.edu.tr/CSYX/..

Keywords: Convolutional Neural Network, COVID-19, Image Processing, Deep Learning, Computer-Aided Diagnostic Systems.

Göğüs Röntgeni Görüntülerine Dayalı COVID-19'u Sınıflandırmak için Bilgisayar Destekli Bir Tanı Aracı

ÖZET

Amaç: COVID-19 dünya çapında bir salgın olduğu için, evrişimli sinir ağı (CNN) kullanılarak COVID-19 tespiti olağanüstü bir araştırma tekniği olmuştur. Bildirilen çalışmalarda, çeşitli tıbbi görüntüler kullanılarak derin öğrenme yöntemlerine dayalı olarak COVID-19'u tahmin edebilen birçok model oluşturulmuş; ancak, klinik karar destek sistemleri sınırlı kalmıştır. Bu çalışmanın amacı, X- ışını görüntülerine dayalı başarılı bir derin öğrenme modeli ve COVID-19'un doğru tespiti için bilgisayar destekli, hızlı, ücretsiz ve web tabanlı bir tanı aracı geliştirmektir.

Gereç ve Yöntem: Bu çalışmada, sınıflandırma açısından daha önce yayınlanmış birçok CNN modelinden daha iyi performans gösteren X-ışını görüntüleri kullanılarak COVID-19'u tespit etmek için 15 katmanlı bir CNN modeli kullanıldı. Model performansı Doğruluk, Matthews Korelasyon Katsayısı (MCC), F1 Skoru, Seçiçilik, Duyarlılık, Youden Endeksi, Kesinlik (Pozitif Tahmin Değeri: PPV), Negatif Tahmin Değeri (NPV) ve Karışıklık Matrisine (Sınıflandırma matrisi) dayalı olarak değerlendirildi. Çalışmanın ikinci aşamasında Python Flask kütüphanesi, JavaScript ve Html kodları kullanılarak COVID-19 için bilgisayar destekli tanı aracı geliştirildi.

Bulgular: COVID-19 tanısına yönelik model, eğitim setinde ortalama %98.68 ve test setinde %96.98 doğruluk oranına sahiptir. Değerlendirme ölçütlerinden minimum değerler MCC ve Youden Endeksi için %93.4, maksimum değer ise duyarlılık ve NPV ölçütlerinde % 97.8 olarak elde edilmiştir. Daha yüksek bir duyarlılık değeri, daha düşük bir yanlış negatif (FN) değeri anlamına gelir ve düşük bir FN değeri, COVID-19 vakaları için cesaret verici bir sonuçtur. Bu sonuç çok önemlidir, çünkü gözden kaçan COVID-19 vakalarını (yanlış negatifler) en aza indirmek bu araştırmanın ana hedeflerinden biridir.

Sonuç: COVID-19'un dünya çapında hızla yayıldığı bu dönemde, ücretsiz ve web tabanlı COVID-19 X-Ray klinik karar destek aracının oldukça etkili ve hızlı bir tanı aracı olabileceği düşünülmektedir. Bilgisayar destekli sistem, doktorlara ve radyologlara hastalık hakkında klinik kararlar vermede yardımcı olabileceği gibi, teşhis, takip ve prognoz konusunda da destek sağlayabilir. Geliştirilen bilgisayar destekli tanı aracına http://biostatapps.inonu.edu.tr/CSYX/ adresinden genel erişim sağlanabilmektedir.

Anahtar Kelimeler: Evrişimli Sinir Ağı, COVID-19, Görüntü İşleme, Derin Öğrenme, Bilgisayar Destekli Tanı Sistemleri.

INTRODUCTION

The COVID-19 outbreak first started on December 31, 2019, to detect unknown causes of pneumonia in Wuhan City, Hubei Province, China (1, 2). The rapidly transmitted disease was first described as SARS-CoV-2, and later this disease was identified as COVID-19 by the World Health Organization (WHO). It took 30 days for this new and rapidly spreading virus to extended from Wuhan city to other parts of China (3). The COVID-19 was declared an Internationally Important Public Health Emergency on 30 January 2020, and later declared as a pandemic by WHO on 11 March 2020 (4).

This virus is common in animals. However, due to the zoonotic presence of the virus, it was transmitted from animals to humans and then quickly spread around the world through contact between people. Extremely Acute Respiratory Syndrome Virus (SARS-CoV) and the Middle East Respiratory Syndrome Virus (MERS-CoV), which are members of the coronavirus family, have previously caused severe respiratory illnesses and deaths (5). From past to present, the genome of the COVID-19 virus has been mutated. For example; A study from University College London (UCL) reported 198 recurrent mutations for COVID-19 (6). Fever, cough, sneezing, sore throat, severe headache, malaise, and shortness of breath are known to be the most prevalent symptoms of COVID-19 disease (7).

Real-time reverse transcription-polymerase chain reaction (RT-PCR) is the most widely used technique worldwide for detecting COVID-19 disease, but many countries also have immunological tests to diagnose this disease. Radiological images such as computed tomography (CT) and X-ray scans have played a significant role in the early diagnosis of the disease and are used for this purpose (8). X-ray images are thought to have a distinctive potential among screening methods in monitoring various lung-related diseases such as tuberculosis, atelectasis, and pneumonia. Chest X-ray scans are beneficial for observing and tracking the impact of COVID-19 illness in the lungs.

Early diagnosis and treatment can be provided by determining the disease's pathological effects by evaluating COVID-19 with lung scan images of the patients since the RT-PCR test has a sensitivity value between 60% -70% and is time-consuming for the diagnosis of COVID-19 (9). It was recognized that X-ray and CT scans are a more effective way to detect COVID-19 and can be used in conjunction with RT-PRC (10).

Many countries around the world are struggling with deficiency kits for testing and a lack of qualified laboratory staff at the beginning of this pandemic, resulting in increases in false-negative rates for a high incidence of disease. For such reasons, clinicians often focus on chest x-ray and CT scans findings to determine the COVID-19 status (11, 12). In countries where test kits are deficient, CT and X-ray scanning images are widely used to identify COVID-19. Researchers claim that COVID-19 was detected earlier by observing radiological imaging outputs and laboratory findings together (13-15).

In the literature, the Convolutional Neural Network (CNN) method, one of the deep learning algorithms, is frequently used in artificial intelligence (AI) based studies. CNN, MRI (16), X-ray (17), CT scans (18), ultrasonography (19), etc. It has been used effectively for clinical purposes, such as for medical image processing. Besides, through a process very close to human brain function, CNN is a collection of methods that detect relationships.

There are numerous deep learning and machine learning methods that use X-ray images to diagnose diseases in the current literature. A new CNN model that classifies X-ray scans has been proposed in a research article (20). As pre-trained CNNs are to available difficulties in practical implementations, the authors implement a small-sized CNN architecture. The researchers used a 12-class X-Ray dataset, with an 86 percent precision rate recorded in their studies. Another work proposed a different deep learning approach to tuberculosis detection. The authors propose a new CNN model in their method that used an X-Ray dataset. A large dataset including X-Ray scans was created by another study to which they implemented CNN models for binary and multi-class classifications. The relevant dataset, transfer learning, was used with pre-trained ResNet, AlexNet, and VGG16 methods. Though an 82.2 percent accuracy score was recorded for the binary classification, over 90% accuracy rate results were reported for the other classifications. By Ioannis et al., another done work proposed VGG19 and obtained an accuracy of 93.48 percent using X-ray images (21). In another latest study, a model known as COVID-Net received an accuracy rate of 92.4% in the X-ray image dataset (22).

Since COVID-19 is a worldwide pandemic, COVID-19 classification using a CNN model has been an extraordinary research technique. Excellent CNN-based investigations are available to classification and identify COVID-19 using different X-ray image datasets. Although promising results have been obtained from these CNN techniques, they are not yet an option for real test methods. Many models that can predict COVID-19 based on commonly deep learning methods using various medical images have been created; however, web-based clinical decision support systems have been limited.

In this period when COVID-19 is declared a worldwide pandemic, the web-based systems for COVID-19 on X-Ray imaging may be a highly useful and fast diagnostic tool. A computer-aided

system can assist physicians and radiologists in making clinical decisions about the disease and supporting disease diagnosis, follow-up, and prognosis. In this study, a highly successful deep learning model-based on X-ray images is developed for correctly the detection of COVID-19, and a computer-assisted, fast, free, and web-based computer-assisted diagnosis tool that can accurately predict COVID-19 is proposed and accessed at http://biostatapps.inonu.edu.tr/CSYX/.

The remainder of this article is regulated as follows. In Part II, the deep learning method used in the study and the web-based diagnostic tool developed were explained. The experimental results in Part III and the discussion in Part IV are presented.

MATERIAL AND METHODS

Dataset: The design of this research is an experimental clinical study, and the analyzed images were obtained from the related research in an open-access manner. In the study, an open-source data set containing augmented X-ray images for COVID-19 at https://data.mendeley.com/datasets/2fxz4px6d8 was used (23). The data set used in the study was augmented published online. In CNN models, it is a common technique to augment the image data set for preventing over-fitting and for the model from not memorizing all the training data details. The data set includes a total of 1824 X-Ray scan images; 912 COVID-19 positive and 912 COVID-19 negative scans. Figure 1 shows some example X-ray images in the dataset.

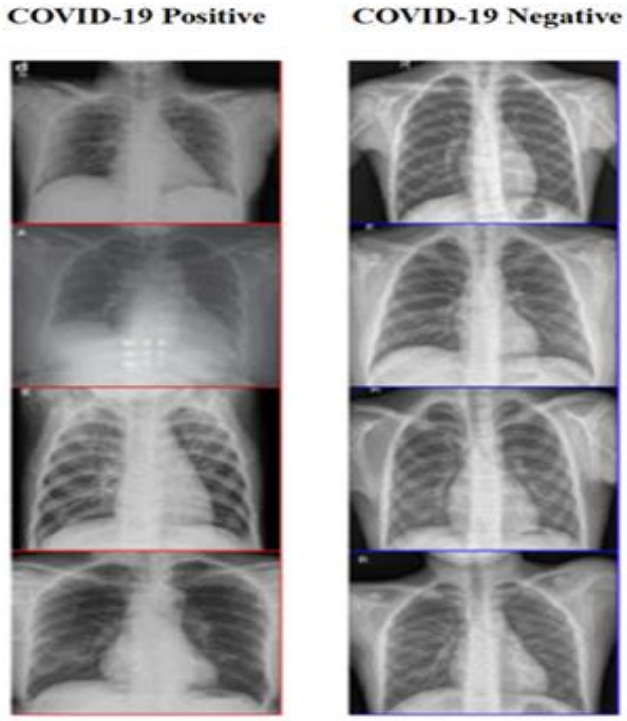

Figure 1. Sample Images of X-Ray Scan Dataset

Methods: All encodings were performed with PYTHON software on the virtual server with 1.5 TB RAM, 16 core @ 3.60 GHz CPU, and Tesla P40 24GB GPU on Intel (R) Xeon (R) Gold 5122 server. The X-ray images' input size is initially resized to 224 x 224 pixels for compatibility with CNN models. CNN model was implemented using Keras and Tensorflow 2.0 libraries. In the study's experiments, 80% of the image data set and the remaining 20% of the training set were randomly divided as testing set to validate the CNN model. The CNN model used in the study contains 15 layers.

Firstly, two sequential convolutional layers are built, with a 224x224x32 output shape with 3x3 cores with the similar size padding to ensure the output's size. A 2x2 top pool layer is then added to the model to reduce the size of the features. Then another convolutional layer of 64 depth is added. A maximum pool layer of size 2×2 results in these curved layers for size reduction, and an activation function is used ReLU in all layers. The features add a flatten layer and add a dense layer in 64depth, with a dropout layer of 0.5. A rigidly connected layer incorporates the characteristics of the previous layers, and the final output of the exactly-connected layers is standardized with a Sigmoid activation function. In the constructed model, the batch size is 16, the learning rate is 0.0001, and the epoch value is 20. Hyperparameters of the model were chosen intuitively and tuned by Adam's optimization method during the experiment. The model performance is evaluated according to Accuracy, Matthews Correlation Coefficient (MCC), F1

Score, Specificity, Sensitivity (Recall), Youden's Index, Precision (Positive Predictive Value: PPV), Negative Predictive Value (NPV), and Confusion Matrix (Classification matrix).

Finally, the CNN model's methodology is depicted in Figure 2, and the layers of the created CNN model are presented in Figure 3.

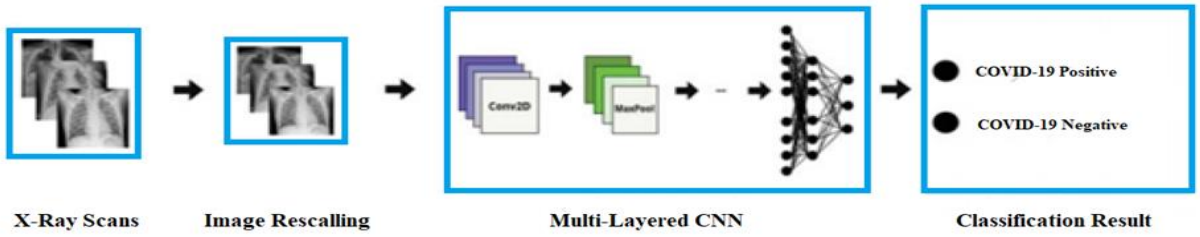

Figure 2. The methodology of the proposed CNN model

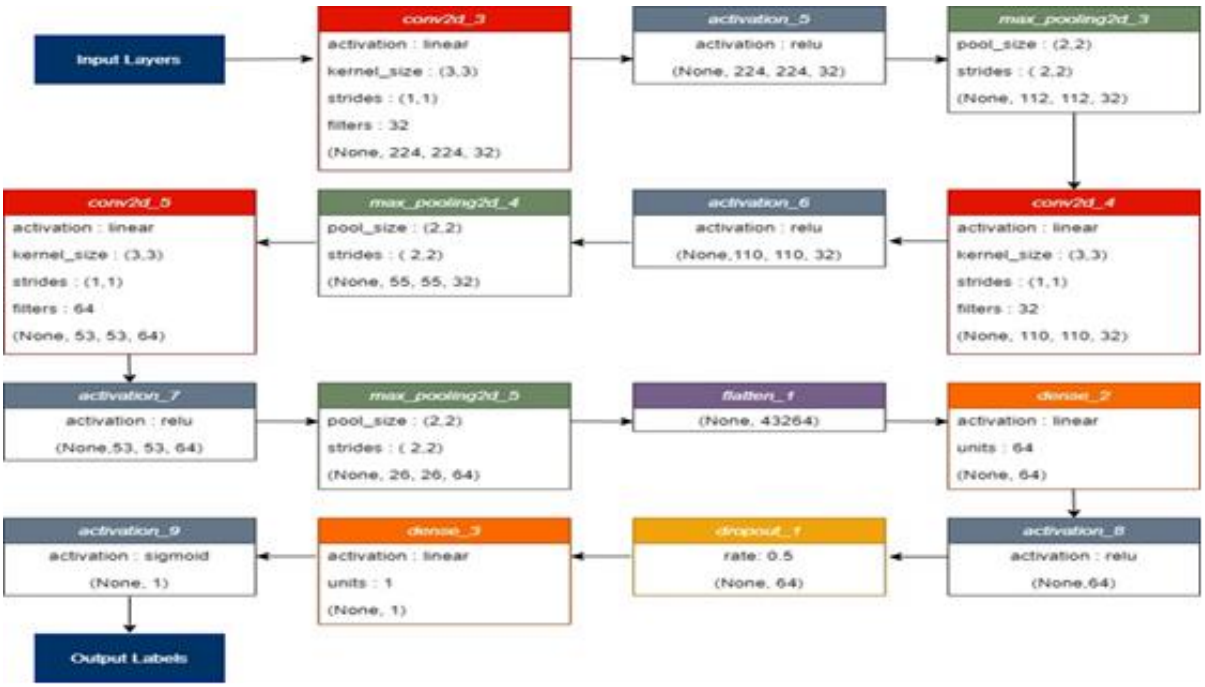

Figure 3. The layers of the CNN Model

Convolution Neural Networks (CNNs): A significant extension of artificial neural learning is deep learning, employed in several scientific and application fields. The basic architecture of the deep learning concept is regarded as neural networks with convolution (CNNs). Different layers are used to create a CNN model. In the CNN model, while a convolution layer is liable for extracting local features, a normalization layer is liable for normalizing local features. The pooling layer is used to down sample local features. The convolution layer is the layer where the convolution stage occurs, and the CNN models learn. This layer performs most of the calculations in the model. Convolution is the most important stage of these networks. Several parameters and hyperparameters are available on all layers. These greatly affect the performance of the model. One of these parameters, filters, extract the necessary functions for the convolution layers and then learn the data using these functions. In CNN, the pooling layer is often used for image size reduction. With this layer, the speed of computation increases, the problem of the over-fitting problem is prevented, reducing the available memory. A common approach used for ordering layers within a convolutionary neural network that can be replicated one or more times in a given model is the inclusion of a pooling layer and after convolutional layer. To build a new collection of the same number of pooled feature maps, the pooling layer operates separately on each feature map. Pooling requires selecting a pooling operation to be implemented to function feature maps, just like a filter. And the flattening layer converts the pooled overall feature (attribute) map matrix into only a single column. It will then be transmitted to the neural network for processing. This layer is also known as a dense layer because it is a fully connected layer. The input from the previous layers becomes flattened in this layer into a vector. After flattening, the past layer's volume is given as an input to the precisely bonded layer. This

layer tries to determine which features fit into a particular class by looking at the past layer's output. As finally, it acts on high-level characteristics that have unique weights. Therefore, as it computes the weights and the previous layer's results, a rigidly connected layer ensures the distinct groups' right probabilities. The outputs are defined by the use of the activation function (24, 25).

Computer-Assisted Diagnosis Tool for COVID-19: In the second phase of the study, a computer-assisted diagnosis tool, which can be accessed free of charge from any internet-enabled device (mobile phone, desktop computer, laptop, etc.), was developed for the COVID-19 disease using X-Ray scan images. This web-based system is developed using Python Flask library, JavaScript, and Html codes (26-28). It has two language options, English and Turkish. When X-Ray scan images of people with suspected COVID-19 are uploaded, the developed system results as COVID-positive or COVID-negative within a few minutes or less. The main menu of the COVID-19 computer-assisted diagnosis tool is displayed in Figure 4. The system consists of three sections. The first section contains a short explanation of the system. In the second section, when any user can upload an X-Ray scan image and click analyze button, the estimate of the COVID-19 diagnosis is displayed in the third section. The system supports image files with the extensions of .dcm , .jpeg , .jpg , or .png. The developed computer-assisted diagnosis tool can be accessed at http://biostatapps.inonu.edu.tr/CSYX/.

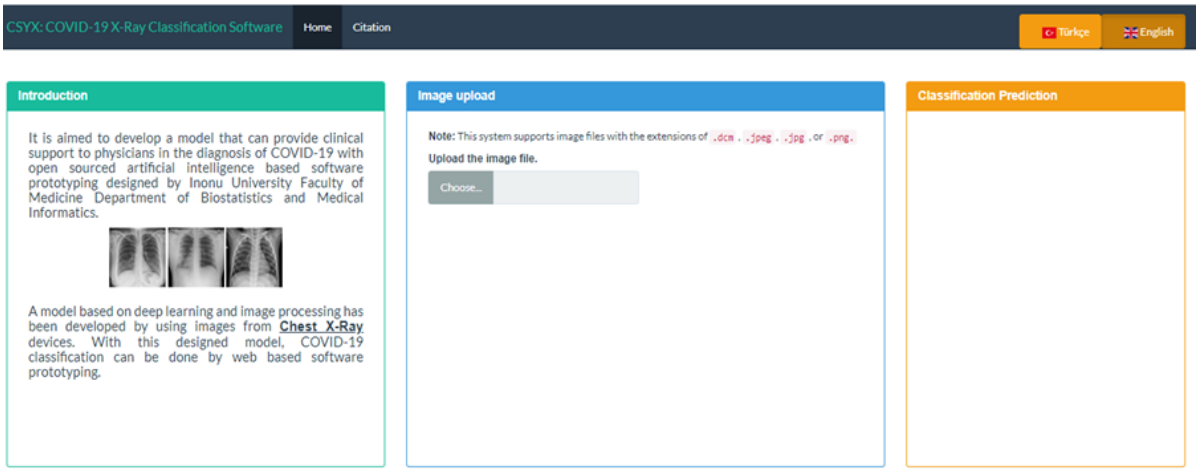

Figure 4. The System Main Menu

RESULTS

Findings of CNN Model: The confusion matrix for the COVID-19 X-Ray scan test data set of the created model is given in Figure 5. Performance metrics obtained from the CNN model created for the diagnosis of COVID-19 are listed in Figure 6. When the experimental results of the trained and tested CNN model are examined, our proposed model achieved an overall accuracy of 96.7% in the testing set, and more importantly, the Precision and Sensitivity (Recall) rates for COVID-19 cases were 95.7% and 97.8% for the COVID-19 classification, respectively.

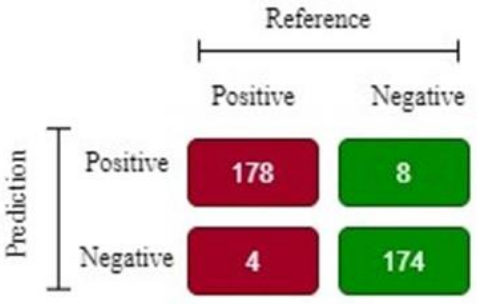

Figure 5. The confusion matrix for the COVID-19 X-Ray testing dataset

As the calculated performance metrics are evaluated with a 95% confidence interval (CI), the minimum value is 93.4% for MCC and Youden's index, and the maximum value is 97.8 for sensitivity and NPV in Figure 6.

Metric	Value (%)	%95 CI (%)
Accuracy	96.7	(94.9-98.5)
F1-Score	96.7	(94.9-98.6)
Sensitivity (Recall)	97.8	(94.5-99.4)
Specificity	95.6	(91.5-98.1)
MCC	93.4	(91-96)
Youden's Index	93.4	(86-97)
Precision (PPV)	95.7	(91.7-98.1)
Negative Predictive Value (NPV)	97.8	(94.3-99.4)

Figure 6. Performance criteria for the CNN model in the testing dataset

Findings of Developed COVID-19 X-Ray Computer Assisted Diagnosis Tool: The results for the COVID-19 X-Ray positive and negative images randomly loaded from outside to the system are illustrated in Figures 7 and 8, respectively. As can be seen, the system can successfully classify COVID-19 status as positive and negative based on the uploaded X-Ray image.

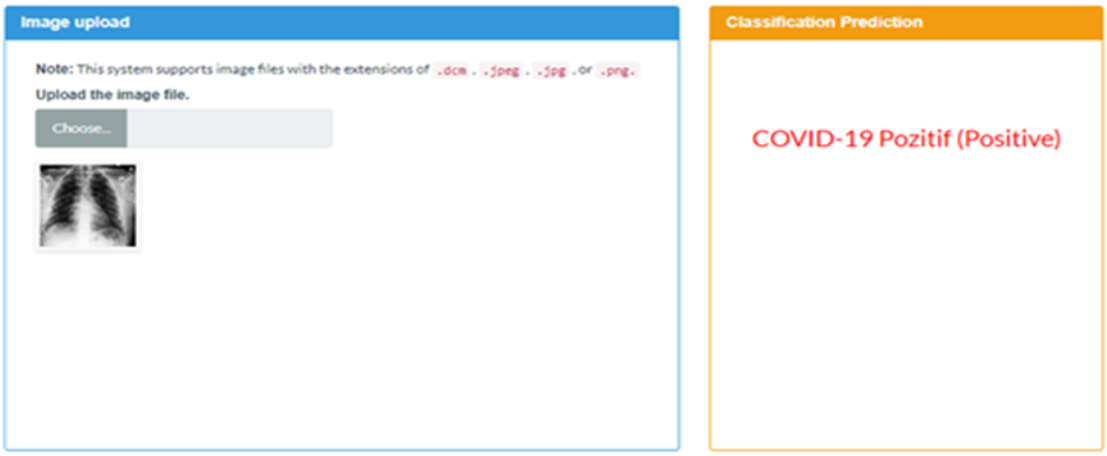

Figure 7. Prediction Result of COVID-19 Positive X-Ray Scan Image in System

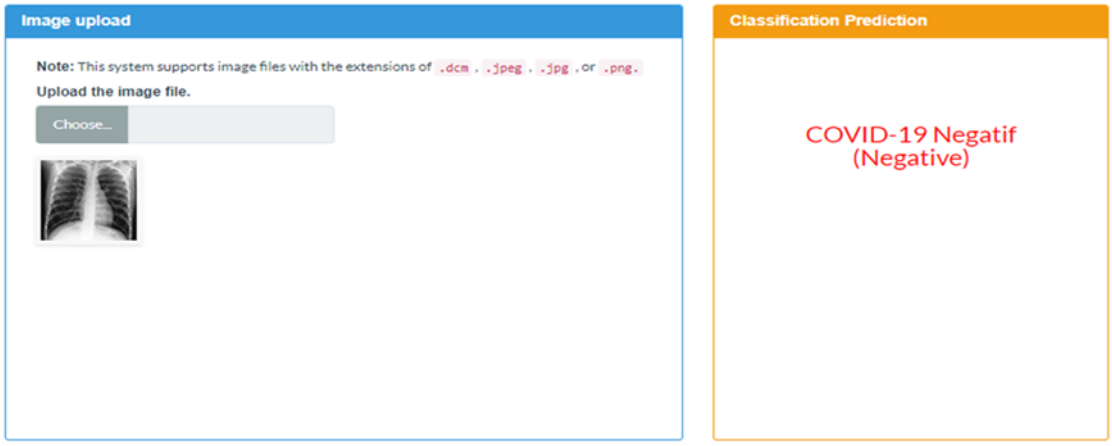

Figure 8. Prediction Result of COVID-19 Negative X-Ray Scan Image in System.

DISCUSSION

COVID-19 is a long-time danger to the healthcare systems and economies of nations. In the world, millions of people have died due to the disease. Deaths have been caused by respiratory failure, resulting in the loss of other organs. As there are many emergencies, hospital capacities are full, and clinicians have limited time. Therefore, computer-aided diagnostic systems can save lives. There is also a great deal of variation in the sample scan images taken from X-ray machines because of differences in the radiologist's expertise (5, 14). Since speed, accessibility, and ease of application are extremely important in the clinical diagnosis of the current state of COVID-19, combining medical imaging methods with artificial intelligence technologies would be very useful from clinical aspects.

In this study, a successful CNN architecture was created to classify COVID-19 as positive and negative (to detect the disease) from X-Ray scan images. The created model achieved 96.7% accuracy in the testing set. Another significant result is achieving the positive predictive value and sensitivity metrics obtained from the model for COVID-19 cases. A higher sensitivity value means a lower false negative (FN) value, and a low FN value is an encouraging result for COVID-19 cases. This considerable result is significant because minimizing the overlooked COVID-19 cases (false negative) is one of this research's main aims.

Published research articles on the prediction of COVID-19 have been reported using different structures of CNN models. In a study conducted using the same data set in the literature, CNN, CNN / Random Forest, and CNN-support vector machine (SVM) methods were used, and the highest accuracy rate was obtained from the CNN model with 95.2% (29). In another study using the same data set in the literature, using the combination of MobileNet, ResNet50, InceptionV3, and InceptionV3 and MobileNet models, 95.18%, 94.39%, 95.75%, and 96.49% accuracy rates were obtained, respectively (30).

In another study, ResNet18, ResNet50, ResNet101, VGG16, and VGG19 models were used in different COVID-19 X-Ray scan image datasets. For the classification of features, the Support Vector Machines (SVM) classifier was created with some kernel functions. The ResNet50 model and the SVM classifier achieved an accuracy score of

94.7%, the highest among all results (31). In another study, different CNN models (AlexNet, VGG19, ResNet, and SqueezeNet) were created for the transfer - learning called DeTraC in a different COVID-19 X-Ray scan image dataset. An accuracy rate of 93.1% was achieved with DeTraC for detecting COVID-19 (32). In another recent study, a CNN method named CNN-COVID was developed using X-ray scan images, and the method was tested in two different data sets. With this method, accuracy of 0.9722 for the first data set and 0.9884 for the second data set was obtained (33).

In many studies, outstanding results have been obtained for COVID-19 prediction. However, in these studies, a web-based diagnostic system for COVID-19 has not been developed. Compared to such studies in the literature, the superiority of the current study is a web-based diagnostic system that can quickly predict COVID-19 and is developed for use worldwide.

The web-based system developed in the second phase of this study using a highly successful deep learning architecture for detecting COVID-19 is one of the few studies that can be classified from X-Ray scan images for COVID-19 disease. It is thought that the developed system will help clinicians and other healthcare professionals in clinical evaluations. It is envisaged that the disease's diagnosis and treatment processes will be carried out more effectively with the development of a system that can help medical methods used to diagnose individuals with suspected COVID-19. In addition, with the effective use of the proposed artificial intelligence-based software, it is expected to support the disease's diagnosis processes and reduce the possible financial burden and inappropriate medical procedures. The proposed model and developed system significantly advance the existing approach focused on radiology and can be a useful tool for healthcare professionals and radiologists to help them detect and diagnose, and follow-up COVID-19 cases during the COVID-19 pandemic. We believe that with this computer-aided diagnostic system, diagnostic time for COVID-19 will be reduced, and diagnostic accuracy will be significantly improved.

As a result, the article's primary contributions are as follows:

1. The model constructed with a 15-layer CNN architecture for COVID-19 classification provided 98.68% accuracy in the training set and 96.98% in the test set.

2. The system developed based on the CNN model can predict COVID-19 accurately and effectively. Also, it performs the estimation process in a minute or two.

3. It is thought that the web-based system developed can provide support to physicians in the clinical decision-making process to diagnose COVID-19.

Taken together, the preliminary results of the current study are auspicious, and the results can be further improved as more data for training becomes available. Future studies plan to create a model with higher performance criteria by using more training data sets of the system.

CONCLUSION

It is thought that the deep learning-based web-based diagnostic tool will help physicians and radiologists in the diagnosis of COVID-19 by significantly shortening the diagnosis time.

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RESEARCH ARTICLE

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The Investigation of the Relationships among Coronavirus Anxiety, Cyberchondria, and Online Shopping

ABSTRACT

Objective: During the COVID-19 pandemic some mental disorders has been especially increased. The purpose of this study is to evaluate the relationship between individuals' coronavirus anxiety, cyberchondria, and online shopping addiction features during the pandemic we are in, and try to explain the factors associated with these features.

Methods: The data consist of 407 people between the ages of 18-65 who answered a sufficient number of questions on the scales with the help of the online environment by Google questionnaire method between January 18nd, 2021 and February 18th, 2021. Participants were asked to fill in the socio-demographic form, cyberchondria severity scale (CSS), Bergen shopping addiction scale (BSAS), and coronavirus anxiety (CAS) scales.

Results: In this study, 79.6% of the participants stated that their anxiety increased, 63.4% stated that the frequency of shopping online increased, and 39.8% stated that the number of health searches on the internet increased during the COVID-19 pandemic. Regarding the correlations of the CAS, CSS, BSAS scales with each other, a statistically significant positive moderate correlation was found between CAS and CSS (r: 0.495, p <0.001).

Conclusions: Pandemic has changed lots of routines about our daily life. Individuals' spending a long time on the internet at home and that may be an important risk factor for online shopping addiction and cyberchondria during the COVID-19 pandemic. For this reason, informing individuals about mental problems caused by the intense use of the internet during the pandemic is important in terms of mental health.

Keywords: SARS-CoV-2, Coronavirus, Anxiety, Cyberchondria, Online Shopping, Compulsive Behavior.

Koronavirüs Kaygısının Siberkondria Ve Online Alışveriş Bağımlılığı İle İlişkisinin İncelenmesi

ÖZET

Amaç: COVID-19 pandemisi döneminde bu yeni hastalıkla ilgili birçok belirsizliğin olması, sosyal izolasyon uygulanması, pandeminin yol açtığı bir takım ekonomik zorluklar ile beraber özelikle bazı ruhsal bozukluklarda belirgin artış görülmüştür. Pandemi döneminde en fazla artan ruhsal belirtilerden biri şüphesiz anksiyetedir. Bu çalışmanın amacı içinde bulunduğumuz pandemi sürecinde bireylerin koronavirüs anksiyetesi, siberkondria ve online alışveriş bağımlılığı özellikleri arasındaki ilişkiyi değerlendirmek ve bu özellikler ile ilişkili diğer faktörleri açıklamaya çalışmaktır.

Gereç ve Yöntem: Bu çalışma için gönüllük esasına uygun olarak çalışmaya dahil olan katılımcılardan 18.01.21 ile 18.02.21 tarihleri arasında Google anket yöntemi ile online olarak veri toplandı. Katılımcılara sosyo-demografik form, siberkondria şiddeti ölçeği (CSS), kompulsif satın alma ölçeği (BSAS) ve koronavirüs anksiyete (CAS) ölçekleri uygulandı. Ölçeklerde yeterli sayıda soruyu yanıtlayan 18-65 yaş arası 407 kişi ile çalışma tamamlandı.

Bulgular: Çalışma sonucunda COVID-19 pandemisi döneminde katılımcıların %79,6'sı kaygılarının arttığını, %63,4'ü internet üzerinden alışveriş yapma sıklıklarının arttığını, %39,8'ü ise internet üzerinden hastalık arama davranışlarının arttığını belirtmişlerdir. CAS, CSS, BSAS ölçeklerin birbirleri ile korelasyonları incelendiğinde ise CAS ile CSS arasında istatistiksel olarak anlamlı pozitif yönde orta düzeyde bir ilişki saptanmıştır (r:0,495, p<0,001).

Sonuç: Pandemi, sosyal izolasyon ve evde kal çağrıları sonucu bireylerin evde daha uzun süre internette vakit geçirmeleri online alışveriş bağımlılığı ve siberkondria için önemli bir risk faktörü olabilir. Bu sebeple pandemi süresince internetin yoğun kullanımının yol açacağı ruhsal problemlerle ilgili bireylere bilgilendirme yapılması toplum ruh sağlığı açısından önem taşımaktadır.

Anahtar Kelimeler: SARS-CoV-2, Koronavirüs, Anksiyete, Siberkondria, Online Alışveriş, Zorlayıcı Davranış.

INTRODUCTION

The COVID-19 pandemic that started in the past year has affected the whole society in many ways. COVID-19, a new disease caused by this new virus, previously unknown, has caused individuals to reconsider their sense of trust, relationships, and their views on death and life. The lack of adequate information about COVID-19 and the virus that can change every day has led individuals to research more on the internet. Although some of these researches conducted via the Internet are useful and functional, the excessive and repetitive online information research about diseases is a pathological phenomenon which is defined as cyberchondria (1). Although cyberchondria is a fairly new situation and is still being defined, the number of studies on the subject has increased with the publication of the Cyberchondria Severity Scale (CSS) in 2014 (2). Besides, with the COVID-19 pandemic, there has been an increase in the behavior of searching for diseases on the internet. According to a report published in the United States, internet searches related to coronavirus increased by approximately 36% after the first case was announced in the United States (3). The increased search for information on the Internet has also encouraged researchers to do more research on cyberchondria, and the number of publications on cyberchondria has increased during the pandemic (2,4,5). Moreover, in some previous studies in the literature, it has been found that cyberchondria is also strongly associated with increased health anxiety (2).

During the COVID-19 pandemic, people also faced situations such as intolerance to uncertainty, impaired sense of trust, and fear of death, along with an increase in certain mental disorders (6,7). Anxiety disorders, depression, online shopping, and gambling addictions are the common mental disorders that have been shown to increase during the pandemic (7–10). Undoubtedly, the most increasing psychological symptom during the pandemic period is anxiety. A scale was developed by researchers to measure the coronavirus anxiety in 2020 and made usable in evaluation processes (6).

Due to necessity for staying at home during pandemic most of the people prefer to use online shoppping instead of in store shopping options. However, excessive form of online shopping may also lead negative outcomes such as online shopping addiction, familiy, and economic problems. Previous studies in the literature showed that individuals can tend to do activities such as gambling, pornography, watching online TV series, video games, and online games as coping behaviors because of the compulsory stay-at-home orders, various constraints required to ensure social isolation (8-10). On the other hand, our knowledge about online shopping addiction, which seems more innocent than other addictions but has both an economic and addictive effect on people, is very limited (10).

In studies conducted before coronavirus, it is estimated that compulsive purchasing behavior is quite common, with a rate of 5.8%-8% (11). However, we did not find a study in the literature evaluating how cyberchondria and compulsive purchasing behaviors changed together during the COVID-19 pandemic. The purpose of this study is to evaluate the relationship between individuals' coronavirus anxiety, cyberchondria, and online shopping addiction during the pandemic we are in, and try to explain the factors associated with these features.

MATERIAL AND METHODS

Ethics, Participants, and Procedures: IRB approval for the study was procured from the Ethics Committee of Duzce University Medical Faculty [2020/261]. All of the study procedures were applied following World Health Organization Declaration of Helsinki and local laws and regulations.

The data of this study was collected between 18.01.21 and 18.02.21 on an online basis with the Google questionnaire method. Participants who accepted to participate were first informed about the purpose of the study, procedures, confidentiality of the research data, and how to communicate with the researchers as needed. The informed consent form was completed by marking the informed consent form for the participants who declared that they had read and understood the general information, understood that they were involved voluntarily and that they can withdraw their consent at any time without any consequences. The study started with the consent of every participant. Participants were asked to fill in the socio-demographic form, cyberchondria severity scale (CSS), Bergen shopping addiction scale (BSAS), and coronavirus anxiety (CAS) scales. The study was completed with 407 people between the ages of 18-65 who answered all required questions in the scales.

Measures

1. Bergen Shopping Addiction Scale (BSAS): BSAS was created in 2015 by Andreassen et al. It is a 5-point likert scale that can be scored between 0-112 points consisting of 28 questions (12). The Turkish validity and reliability study was conducted in 2018 with the name of "compulsive online purchasing "(13).

2. Cyberchondria Severity Scale (CSS): The scale was developed by McElroy and Shevlin in 2014. CSS measures excessive online health research. CSS consists of 33 items in total, 5 subscales are defined, and participants can score between 33-165 points (14). The Turkish validity and reliability study was performed by Selvi et al. (15).

3. The Coronavirus Anxiety Scale (CAS): The scale was created by Lee in 2020 and consists

of 5 items in total (8). According to CAS the score of CAS is correlated with coronavirus anxiety. Its Turkish validity and reliability study was conducted by Evren et al. (16).

5. Socio-demographic form: The form consisting of 17 questions such as age, gender, physical and mental illness history, history of COVID-19, etc. The socio-demographic form was created by the researchers in this study.

Statistical Analysis: All analyses were conducted with the use of Statistical Package for Social Sciences (SPSS-26.0) for Windows. All continuous variables were tested for normality and homogeneity of variance. The student's t-test was used for normally distributed data, and Mann–Whitney U test was used for data that were not normally distributed. The Kruskal Wallis test was used to compare more than one group that were not normally distributed. Correlations between continuous variables were evaluated using Spearman's correlation test. A p-value below 0.05 was considered statistically significant.

RESULTS

The socio-demographic, shopping, internet using characteristics of the participants and these characteristics' correlations with the CAS, CSS, and BSAS scales are given in Table 1. The sample of this study consists of a total of 407 people, 260 (63.9%) of the participants were female and 147 (36.1%) were male. The mean age of the sample was 29.54 ± 10.38, while the mean age of men was 35.78 ± 11.0, the mean age of women was 26.01 ± 8.13. A statistically significant difference was found between men and women in terms of age (Z: -9.079, p <0.001). The average monthly income of the participants was determined as 4.050 ± 3.735 TL . There was no correlation with mean monthly income with the CAS, CSS, and BSAS scales (r: -0,168; r: -0,160; r: -0,031, respectively). Participants reported that they made an average of 2.42 ± 3.38 shopping per month before the pandemic, and 4.85 ± 4.96 shopping during the COVID-19 pandemic period. The average technological (phone, tablet, computer) use of the participants was 5.72 ± 3.6 hours in the last two weeks. In terms of the relationship between age and CAS, CSS, and BSAS scales, there is very low negative correlation was found between age and CAS,CSS, and BSAS scores (respectively; r: -0,190; r: -0,157; r: -0,112).

Table 1. The socio-demographic characteristics of participants and the correlations between socio-demograhic characteristics and CAS, CSS, and BSAS scores

		n(%)	Mean(SD)	CAS(r)	CSS(r)	BSAS(r)
Age	Female	260(63.9)	26.01(8.13)	-0.052	-0.030	-0.092
	Male	147(36.1)	35.78(11.00)	-0.114	-0.202*	0.073
	Total	407(100)	29.54(10.38)	-0.190**	-0.157**	-0.112*
Monthly income as Turkish liras			4.050(3.735)	-0.168**	-0.160**	-0.031
Daily time for internet using as hour			4.85(4.96)	0.056	0.078	0.144*
			Median(IQR)			
Number of online shopping before COVID-19 pandemic			2(3)	0.085	0.160**	0.226**
Number of online shopping during COVID-19 pandemic			3(4)	0.148**	0.147**	0.290**

Spearman korelasyon test, r: correlation coefficient ,*. p <0.05 . **. p <0.01 level BSAS: Bergen Shopping Addiction Scale, CSS: Cyberchondria Severity Scale, CAS:The Coronavirus Anxiety Scale

Regarding anxiety, online shopping, and cyberchondria characteristics of participants, 79.6% of the participants stated that their anxiety increased, 63.4% of the participants stated that the frequency of shopping on the internet increased, and 39.8% of the participants stated that the amount of time for online searches for diseases increased.

Examination of CAS, CSS, BSAS scales according to COVID-19 features of participants are given in Table 2. According to Table 2, while 17.2% (n: 70) of the participants reported to had COVID-19, 35.1% of participants had contact with an individual with COVID-19. 71.3% of the participants reported at least one family member who had COVID-19 during the pandemic. BSAS scores of the participants who reported to had COVID-19 were found to be (24.6 ± 18.6) statistically lower than those who did not report COVID-19 history (30.6 ± 18.6) (p = 0.019). Regarding contact history with a person with COVID-19, BSAS scores of the participants with a history of contact with COVID-19 individuals were found to be 24.0 ± 18.8 statistically significantly lower than those without any contact history (28.0 ± 18.4) (p = 0.034). CAS and CSS scores of individuals who have at least one family member had COVID-19 were found to be (1.3 ± 2.3; 68.2 ± 22.3, respectively) statistically significantly lower than those who did not have any family member with COVID-19 (2.6 ± 3.8; 74.4 ± 22.5, respectively) (p <0.001, p = 0.004, respectively) (Table 2).

Table 2. The relationships among COVID-19 related features of participants and CAS, CSS, and BSAS scores.

	Yes	No	CAS		CSS		BSAS	
	n(%)	n(%)	Z	p	Z	p	Z	p
Having the personal history of COVID-19	70(17.2)	337(82.8)	-0.445	0.65	-0.124	0.90	-2.351	0.019
Having the history of contact with someone who had COVID-19	143(%35.1)	264(64.9)	-0.084	0.93	-0.396	0.69	-2.116	0.034
Having the history of at least one familiy member who had COVID-19	290(71.3)	117(28.7)	-3.481	<0.001*	-2.841	0.004	-1.627	0.104
Healthcare professional	69(17.0)	338(83.0)	-.328	0.743	-1.267	0.205	-1.377	0.169

Mann-Whintney U test, BSAS: Bergen Shopping Addiction Scale, CSS: Cyberchondria Severity Scale,CAS:The Coronavirus Anxiety Scale

In terms of history about physical illness or mental disorder of participants 34 (8.4%) of the participants reported physical illness and 43 (10.6%) of the participants reported mental disorder. Most common reported mental disorders were anxiety disorder (n: 16, 3.9%), depression (n: 6, 1.5%), panic disorder (n: 6, 1.5%), obsessive-compulsive disorder (OCD) (n: 6, 1.5%), bipolar affective disorder (n: 4, 1%), Attention Deficiency Hyperactivity Disorder (ADHD) (n: 3, 0.7%), borderline personality disorder (n: 1, 0.2%), trichotillomania (n: 1, 0.2%). When the scale scores were compared between those who reported physical illness and those who did not, a statistically significant difference was found between CAS and CSS (p = 0.04; p = 0.016 respectively). When examined in terms of the mental health history of participants, a statistical difference was found in terms of CAS (p <0.001).

While 69 of the participants (17%) stated that they are healthcare professionals, there was no statistically significant difference between the CAS, CSS, and BSAS scales scores in terms of being a healthcare professionals or not. There were also no statistically significant relationship between the education levels of the participants and the CAS, CSS, BSAS scales' scores. Some of the relationships of the social characteristics of participants and scales' scores are summarized in Table 3 (Table-3).

Table 3. The relationships among physical and mental illness history, marital status, and education features of participants and CAS, CSS, BSAS scores

		n %	CAS Mean (SD)	Z*	p	CSS Mean (SD)	Z*	p	BSAS Mean (SD)	Z*	p
Physical illness History	Yes	34 (8.4)	3.38 (3.93)	-2.014	0.04	81.50 (24.01)	-2.416	0.016	21.85 (19.46)	1.334	0.182
	No	373 (91.6)	2.1743 (3.46)			71.85 (22.3)			26.02 (18.65)		
Mental Disorder History	Yes	43 (10.6)	4.37 (5.10)	-3.289	<0.01	80.39 (27.50)	-1.830	.067	30.42 (21.15)	-1.584	0.113
	No	164 (89.4)	2.02 (3.19)			71.74 (21.78)			25.12 (18.37)		
Mariatal Status	Single	1493 (36.6)	2.6 (3.74)	-2.657	0.008	74.8 (23.5)	-2.364	0.018	26.78 (19.7)	-1.171	0.232
	Married	258 (63.4)	1.71 (2.9)			68.9 (20.4)			23.7 (16.6)		
Education	Elementary school	7 (1.7)	2.14 (3.76)	1.413**	0.842	72.42 (25.2)	3.084**	0.544	24.57 (19.4)	3.300**	0.509
	High School	75 (18.4)	2.48 (3.6)			73.17 (23.6)			24.6 (17.25)		
	College	248 (60.9)	2.28 (3.5)			71.7 (22.2)			25.76 (19.1)		
	Master	55 (13.5)	2.36 (3.8)			77.6 (23.72)			28.92 (19.6)		
	PhD	22 (5.4)	1.36 (1.9)			68.5 (18.1)			21.1 (16.6)		

*: Mann-Whintney U **Kruskal-Wallis Test, BSAS: Bergen Shopping Addiction Scale, CSS: Cyberchondria Severity Scale,CAS:The Coronavirus Anxiety Scale

When the scores of the participants from the CAS, CSS, and BSAS scales were examined in terms of gender, there was a significant difference between men and women for all three scales' scores (p < 0.01; p = 0.003; p = 0.002 respectively). The mean total score obtained from the CAS scale was

2.87 ± 3.83, the mean score obtained from the CSS was 75.22 ± 22.98, and the mean score obtained from the BSAS was 27.97 ± 19.54 in the female group. The examinations of CAS, CSS, BSAS scales in terms of gender are given in Table 4 (Table 4).

Table 4. CAS, CSS, BSAS Scores of participants in terms of gender

	Female		Male		Total			
	mean	SD	mean	SD	mean	SD	Z	p*
CAS	2.87	3.83	1.21	2.55	2.28	3.51	-5.427	<0.001
CSS	75.22	22.98	68.12	21.15	72.66	22.57	-2.956	0.003
BSAS	27.97	19.54	21.63	16.53	25.68	18.73	-3.111	0.002

* Mann-Whintney U test BSAS: Bergen Shopping Addiction Scale, CSS: Cyberchondria Severity Scale, CAS:The Coronavirus Anxiety Scale

One of the purposes of this study was to examine relationships between CAS, CSS, and BSAS scores. The correlations of the CAS, CSS, and BSAS scales with each other were examined in Table-5. A statistically significant positive moderate correlation was found between CAS and CSS (r: 0.495, p <0.01). A statistically significant positive weak correlation was found between CAS and BSAS (r: 0.293, p <0.01). A statistically significant positive weak correlation was found between CSS and BSAS (r: 0.371, p <0.01) (Table-5).

Table 5. The correlations of CAS, CSS VE BSAS scores in all participants

	CAS(r)	CSS(r)	BSAS(r)
CAS	1.000		
CSS	0.495**	1.000	
BSAS	0.293**	0.371**	-0.316**

Spearman korelasyon test, *. p <0.05 . **. p <0.01 level BSAS: Bergen Shopping Addiction Scale, CSS: Cyberchondria Severity Scale,CAS:The Coronavirus Anxiety Scale

DISCUSSION

In this study, the relationship of coronavirus anxiety severity with cyberchondria, and online shopping addiction was investigated in the general population during the COVID-19 pandemic. In the present study, 79.6% of the participants stated that their anxiety increased, 63.4% of the participants stated that the frequency of shopping on the internet increased, and 39.8% of the participants stated that the amount of time for online searches for diseases increased during pandemic. There were several factors and results in terms of the relationships between socio-demographic characteristics and CAS, CSS, and BSAS which will be discussed in the following paragraphs of this paper.

The pandemic period we are in has led to psychological problems in varying levels in many individuals due to many reasons such as social isolation, loneliness, economic difficulties, etc. (3,8,17,18). Anxiety comes at the forefront of mental problems that increase during the pandemic period. However, depression, behavioral addictions such as online shopping, gambling also attract attention by researchers as mental disorders that increase during the pandemic period (4,8,17).

In the present study, 79.6% of the participants stated that their anxiety increased during the COVID-19 pandemic. There are several studies in the literature claiming that pandemic causes people to feel more anxious than usual in several ways (5-8,18,19). For instance; in a study conducted at the beginning of the COVID-19 pandemic in Spain; the stress, anxiety, and depression levels of 976 individuals were evaluated during the first and second half of March. They found that the stress, depression, and anxiety levels of the participants in the second half of March were found to be higher (19).

Cyberchondria and online shopping addiction are in demand for psychiatry research before the pandemic. In this study, 39.8% of participants stated that the number of online searches about their health increased during this pandemic. Since COVID-19 is a very new disease for all world, people search about COVID-19 more and more on the internet. For example; in a study conducted in the United States of America (USA), it was reported that seeing only the first COVID-19 case led individuals to question the symptoms of COVID-19 on online platforms and this searching increased by 36% in just one day (3).

On the other hand, most of the researchers also believe that behavioral addictions also increase in the pandemic due to several reasons (3,4,18,19). One of the important results of the present study, we found that 63.4% of the participants stated that the frequency of shopping on the internet increased during pandemic. Participants in the present study also stated the average number of online shopping they made during the pandemic as 3. The average number of online shopping of the same participants before the pandemic was found to be 2. Online shopping is seen as a functional way that reduces the need to go out in pandemic conditions. Also, the increase in daily internet usage time due to the reasons such as remote working from home due to the pandemic and online shopping has caused many behavioral addiction problems such as online gambling, online shopping addiction (9,20,21,22,23).

Regarding the relationships between the socio-demographic characteristics of the participants and CAS, CSS, and BSAS scale scores; a positive correlation was found between the BSAS scores and the number of monthly online purchases of the

participants both before and after the pandemic. Besides, there is also a weak correlation was found between the average daily internet usage time and the BSAS score. It is an expected result for us. Since the BSAS score increases in correlation with individuals who shop more online, but one of the important findings of the present study is that as the average daily internet usage time increased during the pandemic period, the BSAS score also increased. This means people who spend more time on the internet have much more online shopping tendency than those who spend less time on the internet.

When the CAS, CSS, and BSAS scores were examined according to whether the participants were healthcare professionals, no significant relationship was found between healthcare professionals or others in terms of their CAS, CSS, or BSAS scores. It can be thought that healthcare professionals may exhibit more intense coronavirus anxiety due to their job under intense stress during the pandemic. However, in the present study and another similar study in the literature, it was reported that being a healthcare professional was not associated with coronavirus anxiety (5). This result may be because the concept of "healthcare professionals" was not defined in sufficient detail in the present study. Questioning healthcare professionals who are only in contact with coronavirus patients such as doctors and nurses may help to reach more detailed results about this issue. In addition to this, there is another possibility about this finding. Since healthcare professionals have more accurate information about the COVID-19 and the mechanism of action of the virus may have affected as an anxiety-reducing factor on healthcare professionals.

In terms of the examination of CAS, CSS, and BSAS scores in terms of the history of physical or mental illness, both the CAS and CSS scores of the participants who reported a history of physical illness were found to be statistically significantly higher. On the other hand, only CAS scores of participants who reported any history of a mental disorder were found to be higher than those who never report any mental disorder history. Although every individual feels anxious about the virus and COVID-19 during the pandemic, this anxiety is experienced at higher levels in individuals who are currently followed for any mental disorder. The findings of the present study validated this expectation. Similarly, it is an expected result that individuals with any physical disease have higher CAS scores due to fears such as getting the COVID-19 and having the disease more severe under the condition of present diseases. Besides, it is one of the results we expect that people with physical illnesses have higher CSS scores. In the study of Jungman and Witthoft in which they investigated the factors associated with coronavirus anxiety, it was concluded that individuals with higher health anxiety also have higher coronavirus anxiety and that their cyberchondria levels are also associated with this anxiety level (5). In addition to higher health anxiety and cyberchondria, other factors that were claimed to be related to coronavirus anxiety were highlighted as the ability to regulate emotions and being informed about the pandemic (5). Similarly, in a different study conducted in the USA, the depressive symptoms, anxiety levels, sleep disorders, and quality of life characteristics of a sample of 898 young adults during the pandemic period were examined. In this study, it was found that participants with a diagnosis of the mental disorder showed 6 times more depression and 4 times more anxiety symptoms during pandemic than others who do not have any mental disorder (24). Also, in this study, it was stated that the group with a history of mental disorders had more coronavirus-related anxiety during the pandemic, and their sleep and life quality were lower than others who do not have any mental disorder (24).

Regarding examination of CAS, CSS, and BSAS scores in terms of gender, it was observed that the CAS, CSS, and BSAS scores of women were statistically significantly higher than men. Similar to other studies investigating anxiety levels during the pandemic, coronavirus-induced anxiety levels were found to be higher in women in our study (5,25,26). It is known that anxiety susceptibility traits and all anxiety disorders are more common in the female gender and this may support this result in the present study (27).

When CAS, CSS, and BSAS scores are examined according to the marital status of the participants; CAS and CSS scores of the single participants were statistically significantly higher than the same scores of the married participants. There is a possibility that married individuals have potentially higher social support which protects them both from coronavirus anxiety and cyberchondria. However, in a study conducted in a previous pandemic, it was found that variables such as marital status, age, living together with other adults do not have a protective or calming effect on the possible psychological effects of the pandemic (28). Still, it seems that having family support keeps people calmer during pandemics based on our findings.

In terms of the examination of scores based on age, a weakly significant correlation was found between the mean age of the participants and the CAS, CSS, and BSAS scores. While some of the other studies investigating the effect of age on coronavirus anxiety found more intense levels of anxiety in younger individuals, some other studies suggested that coronavirus anxiety increased with increasing age (19,25).

Regarding examination of the relationship between CAS, CSS, and BSAS scores and COVID-19 history, it was observed that BSAS scores of

individuals who had COVID-19 or contact history were higher. Also, the CAS and CSS scores of those who have a family member with a history of COVID-19 were significantly higher than those who did not have a family member with a history of COVID-19. It seems that having a family member with COVID-19 affects coronavirus anxiety and cyberchondria levels rather than having the COVID-19 in person. There is another possibility about this result is that having a family member who had COVID-19 may cause this situation indirectly by causing people to increase their awareness of COVID-19 and following rules about precautions about the virus. On the other hand, the knowledge that recovering from COVID-19 once makes people have some antibodies towards COVID-19 for a certain period of time, maybe another feature that may lead to this result.

Regarding the examination of the relationships among the CAS, CSS, and BSAS scores, it was found that the CAS scores had a positive correlation with both CSS and BSAS. This finding can be concluded that individuals with high coronavirus anxiety search for more symptoms of illness on the Internet. Since they spend more time on the internet, at the same time they do more online shopping than those who spend less time on the internet. Recently published studies also supported this finding and pointed out that individuals with a higher cyberchondria score also have higher coronavirus anxiety (5,29). In a study conducted in Germany with 1615 participants, the presence of cyberchondria was found to be associated with higher coronavirus anxiety, and it was suggested that cyberchondria may have a regulatory role between the ongoing general anxiety level and coronavirus anxiety (5). Since we did not measure the general anxiety level of participants we can not point out a relationship between general anxiety traits and coronavirus anxiety. But, still, it seems that cyberchondria is associated with coronavirus anxiety during the pandemic.

In another longitudinal study, researchers evaluated the anxiety levels of healthy individuals with low anxiety scores in 2016. Then researchers let participants search about some diseases, symptoms, etc. for 2 months. At the end of 2 months, period researchers evaluated the anxiety levels of participants again and found that the same group had higher anxiety scores at the end of the second month compared to the baseline (30). There is a need for new researches in this field to understand whether the anxiety affects cyberchondria tendency or cyberchondria makes individuals more anxious than others. It should be kept in mind that individuals with high coronavirus anxiety may also be searching on the internet by doing more research about a new virus and the health problems it causes. As a matter of fact, in some previous studies, it has been shown that individuals who are concerned about their health use the internet more to inquire about information about diseases (29,31).

Additionally, CSS scores were found to be correlated with BSAS scores. Online shopping may affect by reducing anxiety levels, given that individuals who shop online are more anxious. In a study conducted in Finland with 211 participants and examining the shopping habits of individuals during the pandemic period, researchers stated that the cyberchondria tendencies of the participants were related to their usual online shopping features (32). In this study, researchers also stated that online shopping addiction was related to the self-isolation as well (32).

People mostly visit psychiatry outpatient clinics for asking help about their anxiety during the pandemic. The main aim of this study to examine the relationship between CAS, CSS, and BSAS. Knowing the relationships between these features may indirectly help reduce cyberchondria and online shopping addiction through interventions that will help individuals reduce their anxiety levels.

Besides, it seems that if the government provides more accurate information about the possible symptoms of the COVID-19 and the conditions that are expected after the infection can also affect the coronavirus anxiety, cyberchondria, and online shopping addiction scores.

CONCLUSION

It is obvious that during the pandemics, most people feel more anxious and search more about their health online. The present study showed that cyberchondria may be an incompatible coping method that is used for reducing intense anxiety against coronavirus. On the other hand, cyberchondria itself can increase existing anxiety because of existing misinformation on the internet.

Besides, it seems that spending more time on the internet seems to affect online shopping behaviors as well. Due to just these two reasons pandemic seems to be a risk factor for both cyberchondria and online shopping addiction in society. For this reason, mental health professionals should inform individuals about mental problems caused by the intense use of the internet during the pandemic which is also crucial for public health. Also, mental health professionals should encourage the use of more adaptive coping mechanisms for anxiety during the pandemic such as exercise, reading books, cooking, spending some time with art, etc.

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RESEARCH ARTICLE

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Famotidine in COVID-19 Treatment

ABSTRACT

Objective: Famotidine is an H2 receptor antagonist (H2RA) and has been shown to have antiviral properties in in vitro studies. Pantoprazole is one of the proton pump inhibitors (PPI). In this study, it was aimed to compare the efficacy of famotidine with pantoprazole in the treatment of COVID-19.

Methods: Patients who were hospitalized and given famotidine and pantoprazole treatment for at least 48 hours were included in the study. Demographic, clinical and laboratory findings of the patients were analyzed retroprospectively from the patient files. The patients were divided into two groups as the famotidine group and the pantoprazole group. The groups were compared in terms of the need for intensive care and mortality rates. In addition, among the groups, the number of patients with normal oxygen saturation at discharge, number of days needed for oxygen support, number of days with fever, and length of hospital stay were evaluated.

Results: A total of 179 Covid-19 patients (85 famotidine, 94 pantoprazole) were included in the study. Demographic findings and other symptoms except dyspnea were similar in both groups. Dyspnea, chronic diseases, and the number of patients given steroids were higher in those who were given pantoprazole ($p<0.05$). Mortality and ICU need were similar in both groups (respectively; $p=0.25$, $p=0.26$). The number of days with fever, duration of hospitalization, and the number of days requiring oxygen support were less in those given famotidine (respectively; $p=0.04$, $p=0.003$, $p=0.014$).

Conclusions: Famotidine did not reduce the need for intensive care and mortality in COVID-19 patients treated in the hospital. New therapeutic agents are needed to reduce disease severity and mortality.

Keywords: COVID-19, Famotidine, Pantoprazole, Mortality.

COVID-19 Tedavisinde Famotidin Kullanımı

ÖZET

Amaç: Famotidin, bir H2 reseptör antagonistidir ve in vitro çalışmalarda antiviral özelliklere sahip olduğu gösterilmiştir. Pantoprazol, proton pompası inhibitörlerinden biridir. Bu çalışmada, COVID-19 tedavisinde Famotidinin ile Pantaprazolun etkinliğinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya en az 48 saat famotidin ve pantaprazol tedavisi verilen ve hastanede yatan hastalar dâhil edildi. Hastaların demografik, klinik ve laboratuvar bulguları hasta dosyalarından geriye dönük olarak incelendi. Hastalar famotidin grubu ve pantoprazol grubu olarak iki gruba ayrıldı. Gruplar yoğun bakım ihtiyacı ve ölüm oranları açısından karşılaştırıldı. Ayrıca gruplar arasında taburculukta oksijen saturasyonu normal olan hasta sayısı, oksijen desteğine ihtiyaç duyulan gün sayısı, ateşli gün sayısı ve hastanede kalış süresi değerlendirildi.

Bulgular: Çalışmaya toplam 179 Covid-19 hastası (85 famotidin grubu, 94 pantoprazol grubu) dâhil edildi. Demografik bulgular ve dispne dışındaki diğer semptomlar her iki grupta benzerdi. Pantoprazol verilenlerde dispne, kronik hastalıklar ve steroid verilen hasta sayısı daha yüksekti. Mortalite ve YBÜ ihtiyacı her iki grupta benzerdi (sırasıyla; $p=0.25$, $p=0.26$). Famotidin verilenlerde ateşli gün sayısı, hastanede kalış süresi ve oksijen desteği gerektiren gün sayısı daha azdı (sırasıyla; $p=0.04$, $p=0.003$, $p=0.014$).

Sonuç: Famotidin, hastanede tedavi gören COVID-19 hastalarında yoğun bakım ihtiyacını ve mortaliteyi azaltmadı. Hastalık şiddetini ve ölüm oranını azaltmak için yeni tedavilere ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Famotidin, Pantoprazol, Mortalite.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was started in Wuhan (China) in December 2019 and expanded dramatically worldwide. The virus, which caused one of the biggest epidemics of the 21st century, has had devastating effects in many countries due to its high contagiousness and high mortality rates (1). Over 110 million cases and 2.5 million deaths have been reported globally (2). The most common symptoms of COVID-19 are fever, dry cough, and tiredness. In severe cases, shortness of breath, confusion, persistent pain or pressure in the chest, and high temperature (above 38 C) are seen. Approximately 80% of symptomatic patients recover without the need for hospital treatment. While approximately 15% of them have a serious infection and need oxygen support, 5% of them become critically ill and need intensive care (3). (WHO-2020) Data from patients infected with SARS-CoV showed that severe cases characterized by cytokine storm inevitably progress to Acute Respiratory Distress Syndrome (ARDS). Tissue damage caused by the virus can induce overactivation of macrophages and granulocytes and overproduction of proinflammatory cytokines. This event results in Cytokine Storm (cytokine storm-CS) called Macrophage Activation Syndrome (MAS), and thus further tissue damage occurs (4).

From the first days of the pandemic, antivirals that could be effective on COVID-19 have been investigated and antivirals are shown to be effective in the treatment of SARS-CoV and Middle East Respiratory Syndrome coronavirus (MERS-CoV) have been started to be used in in vitro and in vivo studies. However, unfortunately, since complete success cannot be achieved with these treatments, the effectiveness of drugs with antiviral and anti-inflammatory effects, which are thought to be effective against COVID-19, are being investigated (5). Famotidine is an H2 receptor antagonist (H2RA) that suppresses stomach acid production. Previous data show that H2RAs have antiviral properties that inhibit in vitro HIV replication (6). In this study, it was aimed to investigate the effectiveness of Famotidine treatment in COVID-19.

MATERIAL AND METHODS

Study Place and Design: This study was conducted in Sakarya Training and Research Hospital, which has a total of 1000 beds. The study protocol was approved by the institutional review board of the Sakarya University (IRB No: 71522473/050.01.04/465). Patients who used famotidine or pantoprazole for at least 2 days in addition to the standard COVID-19 treatment were included in the study. Patients who died before the second day of the standard treatment and those who were switched to another while using one of the compared drugs were not included in the study.

Patients and Standard Therapy: The patients were divided into two groups as the famotidine group and the pantoprazole group. The groups were compared in terms of the need for intensive care and mortality rates. In addition, among the groups, the number of patients with normal oxygen saturation at discharge, number of days needed for oxygen support, number of days with fever, and length of hospital stay were evaluated.

Statistical Analysis: We evaluated the data with SPSS v.23 statistics program. We gave the number and percentage distributions to examine the descriptive features in the analysis. We calculated the central tendency and prevalence measures (mean, median, standard deviation, 1st, and 3rd quartiles) of data with continuous variable character. We used the chi-square test (Pearson and Fisher's exact test) to compare categorical variables. We evaluated the suitability of continuous variables to a normal distribution using the Shapiro Wilk test, and numerical data that did not conform to normal distribution we compared by using Mann Whitney U test. We accepted the statistical significance value as $p < 0.05$ at 95% confidence interval.

RESULTS

179 Covid-19 patients were included in the study. Pantoprazole was given to 94 (52.5%) of the patients, while famotidine was given in 85 (47.5%) of them. When the patients were grouped according to their use of famotidine and pantoprazole, the mean age was 62.0 ± 15.8 and 65.8 ± 14.5, respectively, and there was no statistically significant difference between the groups' mean age ($p=0.65$). While 50.6% (n=43) of those using famotidine were female, 49.4% (n=42) were male; 47.9% (n=45) of those using pantoprazole were female and 52.1% (n=49) were male ($p=0.71$). The distribution of some of the characteristics of the patients during their application according to the gastric protective drug they use is given in Table 1.

Chronic diseases, immunosuppressive therapy, malignancy, hydroxychloroquine, enoxaparin, antibiotics, acetylsalicylic acid, tocilizumab/anakinra, convalescent plasma and vitamin D were similar in patients using famotidine and pantoprazole ($p>0.05$). Also, the presence of symptoms was similar in both groups ($p>0.05$).

The relationship between the gastric protective medication used by the patients and the average of the laboratory values at the time of application is given in Table 2.

Table 1. The distribution of some characteristics of the patients during their application according to the gastric protective drug they used

(n=179)	Famotidine	Pantoprazole	
	n (%*)	n (%*)	p
Presence of chronic illness			
Hypertension	28 (32.9)	42 (44.7)	0.10
Diabetes mellitus	17 (20.0)	30 (31.9)	0.07
Coronary artery disease	11 (12.9)	17 (18.1)	0.34
Chronic obstructive pulmonary disease	8 (9.4)	13 (13.8)	0.35
Chronic renal failure	8 (9.4)	5 (5.3)	0.29
Receiving immunosuppressive therapy	3 (3.5)	3 (3.2)	0.90
Presence of malignancy	2 (2.4)	3 (3.2)	0.73
Comorbidity presence	20 (23.5)	35 (37.2)	0.04
Drug use			
Favipiravir	74 (87.1)	92 (97.9)	0.005
Hydroxychloroquine	11 (12.9)	6 (6.4)	0.13
Enoxaparin	69 (81.2)	79 (84.0)	0.61
Antibiotic	46 (54.1)	52 (55.3)	0.87
Steroid	33 (38.8)	60 (63.8)	0.001
Asetylsalicylic acid	16 (18.8)	27 (28.7)	0.12
Tociluzimab/Anakinra	2 (2.4)	8 (8.5)	0.10[a]
Convalescent Plasma	8 (9.4)	9 (9.6)	0.97
Vitamin D	2 (2.4)	2 (2.1)	0.91
Presence of symptoms			
Fatigue	43 (50.6)	60 (63.8)	0.07
Cough	39 (45.9)	52 (55.3)	0.20
Dyspnea	23 (27.1)	55 (58.5)	<0.001
Muscle-joint pain	34 (40.0)	33 (35.1)	0.49
Fever	29 (34.1)	26 (27.7)	0.35
Anosmia	8 (9.4)	11 (11.7)	0.61
Diarrhea	10 (11.8)	9 (9.6)	0.63
Headache	10 (11.8)	8 (8.5)	0.47
Sore throat	7 (8.2)	6 (6.4)	0.63
Respiratory rate	85 (47.4**)	94 (52.6**)	
X̄±SD (Median)	21.4±2.2 (22.0)	21.4±2.0 (22.0)	0.78[b]

*Percentages are column percentages. **Percentages are percent of rows. [a]Fisher's exact test was used. [b]Mann Whitney U test was performed due to skewed distribution.

Table 2. The relationship between the gastric protectant used by the patients and the mean laboratory values at the time of application. Laboratory values Stomach protection used in the treatment

Laboratory values	Famotidine (n=85)	Pantoprazole (n=94)	Total	p value*
WBC				<0.001
X̄±SD(Median)	5.9±2.9 (5.4)	7.6±3.7 (6.8)	6.8±3.5 (5.8)	
1st quarter-3rd quarter	4.3-6.3	5.1-9.2	4.6-8.3	
Lymphocyte				0.15
X̄±SD (Median)	1370.8±767.8 (1270.0)	1231.0±711.4 (1065.0)	1297.4±739.9 (1169.0)	
1.st quarter- 3rd quarter	841.0-1800.0	759.0-1518.0	785.0-1640.0	
Hemoglobin				0.007
X̄±SD (Median)	13.1±1.8 (13.3)	12.4±1.8 (12.5)	12.7±1.8 (13.0)	
1st quarter-3rd quarter	12.2-14.1	11.3-13.7	11.7-13.9	
Hematocrit				0.02
X̄±SD (Median)	40±5.6 (40.5)	38±6.1 (38.5)	38.9-5.9 (39.3)	
1st quarter -3rd quarter	36.7-43.4	33.9-42.3	35.6-43.1	
Ferritin				0.11
X̄±SD (Median)	470.1±579.2 (266)	573.8±682 (378)	524.6±635.6 (316)	
1st quarter-3rd quarter	132-478	157-736	146-618	
LDH				0.009
X̄±SD (Median)	304.8±130.5 (277)	384.3±297.2 (319)	346.5±236.2 (313)	
1st quarter-3rd quarter	214-351	258-419	240-395	
D dimer				0.02
X̄±SD (Median)	1058.5±1793.4 (500)	1316.4±1639.7 (639.5)	1193.9±1714.4 (568)	
1st quarter -3rd quarter	218.0±1120	403-1570	312-1220	
C-Reactive Protein				0.001
X̄±SD (Median)	52.8±56.3 (40)	83.3±68.8 (73.5)	68.8±64.8 (53.2)	
1st quarter-3rd quarter	12.7-62.4	26-122	15.2-107	
CK				0.46
X̄±SD (Median)	287±1148 (90.0)	175.1±232.3 (78)	228.2±808.2 (82)	
1st quarter-3rd quarter	60-197	46-192	52-197	

* Mann Whitney U test was used because of the skewed distribution.

The relationship between the gastric protective treatment they used in the treatment and the number of days of hospitalization, the number of days when oxygen saturation improved and fever

subsided is given in Table 3. Oxygen saturation was low in 21 (24.7%) of the patients using famotidine at the first admission, while it was low in 52 (55.3%) of those using pantoprazole (p<0.001). Oxygen saturation decreased in the first days of follow-up in four of the patients who were given both famotidine and pantoprazole during their hospitalization. Oxygen saturation improved in 76 (78.4%) of 97 patients with low oxygen saturation (mean: 6.32±4.1 days). The mean hospitalization period of patients using famotidine for treatment was 7.7±4.6 days, and the mean hospitalization period of patients using pantoprazole was 9.4±5.4 days (p=0.003). While the fever of the patients using famotidine for treatment decreased in an average of 2.4±1.4 days, the fever of the patients using pantoprazole decreased in an average of 3.0±1.4 days (p=0.04).

Table 3. Relationship between gastric protective treatment used by the patients in treatment and the number of days of hospitalization, days when saturation improved and fever subsided.

	Famotidine	**Pantoprazole**	**Total**	**p value***
Hospitalization time (days)				0.003
n	85	94	179	
X̄±SD (Median)	7.7±4.6 (6)	9.4±5.4 (8)	8.6±5.1 (7)	
1st quarter-3rd quarter	5-9	6-12	5-10	
Time to recovery saturation (days)				0.014
n	21	55	76	
X̄±SD (Median)	5.0±3.5 (4)	6.9±4.2 (6)	6.3±4.1 (6)	
1st quarter-3rd quarter	3-6	4-8	3.5-8	
Duration of fever (days)				0.04
n	29	26	55	
X̄±SD (Median)	2.4±1.4 (2)	3.0±1.4 (3)	2.7±1.4 (2)	
1st quarter-3rd quarter	1-3	2-3	2-3	
Oxygen saturation				
Improved / Not improved n (%)	21 (75)/7 (25)	55 (80)/14 (20)		0.61

* Mann-Whitney U test was used due to the skewed distribution.

In our study, mortality and the need for follow-up in the intensive care unit, were similar in both groups (Table 4). Gastrointestinal bleeding was detected in a patient using famotidine.

Table 4. Survival and need for intensive care according to the gastric protective drug used by the patients.

	Famotidine	**Pantoprazole**	
	n (%*)	**n (%*)**	**p**
Survival status			0.25
Deceased	5 (5.9)	10 (10.6)	
Discharged with healing	80 (94.1)	84 (89.4)	
Intensive care need			0.26
No	77(90.6)	80 (85.1)	
Yes	8 (9.4)	14 (14.9)	
Total	85 (45.7)	94 (52.5)	

* Percentages are column percentages.

DISCUSSION

This study investigates the real-life effectiveness and safety of famotidine in moderate and severe COVID-19 patients in a tertiary care hospital. Mortality and intensive care need in patients given famotidine were found to be statistically similar to those given pantoprazole (p>0.05).

Histamine is a natural body precursor synthesized from L-histidine. Histamine acts through 4 types of receptors (H1R, H2R, H3R, H4R). It causes immune system activities such as mast cell degranulation, antibody synthesis, Th1 cytokine production through H2R (7). It can cause tissue damage in the lungs by stimulating inflammation and cytokine release (8). Both H1 and H2 receptor antagonists have been demonstrated to inhibit both histamine and cytokine secretion. Also, the immunomodulatory activity H2 receptor antagonists has been shown in multiple studies (9).

The antiviral effect of famotidine has not been studied in detail in patients. Bourinbaiar et al. reported that H2R antagonists, including famotidine, inhibited human immunodeficiency virus replication without affecting lymphocyte viability in vitro (6). Likewise, it was thought to directly inhibit the SARS-CoV-2 virus, but recent studies using two different cell lines, including a human cell line originating from lungs have failed to demonstrate any direct inhibitory effect of famotidine on SARS-CoV-2 infection (10).

Freedberg et al. reported that in patients hospitalized with COVID-19 who were not initially

intubated, the use of famotidine resulted in a 2-fold reduction in clinical worsening leading to intubation or death, and this effect was not seen in patients using PPI (11). In our study, mortality and ICU requirement were similar in patients who received famotidine and those who received PPI. In patients given famotidine, the duration of hospitalization, recovery time of oxygen saturation and the number of days when fever decreased to normal values were found to be significantly less than those given PPI. However, we think that this effect is related to the fact that patients who were given famotidine had a milder clinical picture and had fewer risk factors than those given PPI. The number of patients presenting with dyspnea and comorbidities such as hypertension and diabetes mellitus, whose relationship with mortality was shown in previous studies, were higher in patients who were given PPI. In addition, LDH, D-dimer and C-reactive protein levels were higher in patients with PPI. It has been shown in previous studies that these laboratory parameters increase in direct proportion to the severity of the disease (12). Our study has some limitations. Since drugs such as enoxaparin and acetylsalicylic acid, which can cause gastrointestinal system side effects, were given to all patients in the center where the study was conducted, gastric medications such as famotidine or pantoprazole are started for all patients followed in the hospital. For this reason, patients who were given famotidine could not be compared with patients who did not use any gastric medication. Another limitation of our study is that patients given pantoprazole had more severe COVID-19 patients compared to patients who were given famotidine. This is due to the retrospective design of the study. If the baseline values of the patients in the two groups were found to be similar, we could have made a more precise judgment.

As a result, famotidine was not reduce the need for ICUs and mortality in COVID-19 patients treated in hospital. Since there is no antiviral whose efficacy has been shown with certainty, randomized controlled studies are needed to clearly demonstrate the effectiveness of famotidine, which is used for alternative treatment searches, in COVID-19 disease.

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RESEARCH ARTICLE

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Thiol-Disulphide Homoeostasis in COVID-19: Evaluation of its Relationship with Complete Blood Count Parameters

ABSTRACT

Objective: In this study, we aimed to evaluate the relationship between thiol-disulfide homoeostasis and hemogram parameters in COVID-19 patients.

Methods: Total thiol(TT), Native thiol(NT), dynamic disulfide status(DDS), DDS/NT, DDS/TT, NT/TT ratio and CBC parameters were analyzed in 68 patients with positive COVID-19 and 31 healthy individuals.

Results: TT, NT, DD, hemoglobin and hematocrit levels were higher in the control group than in patient groups. TT, NT, DD and lymphocyte levels of COVID-19 patients treated in medical floor were higher than those treated in intensive care unit; WBC, neutrophil and NLR were low($P<0.05$).PLR was higher in intensive care patients compared with the control group($P<0.05$).COVID-19 patients who did not need mechanical ventilation were retrospectively evaluated according to their mortality. TT, NT, DDS and lymphocyte levels were higher; WBC, Neutrophil, PLR and NLR were lower($P<0.05$) in survivors. The diagnostic performance of TT, NT and DDS levels to define requirement of intensive care treatment in COVID-19 patients were evaluated by using Receiver Operating Characteristic (ROC) curve analysis. By using ROC analysis, the optimum cut-off points for of TT, NT and DDS levels showed high sensitivity and specificity for requirement of intensive care treatment($P<0.05$).

Conclusions: According to our results, it has been observed that the thiol-disulfide balance is disrupted In COVID-19 patients. It may be beneficial to monitor the thiol-disulfide balance in the follow-up and treatment of the patients.

Keywords: COVID-19, Total Thiol, Native Thiol, Dynamic Disulfide Status, Complete Blood Count.

COVID-19'da Tiyol-Disülfid Dengesi: Tam Kan Sayımı Parametreleri ile İlişkisinin Değerlendirilmesi

ÖZET

Amaç: Bu çalışmada, COVID-19 hastalarında tiyol-disülfid homoeostazı ile hemogram parametreleri arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve Yöntem: Total tiyol (TT), Native tiyol (NT), dinamik disülfid durumu (DDS), DDS / NT, DDS / TT, NT / TT oranı ve CBC parametreleri COVID-19 pozitif 68 hasta ve 31 sağlıklı bireyde analiz edildi.

Bulgular: Kontrol grubunda TT, NT, DD, hemoglobin ve hematokrit düzeyleri hasta gruplarına göre daha yüksekti. Serviste tedavi gören COVID-19 hastalarının TT, NT, DD ve lenfosit seviyeleri yoğun bakım ünitesinde tedavi edilenlere göre daha yüksekti; WBC, nötrofil ve NLO düşüktü ($P <0.05$). Yoğun bakım hastalarında PLR, kontrol grubuna göre daha yüksekti ($P <0.05$). Mekanik ventilasyona ihtiyaç duymayan COVID-19 hastaları mortalitelerine göre geriye dönük olarak değerlendirildi. TT, NT, DDS ve lenfosit seviyeleri daha yüksekti; Hayatta kalanlarda WBC, Nötrofil, PLR ve NLR daha düşüktü ($P <0.05$). COVID-19 hastalarında yoğun bakım tedavisi gereksinimini tanımlamak için TT, NT ve DDS düzeylerinin tanısal performansı, ROC eğrisi analizi kullanılarak değerlendirildi. ROC analizine göre, yoğun bakım tedavisi gereksinimi için TT, NT ve DDS düzeyleri optimum kestirim değerlerinde, yüksek duyarlılık ve özgüllük göstermiştir ($P <0.05$).

Sonuç: Sonuçlarımıza göre COVID-19 hastalarında tiyol-disülfid dengesinin bozulduğu görüldü. Hastaların takip ve tedavisinde tiyol-disülfid dengesinin izlenmesi faydalı olabilir.

Anahtar Kelimeler: COVID-19, Toplam Tiyol, Doğal Tiyol, Dinamik Disülfür Durumu, Tam Kan Sayımı.

INTRODUCTION

The virus named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) caused Coronavirus disease (COVID-19), which started in the city of Wuhan in December 2019 and spread rapidly to the World (1). This disease was declared as a pandemic by the World Health Organization (WHO) on March, 2020 (2) Coronaviruses, including SARS-CoV-2 are enveloped RNA viruses that can cause respiratory, intestinal, liver and neurological diseases in human, other mammals, and birds (3). It can cause symptoms such as fever, cough, dyspnea, and myalgia. Shock, acute respiratory distress syndrome (ARDS), acute heart damage and acute kidney injury may develop and progress to death. In addition to radiological findings, parameters such as complete blood count (CBC), C-reactive protein (CRP) and D-Dimer are used in the diagnosis and follow-up of the disease (4).

It has been known that oxidative stress has important role in the course of viral infections. It also plays an important role in the proper functioning of the immune system and host defense against pathogens (5). Reactive oxygen species (ROS) are produced in phagocytes to destroy pathogenic macromolecules directly. It can also take place indirect antimicrobial processes (5, 6).

It is known that oxidoreductases associated with the cell surface play a role in the entry of viruses into host cells. For entry of enveloped viruses into target cells, interaction between viral envelope glycoproteins and cellular receptors occur on the surface of the target cell. Conformational changes are produced in the receptors as a result of Thiol / disulfide exchange reactions occurring in glycoproteins. Finally, viral particles enter into host cell with clathrin-mediated or clathrin-independent endocytosis (7, 8). Increased ROS production due to viral infection trigger pro-inflammatory response by affecting several transcription factors such as NF-κB (9). Although cells have special antioxidant systems to deal with increased ROS production, these systems are rapidly depleted during viral infection and uncontrolled oxidative stress occurs. Prolonged oxidative stress can then cause apoptosis or necrosis, leading to a decrease in lymphocyte cell numbers (6, 10).

Thiols are most important defense system against reactive species due to sulfhydryl groups (SH) in their structure. SH groups can be oxidized by the oxidant molecules in the environment and converted into reversible disulfide (SS) bond structures (11). The disulfide bond structures formed in this way are reduced back to thiol (SH) groups, and the thiol-disulfide balance is preserved (12). This balance has important roles in antioxidant protection, detoxification, apoptosis, regulation of enzymatic activity, and cellular signaling mechanisms. Therefore, evaluation of Thiol-disulfide balance in patients in COVID-19 infection may reveal some new information about this disease (12, 13).

In this study, we aimed to evaluate the oxidative stress level in COVID-19 patients with Thiol-disulfide balance as a new oxidative stress marker. We also searched its relationship with underling chronic diseases, therapeutic drugs used in treatment, clinical course, lymphopenia, leukocytosis level, neutrophil lymphocyte ratio (NLR) and platalet lymphocyte ratio (PLR) in COVID-19 patients.

MATERIAL AND METHODS

This study was conducted with 68 individuals who applied to XX University Medical Faculty Training and Research Hospital between May 15 and August 15 with positive COVID-19 PCR results, which were treated and followed up in the service and intensive care unit (ICU), as well as any chronic diseases and drugs admitted to the general internal medicine outpatient clinic on the same dates as a control group with negative PCR test results. Individuals with positive COVID-19 PCR results were divided into two groups as inpatients (33) and ICU (35) patients. Within the scope of the study, the patients' age, gender, chronic diseases and clinical information (application complaints, hospitalization in the medical floor-ICU, intubation status, death or discharge status and the drugs they used) were obtained through the hospital automation system. Patients who refused to participate in the study and were under 18 years of age were excluded from the study. Remaining parts of the samples taken during routine analysis were kept under appropriate conditions and no additonal sample was taken.

After the samples arrived at the biochemistry laboratory, CBC parameters were analyzed immediately. Venous blood samples were centrifuged at 1500 g for 10 minutes after the coagulation process was completed. The samples were not hemolyzed and lipaemic. Sera for total thiol and native thiol measurement were stored at -80 oC until the analyzed. All samples were allowed to come to room temperature and were carefully mixed to homogenize.

Serum Total Thiol, Native Thiold levels were measured in the Olympus AU5800 (BeckmanCoulter, Inc. Brea, CA92821 USA) autoanalyzer using the spectrophotometric method developed by Erel and Neselioğlu (14) CBC were measured by laser measurement and LED Flow Cell method on a CELL-DYN 3700 CD-3700SL (AbbottDiagnostics Liquid, Abbott Laboratories Abbott Park IL, 60064, USA) device. Dynamic disulfide status (DDS) was calculated by taking half of the difference between the measured total thiol (TT) and Native thiol (NT) levels. DDS / NT, DDS / TT, NT / TT were calculated.

All values obtained were evaluated in the SPSS (ver. 20.0; SPSS, USA) program. The mean,

median, min-max value and standard deviations of the measurement results were calculated. The Shapiro-Wilk Test was used to determine whether the data conformed to normal distribution. Student-t test was used when parametric test conditions were met in groups with two independent variables, Mann-Whitney U test if not provided, One-Way Analysis of Variance if parametric test conditions were met in groups with more than two independent variables, and Kruskal-Wallis test if not. Pearson Chi-Square test was used for categorical variables. Correlation and analysis were performed to evaluate the relationship between thiol-disulfide levels of patients with CBC parameters and clinical course. Significance was assessed at least at the $p < 0.05$ level. In addition, the relationship between TT, NT, DD, lymphocyte, neutrophil, WBC, PLR, NLR parameters and the need for intensive care treatment (prognosis) of the patients was also examined by ROC analysis.

RESULTS

Within the scope of this study, the findings of a total of 99 individuals with 31 PCR negative healthy individuals (15-Female, and 16-Male), 68 positive PCR results (33 inpatients (18M, 15F) treated in the medical floor and 35 patients (19M, 16F) treated in the ICU) were evaluated. When the chronic diseases of the individuals were examined, it was found that 44.1% of COVID-19 PCR positive patients had no chronic disease, 22.1% had one and 33.8% had two or more chronic diseases. The most common of these diseases were 36.8% hypertension, 14.7% coronary artery disease, 11.8% diabetes, 5.8% chronic renal failure, 4.4% congestive heart failure and 4.4% COPD.

The results of CBC and Thiol analytes according to the groups are shown in table 1. In the control group, Total Thiol, NativeThiol, Dynamic Disulfide, hemoglobin, hematocrit, lymphocyte levels were higher than both inpatients and ICU patients on the contrary the NLR level was found to be low ($p < 0.05$). In inpatients group, lymphocyte count, Total Thiol, NativeThiol and Dynamic Disulfide levels are significantly higher than those treated in ICU unlike WBC (White Blood Cell), neutrophil and NLR rates were significantly lower ($P<0.05$). Neutrophil and PLR levels were found to be higher in patients treated in ICU than both the control group and the inpatients group ($P<0.05$), while there was no significant difference between the inpatients and the control groups ($P> 0.05$) (Table 1).

Table 1. CBC and thiol parameters according to groups

	Control	**Inpatient**	**ICU**
	Mean± SD	**Mean± SD**	**Mean± SD**
Age	52.6 ± 14.5	56.3 ± 15.8	70.4 ± 13.7
Total Thiol (umol/L)	531.9 ± 77	235.7 ± 107 [a b]	146.5 ± 83.5 [a]
Native Thiol (umol/L)	386.0 ± 66.8	180.4 ±76.5 [a b]	111.0 ± 62.5 [a]
Dynamic Disulfide (umol/L)	73.0 ± 9.05	27.6 ± 17.6 [a b]	17.8 ± 20.1 [a]
Dynamic Disulfide /Native Thiol (%)	19.3 ± 3.35	14.7 ± 6.7 [a]	19.7 ± 31.5 [a]
Dynamic Disulfide /Total Thiol (%)	13.8 ± 1.69	10.9 ± 3.97 [a]	11.4 ±6.9 [a]
Native/Total Thiol (%)	72.3 ± 3.38	78.0 ± 7.9 [a]	77.2 ± 13.8[a]
WBC (K/uL)	7.1 ± 1.26	6.0 ± 1.45 [a b]	8.9 ± 5.05
Hemoglobin (g/dL)	14.4 ± 1.56	12.6 ± 1.92 [a]	12.4 ± 1.74 [a]
Hematocrit (%)	43.6 ± 4.39	39.7 ± 6 [a]	38.5 ± 5.2[a]
Lymphocyte (K/uL)	2.3 ±0.66	1.56 ± 0.64 [a b]	0.9 ±0.46 [a]
Neutrophil (K/uL)	4.0 ±0.94	3.9 ± 1.5 [b]	6.7 ± 3.85 [a]
Platelet (K/uL)	231.3 ±51.2	200.5 ± 75.8 [a]	236.5 ± 128.1
NLO	1.8 ± 0.62	3.3 ± 3.33 [a b]	10.1 ± 7.25 [a]
PLO	105.3 ± 25.5	101.5 ± 149 [b]	334.4 ± 200.3 [a]

[a] according to control , [b] between the inpatient and ICU patients

When COVID-positive patients are grouped according to survival, Total Thiol, native thiol, dynamic disulfide, lymphocyte is significantly higher in the surviving patients on the contrary WBC, Neutrophil, PLR, NLR was significantly lower ($P<0.05$). When COVID positive patients are grouped according to the mechanical ventilation needed Total Thiol, native thiol, dynamic disulfide, lymphocyte is higher in patients who do not need ventilation unlike WBC, Neutrophil, PLR, NLR levels were found to be low ($P<0.05$). In individuals without chronic disease, the levels of Total Thiol, native thiol, dynamic disulfide, lymphocyte, hemoglobin, hematocrit were high, whereas WBC, Neutrophil, PLR, NLR levels were found to be low ($P<0.05$). TT, NT and DD levels are given in Figure 1 according to death and healing status, mechanical ventilation / spontaneous breathing and chronic disease status. Correlations between CBC and Thiol parameters are shown in Tables 2, 3 and 4.

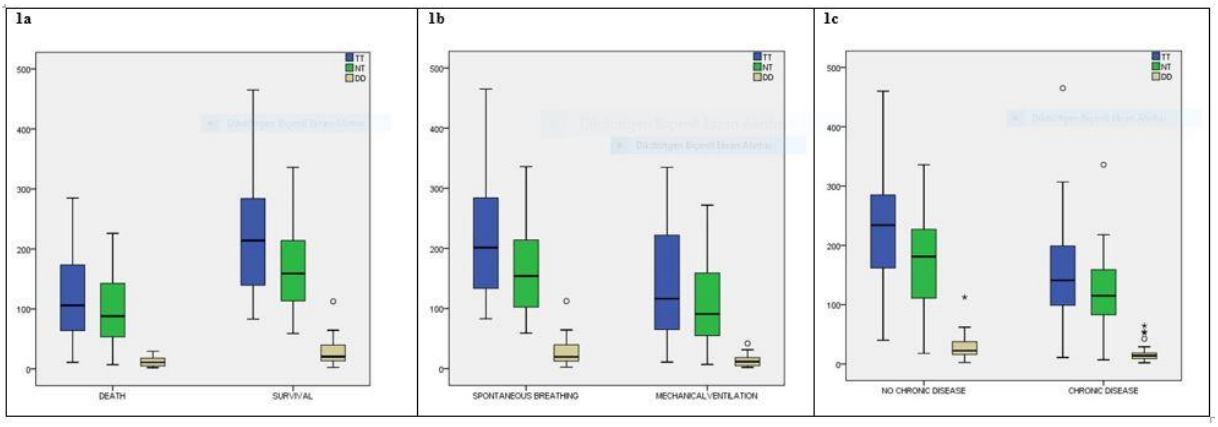

Figure 1. TT, NT, DD levels in PCR positive results 1a: survival status 1b: intubation status 1c: chronical disease status

Table 2. The relationship between thiol and cbc parameters in inpatient group

	Total Thiol	Native Thiol	Dynamic Disulfide	Dynamic Disulfide /NativeThiol (%)	Dynamic Disulfide /Total Thiol (%)	Native/Total Thiol (%)
WBC	-.131	-.088	-.074	-.052	-.052	.052
Hemoglobin	.522**	.576**	.337	-.064	-.064	.064
Hematocrit	.519**	.574**	.319	-.045	-.045	.045
Lymphocyte	.459**	.509**	.323	.024	.024	-.024
Neutrophil	-.326	-.307	-.236	-.096	-.096	.096
Platelet	.109	.073	.089	.062	.062	-.062
NLR	-.413*	-.440*	-.287	-.052	-.052	.052
PLR	-.566**	-.645**	-.347	.096	.096	-.096

Correlations are significant at the 0.05 and 0.01** levels*

Table 3. The relationship between thiol and cbc parameters in intensive care unit patients

	Total Thiol	Native Thiol	Dynamic Disulfide	Dynamic Disulfide /NativeThiol (%)	Dynamic Disulfide /Total Thiol (%)	Native/Total Thiol (%)
WBC	-.360*	-.347*	-.220	.243	.243	-.243
Hemoglobin	.193	.128	.165	.076	.076	-.076
Hematocrit	.141	.081	.095	.051	.051	-.051
Lymphocyte	.043	-.142	.265	.554**	.554**	-.554**
Neutrophil	-.272	-.217	-.176	.129	.129	-.129
Platelet	-.257	-.334*	-.131	.204	.204	-.204
NLR	-.120	.053	-.233	-.295	-.295	.295
PLR	-.117	-.008	-.227	-.277	-.277	.277

Correlations are significant at the 0.05 and 0.01** levels*

Table 4. The relationship between thiol and cbc parameters in the control group

	Total Thiol	Native Thiol	Dynamic Disulfide	Dynamic Disulfide /NativeThiol (%)	Dynamic Disulfide /Total Thiol (%)	Native/Total Thiol (%)
WBC	-.120	-.144	-.053	.100	.100	-.100
Hemoglobin	.483**	.481**	.141	-.424*	-.424*	.424*
Hematocrit	.514**	.510**	.152	-.440*	-.440*	.440*
Lymphocyte	-.155	-.180	-.133	.065	.065	-.065
Neutrophil	.008	-.002	.043	.039	.039	-.039
Platelet	-.379*	-.408*	-.103	.241	.241	-.241
NLR	.140	.151	.130	-.033	-.033	.033
PLR	-.226	-.230	-.003	.174	.174	-.174

Correlations are significant at the 0.05 and 0.01** levels*

In addition, we evaluated the relationship between the parameters, intensive care treatment requirement (prognosis) of the patients with ROC analysis. The parameters determining the need for intensive care of patients according to the increase and decrease in serum level are shown in Figure 2.

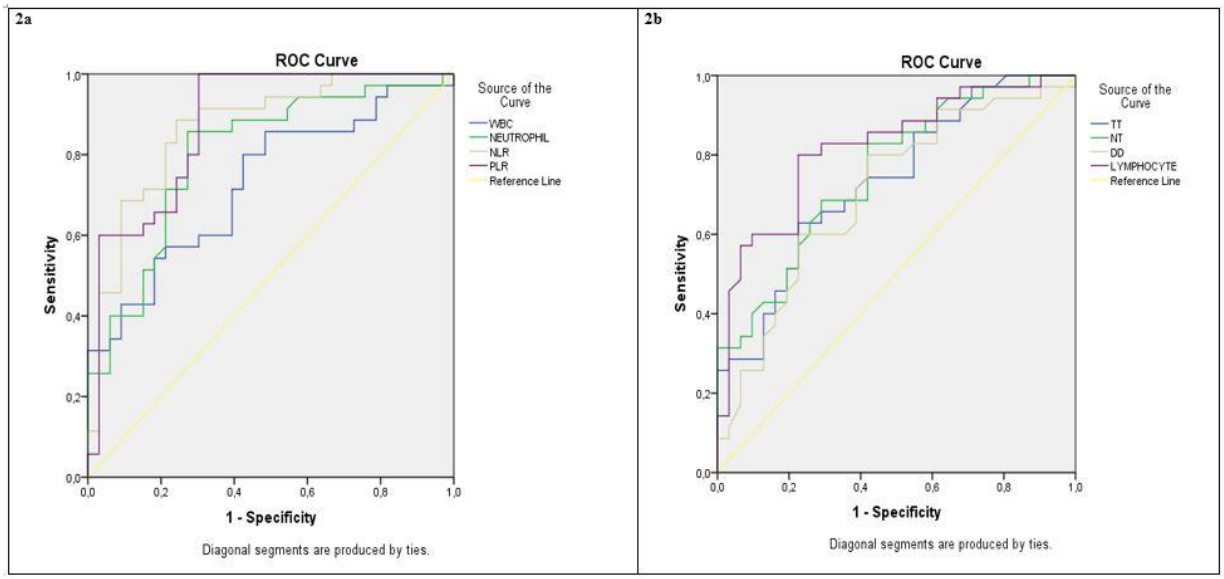

Figure 2. The signifcant relationships between the instensive care unit needed and prognosis 2a: WBC, nötrofil, NLR, PLR increased 2b: lenfosit, total tiol, native thiol, dinamic disulphite decreased

The cut-off values, area under the curve (AUC), likelihood ratio (LR), Confidence Interval (95%), sensitivity and specificity values of these parameters, which are thought to be used in terms of prognosis, are given in Table 5.

Table 5. Serum levels significant parameters for transfer to intensive care

	AUC (%95 CI)			p	Cut Off Value	Sensitivite	Spesifitite
	LB	Area	UB				
WBC *	.609	.728	.848	.001	6.92	.571	0.788
Neutrophil *	.695	.802	.908	.000	4.80	.714	0.788
NLR*	.779	.867	.954	.000	4.26	.829	0.788
PLR*	.793	.877	.961	.000	153.5	.800	0.727
Lymphocyte**	.718	.820	.922	.000	1.08	.800	0.774
Total Thiol **	.616	.735	.854	.001	167.5	.657	0.710
NativeThiol **	.642	.757	.871	.000	135.5	.686	0.710
Dynamic Disulfide**	.579	.706	.832	.004	14.25	.600	0.774

***significant increased, **significant decreased, AUC: Area under the curve, LR: likelihood ratio, %95 CI: %95 Confidence Interval, LB: Lower Bound UB: Upper Bound*

DISCUSSION

The balance of oxidant-antioxidant systems is important during the course of viral infections, both in the antimicrobial and the proinflammatory process. As a new indicator of oxidative stress, Thiol-disulfide balance has been studied in many different diseases. It provides valuable information about the processes that have important roles in maintaining the oxidant-antioxidant balance (11, 13, 15). The major thiols found in plasma are protein thiols and low molecular weight thiols including cysteine, cysteinylglycine, glutathione, homocysteine and γ-glutamylcysteine. Thiol groups are oxidized by disulfide bonds, which are reversibly oxidized by ROS. This mechanism mediates its antioxidant effects (16).

In this study we examined the relationship of thiol-disulfide balance with CBC parameters and its effect on the clinical course of COVID-19 patients. We found that TT, NT, DD, hemoglobin and hematocrit levels were lower in both inpatient and ICU COVID-19 patients compared to the control group. ICU patients showed lower TT, NT, DD and lymphocyte levels and higher WBC, neutrophils and NLR compared with inpatients. We also found that high TT, NT, DD and lymphocyte levels and low WBC, Neutrophil, PLR, NLR levels were significantly associated with reduced mortality and intubation requirement of the patients. Patients who did not have any underlying chronic diseases showed higher TT, NT, DD, lymphocyte, hemoglobin and hematocrit levels but lower WBC, Neutrophil, PLR and NLR levels compared to patients having underlying chronic diseases.

According to studies examining oxidant/antioxidant balance in infection and sepsis, oxidant parameters increased, and antioxidants

decreased, especially in ICU patients (17). It was also reported that the increased oxidant markers such as malondialdehyde in sepsis was related with the degree and mortality of sepsis (18). Esen et al.(19) reported that during infection, oxidant/antioxidant balance was shifted to the oxidant side, thus total thiol level, paroxonase and total antioxidant status decreased, total oxidant capacity and oxidative stress index increased. It also has been shown that antioxidant treatments had positive effects on the prognosis of infection and sepsis (20, 21). Consistent with these finding, our results showed that the thiol/disulfide balance was significantly disturbed in patients with COVID-19 infection.

Ayar et al. (22) found lower NT, TT, DD levels and higher ratio of DD/NT and DD/TT in pediatric-age group of sepsis patients compared to the control group. They stated that these parameters could be used as oxidative stress biomarkers. The researchers also reported that there was no significant difference between the thiol-disulfide balance and survival of the patients. The changes in TT, NT and DD levels in our patients with COVID-19 infection were consistent with their findings in pediatric sepsis patients. However, the higher TT, NT, DD levels were related with survival of patients and clinical course of COVID-19 infection in our study. Aydogan et al. (23) have reported that lower NT, TT, NT / TT ratio and higher DD / TT ratio could be used in early diagnosis of neonatal sepsis. Although TT and NT levels obtained in our study were consistent with their findings, DD levels were low in our patients. This contradiction may result from the differences in patient's age groups. It also might be related with ethio-pathogenesis of diseases.

Kara et al. (24) have compared the thiol / disulfide balance in bacterial and viral infections in their study. Their results showed that NT, TT, NT / TT ratios were lower in both infections compared to the control group, and DD / NT ratios were higher. They also stated that DD levels were lower in bacterial infections than viral infections. Additionally, they found that the WBC count were negatively correlated with NT, TT levels. In our study, we found that TT and NT levels were positively correlated with lymphocyte levels and negatively correlated with NLR and PLR in COVID-19 patients treated at the medical floor. We also found that NT and TT levels were negatively correlated with WBC in ICU patients.

Liu et al. (25) have demonstrated that viral proteins attack the beta chain of hemoglobin, allowing the heme part to decompose into iron and porphyrin in COVID-19 infection. Therefore both the amount and the oxygen carrying capacity of hemoglobin are reduced in COVID-19 patients. Free iron released in this process can also cause oxidative damage by Fenton reactions. Both increased free iron and increased oxidative status also affect T lymphocytes (26, 27). In the experimental studies protein and lipid oxidation were demostrated in erythrocytes due to ROS and membrane damage was observed in erythrocytes by electron microscopy. Similarly, cytotoxic and genotoxic effects have been observed in lymphocytes as a result of oxidative DNA damage (28, 29). It is known that erythrocyte membrane damage due to ROS increases in disease states and this results in a decrease in hemoglobin levels by increasing intravascular hemolysis (30). In our study, we found that TT and NT levels were significantly correlated with lymphocyte, hemoglobin, hematocrit levels in inpatient group, and hemoglobin and hematocrit levels in the control group. These findings suggest that the decrease in hemoglobin and lymphocyte levels in our patients may be due to the increased oxidative stress in COVID-19 infection.

In our study, we demonstrated low levels of TT, NT, DD, lymphocytes, and high levels of WBC, Neutrophils, PLR, and NLR in both patients who died or intubated due to Covid 19 infection. By evaluating ROC analysis, we found that TT, NT, DD levels and CBC parameters showed high sensitivity and specificity for determining requirement of patients to intensive care treatment. It has been reported that the NLR is an independent risk factor of in-hospital mortality for COVID-19 patients. Each unit increase in NLR increases the mortality risk by 8% (31, 32). There are several studies showing conflicting results about association of CBC parameters and NLR with Covid 19 infection (33-35) in the literature. Some of them are consistent with our results and some of them are not. For the first time, we reported optimal cut off values of TT, NT, DD levels and CBC parameters such as WBC, neutrophil counts, NLR, PLR for predicting requirement of patients to intensive care treatment. We also found that high TT, NT, DD and lymphocyte levels and low WBC, Neutrophil, PLR, NLR levels were significantly associated with reduced mortality and intubation requirement of the patients. Therefore, we think that the results of our study will contribute significantly to the literature on these subjects and will provide preliminary data for further research.

As conclusion, the results of this study clearly showed that the thiol-disulfide balance is disturbed in COVID-19 disease for the first time in the literature. Monitoring the thiol-disulfide balance may be beneficial in the follow-up of the patients. The main limitation of this study is its relatively small sample size and further studies with larger sample sizes are needed.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Ethics committee approval was obtained from XX University Faculty of Medicine Clinical Research Ethics Committee for the study with the decision dated 27/05/2020 and numbered 110.

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RESEARCH ARTICLE

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Effects of the COVID-19 Pandemic on Smoking

ABSTRACT

Objective: The aim of this study is to examine the changes in characteristics of smoking habits during the pandemic period.

Methods: This study was conducted on the patients who admitted to Düzce University Medical Faculty Smoking Cessation Outpatient Clinic between June 2020 and January 2021 and a control group with similar age, gender, and educational background characteristics.

Results: The study group with 165 patients who quit smoking during the pandemic period and the control group with 163 patients were included in the study. It was detected that patients who quit smoking during the pandemic period had attempted to quit smoking significantly less compared to those who continue smoking ($p < 0.04$). The fagerström cigarette addiction scale scores of the patients who quit smoking during the pandemic period were found to be significantly lower than the patients who continued to smoke ($p < 0.001$). A significant difference was found between patients who quit smoking during the pandemic period and patients who continued to smoke, in terms of psychological resilience scale total score and all subgroups ($p < 0.001$).

Conclusions: The results of our study show that the rate of efforts to quit smoking increased during the pandemic period, because smokers were affected by the negative relationship between COVID-19 and smoking, and more cessation behavior. We suggest that every patient who admitted to health institutions should be questioned in terms of smoking behavior and the psychological resilience of the patients should be evaluated.

Keywords: Smoking, Smoking Cessation, COVID-19, Psychological Resilience.

COVID-19 Pandemisinin Sigara Kullanımı Üzerindeki Etkileri

ÖZET

Amaç: Bu çalışmanın amacı, pandemi döneminde sigara içme alışkanlıklarının özelliklerinde meydana gelen değişiklikleri incelemektir.

Gereç ve Yöntem: Bu çalışma Düzce Üniversitesi Tıp Fakültesi Sigara Bırakma Polikliniğine Haziran 2020-Ocak 2021 tarihleri arasında sigara bırakmak için başvuran hastalar ile benzer yaş, cinsiyet ve eğitim özelliklerine sahip kontrol grubu hastalar üzerinde yapılmıştır.

Bulgular: Pandemi döneminde sigarayı bırakan 165 hastadan oluşan çalışma grubu ve 163 hastadan oluşan kontrol grubu çalışmaya dahil edildi. Pandemi döneminde sigarayı bırakan hastaların sigarayı bırakmaya devam edenlere göre anlamlı düzeyde daha az denediği saptandı ($p<0.04$). Pandemi döneminde sigarayı bırakan hastaların fagerström sigara bağımlılığı ölçeği puanları, sigara içmeye devam eden hastalara göre anlamlı derecede düşük bulundu ($p<0,001$). Pandemi döneminde sigarayı bırakan ve içmeye devam eden hastalar arasında psikolojik dayanıklılık ölçeği toplam puanı ve tüm alt gruplar açısından anlamlı fark bulundu ($p<0,001$).

Sonuç: Çalışmamızın sonuçları, sigara içenlerin COVID-19 ile sigara arasındaki olumsuz ilişkiden ve daha fazla bırakma davranışından etkilenmesi nedeniyle pandemi döneminde sigarayı bırakma çabalarının arttığını göstermektedir. Sağlık kuruluşlarına başvuran her hastanın sigara içme davranışı açısından sorgulanmasını ve hastaların psikolojik dayanıklılıklarının değerlendirilmesini öneriyoruz.

Anahtar Kelimeler: Sigara, Sigara Bırakma, COVID-19, Psikolojik Dayanıklılık.

INTRODUCTION

The whole world has been struggling with the Covid-19 pandemic for about a year. Many factors that can affect the course of this disease, which has high biological, psychological and sociological consequences in the society, have been investigated, since the last year. The relationship between smoking and COVID-19 has also been one of the most discussed topics. As patient data results are shared, it has been stated that smoking has a significant worsening effect in terms of the severity of the course of the COVID-19 disease (1). It has been noticed that the negative interaction between smoking and COVID-19 creates a desire to quit smoking in many users (2). On the other hand, it is also noteworthy that an unexpectedly low smoking prevalence has been observed in COVID-19 patients (3,4). However, it was emphasized that these results were not proven and may lead to speculative information. Current epidemiological findings indicate that active smoking is associated with increased disease severity and mortality in hospitalized COVID-19 patients (5). The results of the studies conducted on this subject have been followed and discussed by many people who are smokes or non-smokers, and it is emphasized that the information shared in both scientific literature and other communication networks can affect the attempts of quitting smoking (6).

Although the information about the relationship between COVID-19 and smoking is controversial, smoking is generally accepted harmful to health. Although it is known to be harmful, it is a point to be emphasized to continue smoking. It has been reported that continuing to smoke despite all its harmful effects has also been related to the psychological weakness of the person (7). Behavioral interventions that increase the psychological resilience of smokers who have problems in this regard are recommended (8).

Our aim in the study is to investigate the effect of the COVID-19 pandemic on smoking cessation and to compare the psychological resilience of patients who quit smoking during the pandemic and those who do not intend to quit smoking.

MATERIAL AND METHODS

Study Procedures: In this study, power analysis was performed to determine the number of individuals to be included in the patient and control groups. According to the results of the power analysis, it was aimed to reach data of at least 163 patients who quit smoking during the pandemic period and at least 160 patients with similar age, gender, education status and who were smokers as the control group. The data were collected between June 2020 and January 2021.

Data Collection Tools: Demographic information form, fagerstrom nicotine dependence test and psychological endurance scale were applied to all participants.

Demographic Information Form: Age at starting smoking, previous attempts of quitting smoking, and whether the pandemic affected the decision to quit smoking were questioned as well as sociodemographic data of the patients. A pilot form of the information form was applied to 10 patients who decided to quit smoking after the pandemic and 10 control patients who are still smoking and the information form was finalized after the questions that were not understood in the pilot application were reviewed.

Fagerström's Nicotine Dependence Test: FBNT consists of six questions and each question is scored separately. According to the total score obtained from the test, nicotine dpenedfence is classified under three groups including low (0-3 points), medium (4-6 points), and high (7 points) (9). The Turkish adaptation of FBNT was made by Uysal et al (10).

Psychological Hardiness Scale (PHS): Psychological Hardiness Scale consists of 21 items under three sub-dimensions and scored on a 5-point Likert type scale ranging from "Strongly disagree" and "Strongly agree". Turkish validity and reliability study of the scale was conducted by Işık (11). The scale involves individuals expressing their own perceptions. The commitment sub-dimension consists of 1, 2, 3, 5, 6, 18 and 21st items, including expressions such as “I enjoy working very much” and “I think there are interesting and worthwhile things in my life”. The control sub-dimension consists of 4, 10, 11, 12, 15, 19 and 20th items, including expressions such as "I anticipate the problems that may arise and take precautions" and "I generally react strongly to the limitation of my personal freedoms". The challenge sub-dimension consists of 7, 8, 9, 13, 14, 16 and 17th items, including expressions such as “I think every new experience will enrich my life” and “Someone learns and develops from mistakes”. The second and 15th items are scored reversely. The higher scores obtained from the sub-dimensions and the overall scale indicate a high level of psychological hardiness.

RESULTS

In this study, 165 patients who quit smoking during the pandemic period and 163 controls who continued smoking were included in the study. The two groups were similar in terms of gender, age, presence of chronic disease, and educational status. Socio-demographic data and chronic disease status of both groups are given in Table 1.

Table 1. Sociodemographic characteristics of patients who quit smoking and continued smoking during the pandemic period

	Quitted (n=165)	Smoking (n=163)	***P Value***
Age	38.82±13.20	40.81±11.32	0.143
Gender			
Male	94 (57.0)	94 (57.7)	0.898
Female	71 (43.0)	69 (42.3)	
Education			
Primary	51 (30.9)	47 (28.8)	
High school	55 (33.3)	56 (34.4)	0.919
University	59 (35.8)	60 (36.8)	
Marital status			
Maried	91 (55.2)	100 (61.3)	
Single	60 (36.4)	57 (35.0)	0.158
Widow	14 (8.5)	6 (3.7)	
Occupation			
Housewife	18 (10.9)	16 (9.8)	
Officer	29 (17.6)	40 (24.5)	
Worker	38 (23.0)	40 (24.5)	
Self-employed	32 (19.4)	36 (22.1)	0.157
Retired	19 (11.5)	10 (6.1)	
Student	21 (12.7)	10 (6.1)	
Unemployed	8 (4.8)	11 (6.7)	
Chronic disease	47 (28.5)	42 (25.8)	0.580
Chronic disease (n=47 vs n=42)			
At least 1	40 (85.1)	33 (78.6)	0.423
More than 1	7 (14.9)	9 (21.4)	

When the groups were evaluated according to the smoking cessation experiences before the pandemic; it was found that the patients who quit smoking during the pandemic period had attempted to quit smoking significantly less times compared to the control group ($p < 0.04$). It was found that the patients who quit smoking during the pandemic period started smoking at a significantly earlier age compared to the control group ($p < 0.016$, Table 2).

Table 2. Comparison of the starting age and quitting experiences of patients who quitted smoking and who continued to smoke during the pandemic period

	Quitted (n=165)	Smoking (n=163)	***P Value***
Smokers in the family	115 (69.7)	92 (56.4)	**0.013**
Previous attempts of quitting	91 (55.2)	108 (66.3)	**0.040**
Number of attempts of quitting			
1	28 (30.8)[a]	55 (50.9)[b]	**0.015**
2	34 (37.4)[a]	25 (23.1)[b]	
3	12 (13.2)[a]	7 (6.5)[a]	
4+	17 (18.7)[a]	21 (19.4)[a]	
Age of beginning smoking	16.79±4.41	17.85±3.48	**0.016**

Of the patients who continued smoking during the pandemic period 65.6% (n = 107) stated that they knew that being unmasked for a longer time to smoke increases the risk of COVID-19 transmission and 70.6% (n = 115) of them stated that they knew that smoking impairs the immune system. Again, 17.2% (n = 28) of the patients who continued smoking after the pandemic stated that they reduced smoking because they were affected by the pandemic and smoking-related bad news, 8.6% (n = 14) stated that they reduced smoking because they join social environments less, while 10.4% (n = 17) stated that they increased smoking after the pandemic and 63.8% (n = 104) stated that there was no change in their smoking status.

Table 3. Comparison of the smoking behaviors of patients who quit smoking and who continue to smoke during the pandemic period.

	Quitted (n=165)	Smoking (n=163)	***P Value***
I know that being unmasked for a longer time to smoke increases the risk of COVID-19 transmission	121 (73.3)	107 (65.6)	0.130
I know that smoking impairs the immune system	142 (86.1)	115 (70.6)	**0.001**
I know that smokers have COVID-19 more severely	138 (83.6)	114 (69.9)	**0.003**
The pandemic affected my decision of quitting	122 (73.9)	-	-
Change of smoking habits for who continue to smoke			
No change at all	-	104 (63.8)	-
I tried to reduce		28 (17.2)	
It increased		17 (10.4)	
I was smoking more in social environments it reduced		14 (8.6)	

The fagerström nicotine dependence scale scores of the patients who quit smoking during the pandemic period were found to be significantly lower compared to the patients who continued to smoke ($p < 0.001$). A significant difference was found between the patients who quit smoking during the pandemic period and those who continue to smoke, in terms of the total score and all sub-dimensions of the psychological hardiness scale ($p < 0.001$, Table 4).

Table 4. Fagenström scores and Psychological Hardiness Scale scores of patients who quit smoking and continue to smoke during the pandemic period

	Quitted (n=165)	Smoking (n=163)	***P Value***
Fagenström	5.23±1.86	6.80±1.18	**<0.001**
Commitment	18.09±4.77	14.33±4.64	**<0.001**
Control	20.27±3.06	10.89±3.95	**<0.001**
Challenging	16.70±7.36	20.37±6.01	**<0.001**
Total	55.06±10.08	45.58±10.02	**<0.001**

DISCUSSION

The results of the study show that significantly more number of individuals who had never attempted to quit smoking before the pandemic, decided to quit smoking during the pandemic. Similarly, studies show that more number of smokers started thinking about quitting after the pandemic (12, 13). In addition, in our study, it was determined that some of the patients who continued to smoke after the pandemic reduced cigarette consumption both because they were affected by the limitation of social life and the negative relationship between smoking and COVID-19. These results suggest that the pandemic period can be considered as an opportunity to reduce smoking. It has been emphasized that smoking has reduced due to indirect reasons during the pandemic, and people should be encouraged for quitting smoking (14). However, a small number of patients who go on smoking stated that they have increased their smoking during this period. This increase was suggested to be due to the boredom and stress experienced in quarantine. One of the most frequently associated factors with smoking is psychological stress (15, 16). This risk factor, which was also detected in our study, with the addition of feelings of uncertainty and helplessness during the pandemic that has been going on for about a year, may cause smokers to increase the amount of cigarettes they consume or may cause those who quit to start again (17). It is recommended that patients be supported by methods of coping with stress, in order to prevent an increase in smoking such a risky period (18).

In our study, more number of patients who quit smoking during the pandemic period stated that they knew that smoking significantly impaired their immune system compared to the patients who continued smoking. Similarly, we observed that, those who quit smoking during the pandemic period were more knowledgeable about the relationship between smoking and severity of COVID-19 disease. In the study, both groups were asked from where they obtained information regarding the relationship between smoking and COVID-19.

Most of them stated that they obtained this information mostly through social media and public service announcements. We suggest that the power of social media and information spots should be facilitated efficiently to quit smoking in the pandemic. In our study, it was found that some of the participants did not know that the risk of infection increased with removing the mask while smoking. We think that this information should be reminded to through public service announcements. It has been stated that avoiding the increased risk of contamination in smoking environments is a motivating factor for quitting smoking (19).

However, in our study, it was observed that patients who smoke in the pandemic continued to smoke despite knowing that smoking worsens the COVID-19 disease. Similarly, the majority of these patients also knew that smoking impaired the immune system. However, the continuation of smoking despite knowing this negative interaction between smoking and COVID-19 is noteworthy. In our study, it was observed that self-control sub-dimension scores of the patients who continued smoking were significantly lower compared to the patients who quit smoking during the pandemic. Smoking addiction is a common characteristic of individuals who have self-control issues. It is known that people who can get rid of addiction are more successful in controlling their behavior. People with a high level of self-control believe that they can manage a stressful situation rather than being collapsed against it (20).

It was observed that the challenge sub-dimension scores of the patients who continued smoking during the pandemic period were higher compared to the patients who quit smoking during the pandemic. Continuing smoking despite the pandemic can be associated with this risk-taking behavior. It has also been stated that smoking habit is associated with risk taking behavior. It is emphasized that smoking cessation strategies that focus on risky health behaviors should be developed (21). In addition, it is shown that, the perception that cigarette consumption poses low risk in terms of harmful effects leads to a weak intention to quit smoking (22). All these results may explain why individuals still continued smoking despite knowing the harmful effects during the pandemic. We suggest that evaluating the psychological hardiness and risk-taking behaviors can help patients to quit smoking during the pandemic, since it is a period of anxiety and uncertainty.

The fagerström addiction levels of the patients who continued to smoke during the pandemic period were found to be significantly higher compared to the patients who quit smoking. In addition, it was observed that the psychological hardiness of patients with high addiction levels was lower. It has been reported that people who cannot cope with stressful situations tend to engage in addictive behaviors such as smoking (23). In another study, a negative and significant relationship was found between nicotine addiction and psychological hardiness (24). These findings support the results of our study. Fagerström scale scores have been used to determine the addiction level and treatment options, in many smoking cessation centers. We suggest that the psychological dependence level of the patients should be evaluated as well as the Fagerström scale scores, in the planning of smoking cessation. Thus, behavioral therapy can be useful in smoking cessation.

In our study, we found that approximately half of the smokers tried to reduce it, even if they continued smoking. This suggests that this group can be motivated to quit smoking, easily. Besides all other negative effects, the pandemic can be an opportunity to quit smoking. Cross-sectional studies show that smokers have increased willingness and motivation to quit smoking during the pandemic (13). Since it has been proven that smoking worsens lung symptoms and prognosis in COVID-19, public health messages should focus on smoking cessation during epidemic.

Limitations and Strengths

The results of our study will provide effective discussion in the literature in terms of power analysis and the correct method with similar demographic characteristics of the compared groups. Strength of the study is that it is the first study investigating the relationship between smoking and psychological hardiness during the pandemic process. However, the study has some limitations. The fact that our study evaluated only quantitative data and that there were no qualitative data that can be used to express the difficulties caused by cigarette addiction during the pandemic are limitations of the study. In addition, the lack of long-term results of patients who quit smoking is another limitation of the study.

Conclusion

The results of the study show that smokers are affected by the negative relationship between COVID-19 and smoking and attempted to quit smoking, more frequently during the pandemic period. Motivating patients to quit smoking during pandemic may be easier than in other periods. However, it has been observed that the psychological hardiness of patients who continue smoking during the pandemic is lower. Counseling services can be provided to patients who have behavior control problems, so that they can cope with depression in stress situations. Smoking behavior of every patient who admits to the health institution during the pandemic period should be questioned and evaluated in terms of increased respiratory system risk. In addition, given the stress caused by the pandemic in society and individuals, increased psychological vulnerability should be evaluated.

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RESEARCH ARTICLE

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The Risk Factors Affecting Length of Stay and Mortality in Covid 19 Patients: Laboratory Parameters, Comorbidities, and Demographic Characteristics

ABSTRACT

Objective: Covid 19 can cause fatal pneumonia and serious complications. In the course of the disease the levels of different biochemical parameters increased and these parameters provide important information about the prognosis of the disease. The aim of this study was to investigate the relationship between biochemical parameters and length of stay and mortality in Covid 19 patients.

Methods: In this retrospective study, a total of 767 Covid 19 patients hospitalized in our hospital were included. The demographic characteristics, length of stay, comorbid diseases and biochemical parameters of the patients were scanned from the hospital's database and patient files and recorded. Patients were grouped according to the length of stay; 1st Group: 7 days and less, 2ndGroup: 8-10 days, 3rdGroup: 11-13 days, and 4thGroup: 14 days and more.

Results: The mean CRP level was significantly higher in group 4 compared to group 1 ($p = 0.002$). The mean levels of LDH, PRO_BNP, and procalcitonin were significantly higher in group 4 compared to group 1 and group 2 ($p <0.001$, $p = 0.026$, $p = 0.007$, respectively). The mean level of fibrinogen was significantly higher in group 4 compared to group 2 ($p = 0.011$). Presence of DM and HT as comorbidities ($p = 0.022$, $p = 0.006$) and high levels of LDH and ferritin ($p <0.001$, $p = 0.041$) significantly increased the risk of death.

Conclusions: The results of our study show that positive correlation between the levels of CRP, LDH, PCT, PROBNP, and fibrinogen the prolongation of hospitalization in Covid 19 patients and these parameters can be associated with the severity disease. These results show that increased levels of LDH and ferritin, age, prolongation of hospitalization, and the presence of HT and DM increase mortality rate and can be specific parameters in terms of prognosis.

Keywords: Covid 19, Laboratory Tests, Mortality, Comorbidity Diseases, CRP, LDH.

Covid 19 Hastalarında Kalış Süresini ve Mortaliteyi Etkileyen Risk Faktörleri: Laboratuvar Parametreleri, Komorbiditeler ve Demografik Özellikler

ÖZET

Amaç: Covid 19, ölümcül pnömoniye ve ciddi komplikasyonlara neden olabilen güncel pandemik hastalıktır. Hastalığın farklı evrelerinde farklı biyokimyasal parametrelerin düzeyinde artış görülmekte ve bu parametreler hastalığın seyri konusunda önemli bilgiler vermektedir. Bu çalışmada, Covid 19 hastalarındaki yatış süresi ve mortalite oranı ile biyokimyasal parametreler arasındaki ilişkinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya, hastanemizde yatan toplam767 Covid 19 hastası dahil edildi. Hastanenin veri tabanı ve hasta dosyaları incelenerek hastaların demografik özellikleri, yatış süreleri, ek hastalıları ve biyokimyasal parametreler taranarak kaydedildi. Hastalar yatış gününe göre, 1. Grup: 7 gün ve altı, 2. Grup: 8-10 gün arası 3. Grup: 11-13 gün arası, 4. Grup: 14 gün ve üzeri olmak üzere toplam 4 gruba ayrıldı. Hastaların demografik özellikleri, laboratuvar bulguları, ek hastalıkları ve mortalite oranları bu gruplara göre düzenlenerek istatiksel analiz yapıldı.

Bulgular: Hastaların 459 (60%)'u erkek 308 (40%)'i kadındı. Grup 4 hastalarındaki CRP düzeyi, grup 1'deki hastalara göre istatiksel anlamlı olarak yüksekti ($p=0.002$). Grup 4 hastalarındaki LDH, PRO_BNP ve prokalsitonin düzeyi hem grup 1 hemde grup 2'ye göre istatiksel anlamlı olarak yüksekti (sırasıyla $p<0.001$, $p=0.026$, $p=0.007$). Fibrinojen düzeyi, grup 4 deki hastalarda grup 2'deki hastalara göre anlamlı olarak yüksekti ($p=0.011$). DM, HT, LDH ve ferritin düzeyi yüksekliği ölüm riskinin anlamlı olarak artırmıştı (sırasıyla $p=0.022$, $p=0.006$,$p<0.001$, $p=0.041$). Benzer olarak yaş ve yatış gününün uzaması ölüm riskini anlamlı olarak artırmıştı ($p<0.001$).

Sonuç: Çalışmamızın sonuçları, Covid 19 hastalarının yatış süresinin uzamasıyla CRP, LDH, PCT, PROBNP ve fibrinojen düzeyinin doğru orantılı olarak arttığını ve hastalığın şiddetliye ilişkili olabileceğini göstermektedir. Yine bu sonuçlar, LDH ve ferritin düzeyinin, yaş, yatış gününün uzaması, HT, DM gibi ek hastalıkların varlığının mortalite oranını artırdığını ve prognoz açısından daha spesifik parametreler olduğunu göstermektedir.

Anahtar Kelimeler: Covid 19, Laboratuvar Testleri, Mortalite, Ek Hastalıklar, CRP, LDH.

INTRODUCTION

The new type of corona virus 19 (Covid 19) is the pandemic disease that can cause severe pneumonia characterized by acute respiratory distress syndrome (ARDS) and goes on affecting the whole world (1). Severity of Covid 19 is mild or moderate in 80% of the patients. However, 20% of the patients needs to be hospitalized due to the increasing oxygen demand and 5% of them are hospitalized in the intensive care units (ICU) due to severe pneumonia(1).

Various laboratory tests including hematological, biochemical and immunological parameters provide important clinical data in the diagnosis, treatment, prognosis and monitoring of Covid 19 disease (2,3). In addition, these tests are very important parameters in differentiating the severity of the disease and predicting the mortality risk (4).The anti-inflammatory parameters including interleukins, serum reactive protein (CRP), lactatedehydrogenase (LDH), ferritin, procalcitonin (PCT), and D dimer are the most important ones among these tests(2). In several studies, it has been shown that especially an increased level of CRP is directly proportional to the severity of the disease and is a good diagnostic marker that can detect severe Covid 19 disease at an early stage(5-7). PCT is a propeptide of calcitonin devoid of hormonal activity. Although the blood PCT levels are within the normal range in mild Covid 19 patients, it can rise up to 5 times higher than the normal level in severe cases(8). D dimer and fibrinogen levels, which are indicators of hypercoagulation, increase significantly more in severe Covid 19 patients compared to other patients. Especially, an increased level of D dimer is associated with the risk of developing ARDS, hospitalization in ICU and mortality rate (2). It has also been shown that ProBNP, which is an indicator of cardiac pathology, increased in severe patients and associated with poor prognosis(9). LDH level has been shown to be an important indicator of respiratory failure as well as liver failure (10). In several studies, it has been shown that ferritin levels increase approximately 5 times more in severe Covid 19 patients compared to patients with a milder course of disease(3).

Age, gender and comorbidities are among the most important parameters that increase the severity and mortality rate of Covid 19 (10). In several studies, it has been shown that the average age of critically ill Covid 19 patients was 63 and the majority of the cases were males (11). The presence of comorbid diseases, including cancer, immune-suppressive diseases, lung and heart diseases, and especially diabetes mellitus (DM) and hypertension (HT) is associated with an increase in the severity and mortality rate of Covid 19 (12).

The aim of this study is to investigate the effects of demographic characteristics, laboratory findings and comorbidity diseases of Covid 19 patients hospitalized in our hospital on mortality and length of stay in hospital.

MATERIAL AND METHODS

Ethical Approval: Ethical approval for the study was obtained from the Clinical Ethics Committee of Inonu University School of Medicine (No:2020/188).

Study Population: This study included 767 Covid 19 patients hospitalized in the wards and intensive care units (ICU)of Malatya Training and Research Hospital, between March 15 and November 15, 2020. Data were scanned retrospectively from the hospital's database and patient files. Patients with active tuberculosis or hepatitis B and C, suspected or proven bacterial infection focus, those with active diverticulitis or gostrointestinal system perforation, and pregnant women were excluded from the study. Demographic characteristics, comorbidities, laboratory parameters including CRP, PCT, ferritin, LDH, D-dimer, fibrinogen, international normalized ratio (INR), and ProBnP, hospital stay and survival status of the patients were recorded.

Study Design: The patients were divided into 4 groups according to length of stay in the hospital; namely Group 1: 7 days and less, Group 2: 8-10 days, Group 3: 11-13 days, Group 4: 14 days and more. The demographic characteristics, laboratory findings, comorbidities and mortality rates of the patients were statistically analyzed according to these groups.

Statistical Analysis: Data were summarized by median (min-max) and numbers (percentage). Conformity to normal distribution was evaluated by using the Kolmogorov-Smirnov test. The Pearson chi-square and Kruskal Wallis tests were used for statistical analysis, where appropriate. Conover test was used in multiple comparisons. Logistic regression analysis was applied to estimate the odds ratio. The data were analyzed by using IBM SPSS Statistics 26.0 program. A value of $p < 0.05$ was considered statistically significant.

RESULTS

459 (60%) of the patients were males and 308 (40%) were females. The CRP levels of the patients in group 4 were significantly higher compared to the patients in group 1 ($p = 0.002$).The mean LDH, PRO_BNP and PCT levels of the patients in group 4 were significantly higher compared to both group 1 and group 2 ($p < 0.001$, $p = 0.026$, $p = 0.007$, respectively). The fibrinogen levels of the patients in group 4 was significantly higher compared to the patients in group 2 ($p = 0.011$). There was no significant difference between the groups in terms of age and D dimer and fibrinogen levels ($p > 0.05$) (Table 1).

Dischargerate was found to be significantly lower in group 4 compared to group 1 and group 2

(p <0.001). The rate of patients with chronic obstructive disease (COPD) was significantly higher in group 4 and group 2 compared to group 1 (p = 0.017). There was no difference between the groups in terms of other comorbid diseases (p> 0.05) (Table 1).

Table 1. Demographic characteristics and laboratory values of the patients according to the length of stay in hospital

		Length of stay in hospital				p-value
		7 days and less	8-10 days	11-13 days	14 days and longer	
		Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	
Age		68 (18-104) [a]	72 (19-101) [a]	68 (19-95) [a]	70 (21-92) [a]	0.064
CRP		6.76 (0.02-49.67) [a]	8.02 (0.02-55.46) [a,b]	8.05(0.02-31.77) [a,b]	10.9 (0.03-37.15) [b]	**0.002**
LDH		358 (146-1386) [a]	372 (127-2889) [a]	385.5 (176-1241) [a,b]	454 (190-1369) [b]	**<0.001**
FERITTIN		421.9 (7.6-1869) [a]	428.1 (1.09-2000) [a]	471.9 (32.14-1987) [a]	433.95 (16.64-1992) [a]	0.938
FIBRINOGEN		491.4 (235.3-1394) [ab]	460.6 (54.1-1477) [a]	487.75 (15.7-902.1) [a,b]	563.3 (53.6-6325) [b]	**0.011**
D-DIMER		0.6 (0.06-40.6) [a]	0.73 (0.04-36.4) [a]	0.68 (0.06-35.5) [a]	0.77 (0.01-31.3) [a]	0.085
INR		1.17 (0.85-10.9) [a]	1.16 (0.88-66.3) [a]	1.16 (0.88-6.59) [a]	1.19 (0.96-11.6) [a]	0.289
PRO_BNP		392.7 (21.82-30342) [a]	466.7(1.23-30470) [ab]	628.05 (10.49-18601) [b,c]	641.7 (9.23-21851)[c]	**0.026**
PROCALCITONIN		0.10 (0.02-24.6) [a]	0.11 (0.02-97.16) [a]	0.14 (0.03-9.02) [ab]	0.17 (0.02-24.51)[b]	**0.007**
		Count (Percent)	**Count (Percent)**	**Count (Percent)**	**Count (Percent)**	
Gender	Male	115 (61.80%) [a]	154 (55.40%) [a]	90 (60.80%) [a]	100 (64.50%) [a]	0.255
	Female	71 (38.20%) [a]	124 (44.60%) [a]	58 (39.20%) [a]	55 (35.50%) [a]	
Prognosis	Discharge	163 (87.60%) [a]	232 (83.50%) [a]	116 (78.40%) [ab]	101 (65.20%) [b]	**<0.0001**
	Dead	23 (12.40%) [a]	46 (16.50%) [a]	32 (21.60%) [ab]	54 (34.80%) [b]	
CRF	No	183 (98.40%) [a]	276 (99.30%) [a]	145 (98.00%) [a]	149 (96.10%) [a]	0.133
	Yes	3 (1.60%) [a]	2 (0.70%) [a]	3 (2.00%) [a]	6 (3.90%) [a]	
Alzheimer	No	182 (97.80%) [a]	276 (99.30%) [a]	147 (99.30%) [a]	153 (98.70%) [a]	0.501
	Yes	4 (2.20%) [a]	2 (0.70%) [a]	1 (0.70%) [a]	2 (1.30%) [a]	
DM	No	174 (93.50%) [a]	257 (92.40%) [a]	139 (93.90%) [a]	144 (92.90%) [a]	0.939
	Yes	12 (6.50%) [a]	21(7.60%) [a]	9 (6.10%) [a]	11 (7.10%) [a]	
COPD	No	152 (81.70%) [a]	196 (70.50%) [b]	104 (70.30%)[a.b]	106 (68.40%) [b]	**0.017**
	Yes	34 (18.30%) [a]	82 (29.50%) [b]	44 (29.70%)[a.b]	49 (31.60%) [b]	
HT	No	178 (95.70%) [a]	267 (96.00%) [a]	1481 (100.00%) [a]	149 (96.10%) [a]	0.101
	Yes	8 (4.30%) [a]	11 (4.00%) [a]	1 (0.00%) [a]	6 (3.90%) [a]	
CHF	No	179 (96.20%) [a]	267 (96.00%) [a]	139 (93.90%) [a]	145 (93.50%) [a]	0.510
	Yes	7 (3.80%) [a]	11 (4.00%) [a]	9 (6.10%) [a]	10 (6.50%) [a]	
CAD	No	181 (97.30%) [a]	272 (97.80%) [a]	139 (93.90%) [a]	153 (98.70%) [a]	0.060
	Yes	5 (2.70%) [a]	6 (2.20%) [a]	9 (6.10%) [a]	2 (1.30%) [a]	
Arrhythmia	No	181 (97.30%) [a]	271 (97.50%) [a]	143 (96.60%) [a]	147 (94.80%) [a]	0.482
	Yes	5 (2.70%) [a]	7 (2.50%) [a]	5 (3.40%) [a]	8 (5.20%) [a]	

a, b,c: Different characters in each row show a statistically significant difference (p <0.05).**CRF:** Chronic renal failure, **DM:** Diabetes mellitus, **COPD:** Chronic obstructive pulmonary disease, **HT:** Hypertension, **CHF:** Chronic heart failure, **CAD:** Coroner artery disease.

The effects of the laboratory findings, comorbid diseases, age and length of stay on mortality are shown in Table 2. DM and HT significantly increased the risk of death (p = 0.022, p = 0.006, respectively). Other comorbid diseases had no effect on mortality (p> 0.05). We found that, only high levels of LDH and ferritin increased the risk of death significantly (p <0.001, p = 0.041, respectively). It was also found that, advanced age and prolonged stay in the hospital significantly increased the risk of death (p <0.001).

Table 2. The effects of the laboratory findings, comorbid diseases, age and length of stay on risk of mortality

Variables	Odds Ratio	95% C.I.for EXP(B)		p-value
		Lower	Upper	
DM	2.454	1.135	5.306	**0.022**
COPD	1.215	0.765	1.931	0.409
HT	4.724	1.545	14.447	**0.006**
CHF	1.664	0.678	4.087	0.267
CAD	2.032	0.710	5.816	0.186
Arrhythmia	2.509	0.901	6.981	0.078
CRP	1.013	0.983	1.044	0.388
LDH	1.003	1.002	1.004	**<0.0001**
Ferritin	1.001	1.000	1.001	**0.041**
DDimer	1.011	0.968	1.057	0.619
INR	0.996	0.850	1.167	0.957
Procalcitonin	1.097	0.993	1.212	0.070
Age	1.055	1.033	1.077	**<0.0001**
Length of stay in hospital	1.077	1.037	1.118	**<0.0001**
Constant	0.003			**<0.0001**

DM: Diabetes mellitus, **COPD:** Chronic obstructive pulmonary disease, **HT:** Hypertension, **CHF:** Chronic heart failure, **CAD:** Coroner artery disease.

DISCUSSION

The clinical prognosis of Covid 19 disease is divided into three different phases, namely, early infection, pulmonary, and anti-inflammatory phases, and each phase has a typical biochemical marker (2).The early infection phase begins with infiltration of the virus in to the lung parenchyma, with symptoms characterized by fever and cough similar to typical upper respiratory tract infection. The most important laboratory finding during this phase is lymphopenia. In the pulmonary phase, lung infection develops in the form of viralpneumonia and increased levels of CRP are prominent as well as lymphopenia and elevation of transaminases. The inflammatory phase is characterized by ARDS caused by systemic inflammation or cytokine storm. During this phase, patients are usually treated in the ICU. During this period, cardiac and kidney damages caused by the complications of Covid 19 are quite common. In addition, increased levels of CRP, PCT, D dimer, LDH, fibrinogen, ferritin, ProBNP, and creatinine are observed at the forefront, during this phase(2).The increased levels of these parameters are directly associated with the severity of the disease, the mortality rate and the length of stay in the hospital(13, 14).

In many studies, there are contradictory reports regarding which parameters are more specific in determining both the severity of the disease and the risk of mortality. For example, in a study examining the biochemical parameters in mild, moderate and severe Covid 19 cases, it was found that CRP and LDH levels increased 3 days after hospitalization in patients with severe disease and the CRP levels decreased dramatically within 6-9 days, and then there was no difference between the patients. In the same study, it was found that LDH levels were still significantly higher within 6-9 days, and LDH was suggested to be a more important indicator of treatment response (15).In other studies, it has been shown that liver enzymes including ALT and AST are elevated in severe patients, but LDH is a more important parameter in detecting disease severity and poor prognosis (14,16). In a study conducted in China, it was found that CRP and PCT levels were higher in patients with severe disease compared to patients with mild and moderate disease. However only the CRP was suggested to be an independent risk factor in detecting the severity of the disease (17,18). In another study, it was suggested that PCT may be a more specific parameter in determining the prognosis (19). In a meta-analysis, it was found that many biochemical parameters increased in patients with severe Covid 19, however, high levels of ferritin as well as interleukins were found to be more important parameters in distinguishing severe and fatal Covid 19 patients (20). Similarly, in our study, we found that CRP, LDH, PROBNP, PCT and fibrinogen levels were statistically significantly higher in group 4 patients compared to group 1 and group 2 patients; prolongation of the length of stay in the hospital was associated with the severity of the disease ($p < 0.05$). LDH and ferritin levels were independent risk factors, increasing the mortality rate ($p < 0.05$ for both). This finding supports studies suggesting that LDH and ferritin levels were more specific parameters. Similar to other studies, in our study, although many parameters increased, only a few of them affected the prognosis. This may be due to the personal characteristics of the patients, the type of comorbidities, and the rate and severity of complications. In addition, the fact that the patients in our sample were divided into groups according to the total length of stay in the hospital, but not according to being hospitalized in the ICU or wards may have affected our findings.

In a meta-analysis, in which more than 1000 Covid 19 patients were included and a total of 61 studies were reviewed, it was found that severe disease was more common and the mortality rate was higher in male patients. In addition, in the same study, it was shown that the severity of the disease and the mortality rate were higher in elderly people and comorbidities such as HT, cardiovascular disease, chronic renal failure, and COPD increase the severity of the disease, the rate of ICU admission, and mortality (21). In a different meta-analysis, it was found that rate of comorbidities was higher in patients with severe disease and HT and DM were the most commonly seen diseases (22). Similarly, in a study conducted on 32583 patients in Mexico, HT and DM were shown to be the most common comorbidities and affected the severity of the disease(10). In our study, the number of male patients was higher than female patients (60%) and the average age of the patients was 69.5. The rate of male patients was highest in group 4 (64.50%). Advanced age and prolongation of stay in the hospital were indicators of disease severity and significantly increased the mortality rate. At least one comorbidity was present in 51.5% of the patients and the most common comorbidity was COPD. The number of individuals with COPD was statistically significantly higher in group 4 compared to group 1 ($p < 0.0001$). In addition, we found that HT was present in 26 patients and DM was present in 53 patients. However, in the risk analysis, it was determined that HT and DM increased the mortality rate statistically significantly. Unlike other studies, in our study, although the number of patients with HT and DM was less, both increased the mortality risk significantly. This finding suggests that HT may be an important risk factor, even though it is seen less frequently, and the increased risk should be considered in the treatment and monitoring of these patients.

CONCLUSIONS

The results of our study show that CRP, LDH, PCT, PROBNP, and fibrinogen levels

increased in direct proportion with the prolongation of hospital stay in Covid 19 patients and these parameters may be associated with the severity of the disease. In addition, these results show that LDH and ferritin levels, age, length of stay in hospital, presence of comorbid diseases including HT and DM increase mortality rate and may be specific parameters in terms of prognosis.

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RESEARCH ARTICLE

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Determining the Side Effects of Covid-19 (Sinovac) Vaccination on Nurses; an Independent Descriptive Study

ABSTRACT

Objective: It is important to protect nurses fighting against the COVID-19 pandemic through vaccination. This study aims to determine the incidence rate of side effects experienced by nurses after their COVID-19 (Sinovac) vaccination and relevant factors.

Methods: This is a descriptive design study. The sample of the study included 355 nurses who received the Sinovac COVID-19 vaccine in Turkey and who agreed to participate in the study. Data were collected using a questionnaire which was written by the researchers and gathered information on the nurses' sociodemographic and professional characteristics, health status, habits, and vaccine complications.

Results: The study included 355 nurses, of which 82.3% were female. Their median age was 35.42±9.67, and their mean BMI was 24.87±4.54. The most common local side effect experienced after the vaccination was pain (54.6%) while the most common systemic effects were fatigue (39.2%) and headache (34.1%). Pain, among local side effects, was significantly higher among male nurses (p= 0.001) and those who worked more than 40 hours a week (p= 0.001). The systemic side effect of fatigue was experienced at a higher rate among nurses who were diagnosed with COVID-19 before their vaccination (p=0.004), those who drank alcohol (p=0.028), and those who worked more than 40 hours a week (p=0.012). The systemic side effect of fever was more common among nurses with chronic conditions (p=0.037).

Conclusions: The most common systemic side effect experienced after the COVID-19 vaccination was reported as fatigue and the most common local side effect was pain. Considering the relevant factors that affected the incidence rates of side effects, it would be suitable to plan the weekly working hours of nurses no longer than 40 hours. It can be recommended to conduct more randomized controlled studies to determine what else weekly working hours affect among nurses.

Keywords: Nurse, COVID-19, Vaccine, Side Effect.

Hemşirelerde Covid-19 Aşısı (Sinovac) Sonrası Görülen Yan Etkilerin Belirlenmesi; Bağımsız Tanımlayıcı Çalışma

ÖZET

Amaç: COVİD 19 pandemisi ile mücadelede hemşirelerin aşı yoluyla bağışıklanarak korunmaları önem arz etmektedir. Çalışmanın amacı, COVİD 19 aşısı (Sinovac) sonrası hemşirelerde yan etki görülme oranları ve ilişkili faktörlerin belirlenmesidir.

Gereç ve Yöntem: Araştırma tanımlayıcı tipte tasarıma sahiptir. Araştırmanın örneklemini Türkiye'de COVİD-19 aşısı yaptıran ve gönüllü olarak çalışmaya katılmayı kabul eden 355 hemşire oluşturmuştur. Veriler, araştırmacılar tarafından oluşturulan ve hemşirelerin sosyo-demografik ve mesleki özellikleri, sağlık durumları, alışkanlıkları ve aşı komplikasyonlarına ilişkin bilgilerini sorgulayan anket formu ile çevirim içi olarak toplanmıştır.

Bulgular: Çalışmaya 355 hemşire katılmıştır. Hemşirelerin %82,3'ü kadındır. Ortanca yaşları 35,42±9,67, BKİ ortalamaları 24,87±4,54'dır. Aşılama sonrası en sık görülen lokal yan etki ağrı (%54,6) ve en sık görülen sistemik etkiler ise yorgunluk (%39,2) ve baş ağrısı (%34,1) olarak bulunmuştur. Lokal yan etkilerden ağrı erkek cinsiyette (p= 0,001) ve haftalık olarak 40 saatin üzerinde çalışan (p= 0,001) hemşirelerde istatiksel olarak anlamlı düzeyde daha yüksek bulunmuştur. Aşılanma öncesi COVİD-19 tanısı alanlarda (p=0,004), alkol kullananlarda (p= 0,028) ve haftalık 40 saatin üzerinde çalışanlarda (p= 0,012), yorgunluk sistemik yan etkisi daha yüksek oranda görülmüştür. Ateş sistemik yan etkisi ise, kronik hastalığı olan hemşirelerde daha çok görülmüştür (p= 0.037).

Sonuç: COVİD 19 aşılaması sonrası en sık görülen sistemik yan etki yorgunluk ve lokal yan etki ise ağrı olarak bildirilmiştir. Yan etkilerin görülme oranlarını etkileyen ilişkili faktörlere bakıldığında hemşirelerin haftalık çalışma saatlerinin 40 saatten fazla olmayacak şekilde planlanması uygun olacaktır. Haftalık çalışma saatlerinin hemşirelerde başka neleri etkiliyor olduğuna dair randomize kontrollü çalışmaların yapılması önerilebilir.

Anahtar Kelimeler: Hemşire, COVİD-19, Aşı, Yan Etki.

INTRODUCTION

The COVID-19 pandemic was firstly reported as a severe acute respiratory syndrome by the World Health Organization (WHO) in January 2020. The strong contagion of the virus caused the disease to spread rapidly among people which quickly turned it into a pandemic (1). According to the WHO reports, there have been 178,202,610 confirmed COVID-19 cases and 3,865,738 deaths as of June 2021 (2). Regarding Turkey, there have been a total of 5,375,593 cases and 49,236 deaths as of June 2021 (3). The need for vaccinations has come into prominence to decrease the mortality and morbidity rates related to infection in the COVID-19 pandemic affecting the world (4). More than 100 vaccines have been developed and gone into use at different phases during the pandemic (5). Pfizer–BioNTech and Sinovac-Coronovac vaccines, which have been authorized for emergency usage, are two of these vaccines which have been used during the pandemic (6). Vaccination of nurses, who are in the riskiest group fighting against the pandemic, is of great importance (3). However, it has been reported that nurses experience hesitations related to the possible side effects of vaccines and that this might negatively affect the vaccination rates (7-9).

The most common local side effect reported in relevant studies is pain while the most common systemic side effects are fever, fatigue, headache, and muscle aches (10, 11). Studies have reported that health professionals have hesitations regarding vaccinations and are more common among female professionals (12). Even though people have different viewpoints regarding different vaccines, nurses are generally willing to be vaccinated against COVID-19 (13).

Nurses are the most numerous group among healthcare professionals (14). Vaccination of nurses for COVID-19 means 1/5 of all healthcare professionals would be vaccinated in Turkey. It is extremely important to increase the vaccination rate in society and to eliminate incorrect information about vaccines with scientific evidence to make people trust in vaccines. Thus, scientifically addressing the complications experienced by nurses after vaccination and relevant factors will enable to obtain valuable results about COVID-19 vaccines. Evaluating the nurses' experiences about the post-vaccination process in Turkey is believed to contribute to the relevant literature. This study aims to determine the incidence rate of side effects experienced by nurses after their COVID-19 (Sinovac) vaccination and relevant factors.

MATERIAL AND METHODS

This was a descriptive design study. The population of the study included nurses who work in Turkey. According to the 2019 data of the Ministry of Health, the number of personnel working in all healthcare institutions at that time was 1,033,767, the number of healthcare professionals was 654,438 and the number of nurses was 198,103 (15). The rate of nurses among healthcare professionals was almost 30% and their rate was 20% among all personnel in the healthcare sector. The number of healthcare personnel was considered as the sample size with a confidence interval of 95% and an error margin of 5%. The sample size was calculated using the Roasoft program and the incidence rate was taken as 198,103 (20%), which was the number of nurses. Thus, the sample size was calculated as 246. This number was increased by 15% in case of absences (16) and the total number was determined as 283. Comparisons were made considering the working units of the participants and correlational significance based on these comparisons was sought. As no specific method was used to determine the sample units, the highest number of mixed participants - that can be reached via online survey regardless of quota distinction - was targeted and 355 people were reached. The online survey method was used in this study as it is advantageous in terms of time and place regarding the participants, is free, and is the safest under pandemic conditions. The informed consent of the participants was obtained with the survey form.

Study questions were determined as follows: Which side effects were experienced by nurses after they were vaccinated for COVID-19? (i) What is the incidence frequency of post-vaccination side effects experienced by vaccinated nurses? (ii).

The inclusion criteria were working as a nurse, accepting to participate in the study by signing the *Informed Voluntary Consent Form* collected beforehand, and getting vaccinated for COVID-19. Those who had immunosuppressive diseases, who had received chemotherapy within one year before the study was conducted, and who had received cortisone therapy were not included in the study.

Data were collected using the data collection form (13, 17, 18) developed by the researchers after a literature review via the online survey method. The form consists of 18 questions about sociodemographic and professional characteristics, health status, habits, medication, and vaccine side effects of the participants.

Dependent variables of the study were age, sex, marital status, weekly working hours, working unit, smoking and alcohol consumption, chronic conditions, regular medication, regular influenza vaccination, daily sleep routine and sleep duration, body mass index, and taking vitamin/nutritional supplements. Independent variables of the study were the state of experienced unwanted side effects after vaccination.

The written permission of the ethics committee of Necmettin Erbakan University Health Sciences Institute (numbered 07.04.2021-9/21) and the Ministry of Health Scientific Research Platform

(Serap Batı-2021-03-26T10 33 36) was obtained for this study. Informed consent of the participants was obtained before the study was conducted. This study was carried out and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (19).

Statistical Analysis: Raw data obtained in the study were registered, processed, and evaluated into the Statistical Package for Social Sciences (SPSS) 22.0 program at the confidence interval of 95% and significance level of $p<0.05$. Percentage, mean, and standard deviation values were used in the analysis of descriptive data. The Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. The Chi-square test was used for the comparison of categorical data. Regarding the comparisons between the two groups, Student's t-test was used when the parametric conditions were met after the normality analysis. The Mann-Whitney U test was also used when the parametric conditions were not met.

RESULTS

This study included 355 nurses, of whom 82.3% were female. Their median age was 35.42±9.67 (Min:21 Max:56) and their mean BMI was 24.87±4.54.

Table 1. Distribution of nurses by sociodemographic characteristics (N=355)

Variable	Group	n	%
Sex	Female	292	**82.3**
	Male	63	17.7
Age (year)	35.42±9.67 (Min:21 Max:56)		
BMI (kg/m^2)	24.87±4.54 (Min:15.81 Max:53.33)		

Of the nurses, 31.9% had worked as a nurse for more than 5 years while 29.6% had worked as a nurse for more than 20 years. Of them, 23.4% worked in surgical clinics, 18.0% worked in administrative units, and 15.5% worked in family practice/community health centers. The rate of nurses who worked in COVID-19 clinics and COVID-19 intensive care units were 6.2% and 2.3%. Of the nurses, 51.0% stated to work for 40 hours a week (Table 2).

Table 2. Distribution of results on the professional characteristics of nurses (N=355)

Variable	Group	n	%
Professional Time as a Nurse	Less than 1 year	45	12.7
	1-5 years	68	19.2
	6-10 years	52	14.6
	11-15 years	49	13.8
	16-20 years	36	10.1
	21-25 years	43	12.1
	More than 25 years	62	17.5
Working Unit*	Surgical Clinics	83	23.4
	Administrative Units/District Health Departments	64	18.0
	Internal Disease Clinics	55	15.5
	Family Practice/Community Health Centers	45	12.7
	Intensive Care Units	39	11.0
	Emergency Service/112	39	11.0
	COVID-19 Clinic	22	6.2
	COVID-19 Intensive Care Unit	8	2.3
Weekly Working Hours	40 hours	181	51.0
	More than 40 hours	174	49.0

*Listed from the highest to the lowest.

Of the nurses, 19.4% had a chronic condition, and 20.6% regularly took medication. Considering the chronic conditions participants had, 4.22% had thyroid, 3.94% had chronic respiratory diseases, 3.66% had diabetes, and 3.09% had high blood pressure. The highest rate of regularly used medication was thyroid drugs with 6.76%.

Of the nurses, 11.5% got vaccinated for influenza every year, and 6.19% regularly took vitamin D supplements.

Of them, 56.1% slept for less than 7 hours a day while 42.8% slept 7 to 9 hours a day. The rate of those who slept longer than 9 hours a day was 1.1%. Of them, 44.2% drank 1-2 liters of water a day whereas 25.9% drank 2-3 liters of water a day Among the nurses, the rate of being diagnosed with COVID-19 before vaccination was 34.1%. Of the nurses, 54.6% stated that they felt pain around the injection site for at least a week after the vaccination. The side effects experienced were stiffness around the injection site (14.6%), muscle weakness (14.1%), itching (11.59%), redness (10.7%), and swelling (10.4%) (Table 3)

Table 3. Undesirable Side Effects after Vaccination (Local)

Side effects	% Percent
Pain	54.6%
Stiffness	14.6%
Muscle Weakness	14.1%
Itchiness	11.5%
Redness	10.7%
Swelling	10.4%

The factors that affected the local side effects experienced on the injection site after the COVID-19 vaccination are given in table 4. The rate of experiencing muscle pain around the injection site was higher in men than women (p=0.001) and those who worked more than 40 hours a week to those who worked less than 40 hours a week (p=0.001). This rate was also lower among those who took regular medication to those who did not (p=0.030).

Table 4. Affecting factors on the local side effects experienced after vaccination

		Muscle Pain on the Injection Site*					
		Yes		No		Chi-Square	p
		n	%**	n	%**		
Sex	**Female**	32	11.0	260	89.0	13.284	**0.001**
	Male	18	28.6	45	71.4		
Weekly Working Hours	**40 hours**	15	8.3	166	91.7	10.256	**0.001**
	More than 40 hours	35	20.1	139	79.9		
Regular Medication	**Yes**	5	6.8	68	93.2	3.975	**0.030**
	No	45	16.0	237	84.0		
	Total	50	14.1	305	85.9		

*Chi-square test **Row percentage

Significant side effects experienced on around the injection site by the variable of age are given in Table 4. Accordingly, the mean age of individuals who experienced stiffness, swelling, and itching was significantly lower than those who did not experience these (p=0.045, p=0.030, p=0.014) (Table 5).

Table 5. Significant local side effects according to the variable of age

Variable		N	Mean	Standard Deviation	SD	t	p
Stiffness*	**Yes**	**52**	**32.94**	**10.266**	353	2.009	**0.045**
	No	**303**	**35.84**	**9.512**			
Swelling	**Yes**	**37**	**32.16**	**10.735**	353	2.177	**0.030**
	No	**318**	**35.80**	**9.48**			
Itchiness*	**Yes**	**41**	**31.95**	**9.967**	353	2.460	**0.014**
	No	**314**	**35.87**	**9.549**			

*Student's t-test

Of the nurses, 39.1% did not experience any systemic side effects after vaccination. The rate of individuals who experienced a systemic side effect was 22.8% while the rate of individuals who experienced two systemic side effects was 13.2%. Furthermore, the rate of individuals who experienced three or more systemic side effects was 24.7%.

The most common systemic side effects experienced after the vaccination were fatigue (39.2%), headache (34.1%), arthritis (25.1%), and sore throat (10.4%), respectively. The least common side effects were changes in the sensation of taste (4.2%, changes in mucosa (4.2%), and coughing (4.2%) (Table 6).

The factors that affected systemic side effects experienced after the COVID-19 vaccination are presented in Table 5. Accordingly, the incidence rate of experiencing fatigue after vaccination was significantly higher among those who had been diagnosed with COVID-19 at any time before vaccination (p=0.004) and who consumed alcohol (p=0.028).

The incidence rates of appetite changes (p=0.041), itching (p=0.010), and fatigue (p=0.010) were higher among those who worked longer than 40 hours a week.

Table 6. Undesirable Side Effects after Vaccination (Systemic)

Side effects	% Percent
Fatigue	39.2%
Headache	34.1%
Arthritis	25.1%
Sore Throat	10.4%
Nausea	9.9%
Fever	8.2%
Vertigo	8.2%
Nasal Flow	7.9%
Appetite Changes	6.5%
Diarrhea	5.9%
Itchiness	5.9%
Abdominal Pain	5.6%
Cough	4.2%
Changes in Mucosa	4.2%
Changes in Taste Sensation	4.2%

Sex is the only factor that affected appetite changes. The rate of appetite changes was higher among men than women (p=0.00). The incidence rate of fever, was higher among individuals with a chronic condition (p=0.037).

Table 5. Factors affecting the systemic side effects experienced after vaccination

		Yes		No			
		n	**%****	**n**	**%****	**Chi-Square**	**p**
Fatigue*							
Diagnosed with COVID-19	**Yes**	60	50.0	60	50.0	8.419	**0.004**
	No	79	34.1	153	65.9		
Alcohol Use	**Yes**	13	61.9	8	38.1	4.849	**0.028**
	No	126	37.7	208	62.3		
Weekly Working Hours	**40 hours**	59	32.6	122	67.4	6.667	**0.010**
	More than 40 hours	80	46.0	94	54.0		
	Total	139	39.2	216	60.8		
Arthritis*							
Diagnosed with COVID-19	**Yes**	40	33.3	80	66.7	6.244	**0.012**
	No	49	21.1	183	78.9		
	Total	89	25.3	263	74.2		
Appetite Changes*							
Sex	**Female**	13	4.5	279	95.5	11.156	**0.001**
	Male	10	15.9	53	84.1		
Weekly Working Hours	**40 hours**	7	3.9	174	96.1	4.156	**0.041**
	More than 40 hours	16	9.2	158	90.8		
	Total	23	6.5	332	93.5		
Itchiness*							
Weekly Working Hours	**40 hours**	5	2.8	176	97.2	6.597	**0.010**
	More than 40 hours	16	9.2	158	90.8		
	Total	21	5.9	334	94.1		
Fever*							
Chronic Disease	**Yes**	10	14.3	60	85.7	4.349	**0.037**
	No	19	6.7	266	93.3		
	Total	29	8.2	326	91.8		

*Chi-square test **Row percentage

DISCUSSION

COVID-19 vaccines were first administered to healthcare personnel in Turkey and the CoronaVac (Sinovac) vaccine, which is an inactive vaccine, was the chosen vaccine (20). Side effects reported in different vaccine studies were pain, swelling, fever, headache, muscle pain, and fatigue (8, 9, 21-26). The presence of serious side effects was assessed using a systematic compilation evaluating 11 articles consisting of results on the vaccines and it was found that 168 individuals (total n: 58.773) experienced serious side effects of the vaccine but only one of these side effects was actually related to the vaccine (27). Similarly, no serious side effect was reported by the nurses vaccinated for COVID-19 in this study.

The most commonly reported local side effects were pain, loss of strength, and movement restriction around the injected arm (9, 22, 24, 25, 28). A relevant study reported that pain on the injection site (95.5%), edema (13.3%), and limited arm movements (78.1%) were experienced in the group who was administered with the vector vaccine and that local side effects were more common in the vector vaccine than the mRNA vaccine ($p>0.05$) (24). Another study found the rate of experiencing pain was 31.7% among those who were administered the inactive COVID-19 vaccine (25). A study stated that pain experienced on the injection site in the group who got an inactive vaccine increased as the single dose (3/6 mg) of the vaccine administered increased. The rate of itching, one of the local side effects experienced in relevant studies, was reported as 1% in the group who was administered with the inactive vaccine (28). The incidence rate of itching among local side effects was higher in the vector vaccine than the mRNA vaccine by 0.9% (23). Studies stated that itching varied between 6-8% with an increase in line with the dose of the vaccine administered (10). A study conducted in Turkey found that pain (41.5%) and edema (2.6%) were experienced among the local side effects observed after the administration of the inactive vaccine and that there were differences based on sex (9).

It can be stated that the most common local side effects experienced after the administration of inactive vaccines are pain, sensitivity on the arm due to pain, loss of strength/difficulty moving the arm, local swelling due to injection and stiffness and mild itching induced by this swelling.

Additionally, sex affects the pain felt. In a study, which reported that the incidence rate of pain on the injection site of women who got the inactive vaccine was higher ($p<0.001$). Mean age also affected this, as the rate of those experiencing pain in the ≤32 age group was 66.7% while this rate was 57.8% in the ≥32 age group (9). The results obtained from a study where two different vaccines were administered (n: 655.590) indicated that more reactions to vaccines were observed in women and those younger than 35 and that the incidence rate of pain on the injection site increased at the age of ≤43 in the group who received the mRNA vaccine (23). Another study conducted on a group who received an inactive vaccine reported that 23.1% of women and 15.2% of men experienced pain. The rate of individuals who experienced pain in the age group of 30-39 (24.7%) was higher than other age groups (22). The results of the present study are similar to the relevant literature, and the study revealed that pain was experienced more by women and individuals younger than 35. It is possible to state that women and young adults who got an inactive COVID-19 vaccine might more commonly experience local side effects on the injection site. This should be paid attention to while giving pre-vaccination information.

Medication use of individuals also plays an important part in vaccine side effects. A study conducted with a group who received an mRNA vaccine found that individuals who took regular medication and had chronic conditions experienced oral-systemic side effects (blisters in the mouth, bad breath, ulcerations on the lip and tongue), and the side effects varied based on the medication used (8). A cross-sectional study conducted in Turkey showed that the number of side effects experienced by individuals who took regular medication in the group who received an inactive COVID-19 vaccine was higher (60.1%/70.2%) (9). A relevant study, on the other hand, reported no difference between the reactions to the vaccine of individuals who either took regular medication or were not in a group who were given an inactive COVID-19 vaccine. However, the rate of those who reported having experienced side effects was higher in the group who did not take medication regularly (22). In this study, the rate of side effects observed in individuals who took regular medication was higher. Individuals who regularly take medication generally have chronic conditions, so it would be appropriate to inform these individuals about this matter before vaccination.

One of the most common systemic side effects experienced after COVID-19 vaccination is fatigue (8, 9, 21-25). Fatigue was associated with the disruption in regular sleep routines and it was stated that vaccine-induced side effects were more common in those with bad quality of sleep with a significant difference (22). A systematical compilation that evaluated the side effects of four different vaccines revealed that fatigue and headache were reported after the administration of three vaccines and there were no systemic side effects for the inactive COVID-19 vaccine (26).

Working during the COVID-19 pandemic triggers fatigue, depression, and anxiety for healthcare professionals (29). The workload of nurses has increased (30, 31) and they have felt more stressed during this period (32). A previous study conducted with nurses stated that in pre-pandemic times, nurses made more efforts to maintain order in the home which made them tired more often (33). During the pandemic, nurses had to work overtime due to the increasing workload at hospitals and were not able to sleep or rest sufficiently due to the increasing workload at home due to the lockdowns; thus, they became increasingly more tired, and this situation was reflected on them after vaccination.

One of the factors that affected experiencing fatigue is alcohol use. The body is trained to fight against certain organisms causing disease with vaccination and an immune response is expected to form (15). However, alcohol consumption negatively affects this immune response; thus, alcohol consumption is not recommended during the pandemic (34). This study also showed that fatigue was more common among those who consumed alcohol. This indicates that alcohol intake might be associated with the immune response and might negatively affect it, making people feel more exhausted.

Another side effect reported by the nurses after the vaccination was headache at 18-46% (8, 9, 21-25). The underlying reason for this side effect was explained by fatigue and sleep deprivation (35). According to a study conducted in China, one of the most common problems experienced by nurses was headache (50%). This might be due to migraines and they increase by almost 4 times due to working the night shift (QR: 2.294/ 4.695) (36). Considering healthcare personnel, working the night shift affects the quality of sleep while the disruption in the quality of sleep affects appetite and eating habits (37). The current pandemic has changed people's eating habits and generally increased their sugar intake (38). Studies have emphasized that this period has resulted in increased appetite in men between the age of 18-30 (39). During the pandemic, working night shifts, increased working hours, and increased workloads at home and the workplace might cause nurses to feel exhausted and male nurses to experience more changes in appetite.

Studies stated that high fever experienced by individuals after vaccination was observed more as the dose of the medication increased (10, 40). The literature states that the type of vaccine administered affects fever (24). It has also been emphasized that high fever is experienced more after the second dose (23). Studies reported that the

regression of COVID-19 infection slows down in the presence of certain diseases (23). Some of these diseases are diabetes (41), high blood pressure (42), coronary artery disease (43), and chronic obstructive pulmonary disease (44). Studies on medications used revealed that the side effects experienced by individuals who took antihypertensives, antihistamines, and oral contraceptives were different ($p<0.05$) and general side effects increased in individuals who regularly took medication due to their illnesses (r:0.122) ($p<0.05$) (8). Another study reported that individuals with chronic conditions experienced more vaccine side effects but there was no relationship with medication (22). High fever might be experienced more by individuals with chronic conditions after vaccination and individuals in this group should be informed of this and followed up.

Limitations of the Study: This study was conducted with nurses using the online survey method. In addition to limitations due to the quantitative design of the study, this study is limited to healthcare professionals who could use communication technologies, who agreed to participate in the study, and who had studied nursing. Additionally, all the healthcare personnel in Turkey were vaccinated with the Sinovac vaccine; thus, the results cannot be generalized for all vaccines.

CONCLUSION

This study found that no serious side effect was observed after the inactive COVID-19 vaccine, almost two-thirds of those who got vaccinated experienced at least one local or systemic side effect, women and people younger than 35 were more affected by the vaccine. The local side effects of the vaccine, along with increased appetite, and fatigue were experienced more intensely by individuals who worked longer than 8 hours a day, and that getting vaccinated after being diagnosed with COVID-19, the presence of chronic conditions, and alcohol intake might increase the side effects of the vaccine.

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