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Address: Pamukkale Medical Journal, Pamukkale University Faculty of Medicine Dean's Office, Yunusemre Street, no: 3/F, Kınıklı, 200070 Pamukkale, Denizli.
E-mail: tipdergisi@pau.edu.tr
Tel: +902582961619
Fax: +902582961765

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Remdesivir experience in patients diagnosed with COVID-19 in a tertiary hospital

Üçüncü basamak bir hastanede COVID-19 tanılı hastalarda remdesivir deneyimi

Ayşegül Seremet Keskin, Kübra Demir Önder, Filiz Kızılateş

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Abstract

Purpose: Remdesivir is an adenosine nucleotide analog antiviral drug recommended in these treatment combinations. While vaccine and drug studies are underway in the treatment of COVID-19, remdesivir is also being studied in terms of efficacy, safety, and potential side effects. Therefore, we aimed to share our experiences of patients who were diagnosed with COVID-19 and treated with remdesivir in our hospital.

Material and method: Patients over 18 years of age, who were diagnosed with COVID-19 in our hospital between March 15 and March 30, 2020, based on positive RT-PCR and/or thoracic computed tomography (CT) results studied from nasopharyngeal samples, were screened retrospectively. Those who had received Remdesivir treatment were included in our study.

Results: 23 patients were included in our study. Eighteen (79.2%) of the patients were male and 5 (20.8%) were female. Remdesivir initiation time was 8.4±2.6 days from the onset of symptoms and 6±2.6 days from the time of diagnosis. In the follow-up period, we had to hospitalize 18 patients (78.2%) in the intensive care unit (ICU). 14 (60.8%) needed a mechanical ventilator. Post-treatment follow-up showed that 15 (65.2%) recovered, and 8 (34.8%) resulted in mortality.

Conclusion: Since inflammation is as critical as the replication of the virus in the pathogenesis of COVID-19 disease, the use of remdesivir in combination with other antiviral and anti-cytokine therapies may increase the effectiveness. We believe that we need new studies in this regard.

Key words: COVID-19, remdesivir, treatment.

Seremet Keskin A, Demir Onder K, Kizilates F. Remdesivir experience in patients diagnosed with COVID-19 in a tertiary hospital. Pam Med J 2023;16:1-7.

Öz

Amaç: Remdesivir, COVID-19 tedavi kombinasyonlarında önerilen bir adenozin nükleotid analogu antiviral bir ilaçtır. COVID-19 tedavisinde aşı ve ilaç çalışmaları devam ederken, remdesivir de etkinlik, güvenlik ve olası yan etkiler açısından incelenmektedir. Bu nedenle hastanemizde COVID-19 tanısı alan ve remdesivir ile tedavi edilen hastalarımızın deneyimlerimizi paylaşmayı amaçladık.

Gereç ve yöntem: 15 Mart-30 Mart 2020 tarihleri arasında, hastanemize başvuran ve nazofarengeal örneklerden çalışılan RT-PCR testi pozitif olan ve/veya toraks bilgisayarlı tomografi (BT) sonuçlarına göre COVID-19 tanısı alan 18 yaş üstü hastalar retrospektif olarak tarandı. Remdesivir tedavisi alanlar çalışmamıza dahil edildi.

Bulgular: Çalışmamıza 23 hasta dahil edildi. Hastaların 18'i (%79,2) erkek, 5'i (%20,8) kadındı. Remdesivir başlama süresi semptomların başlangıcından itibaren 8,4±2,6 gün ve tanı anından itibaren 6±2,6 gündü. Takip döneminde 18 hastayı (%78,2) yoğun bakım ünitesine (YBÜ) yatırmak zorunda kaldık. 14'ünde (%60,8) mekanik ventilatöre ihtiyaç duydu. Tedavi sonrası takiplerinde ise 15 hastanın (%65,2) taburcu edildiği ve 8 hastanın (%34,8) ölümle sonuçlandığını gösterildi.

Sonuç: COVID-19 hastalığının patogenezinde virüsün replikasyonu kadar inflamasyon da önemli olduğundan remdesivirin diğer antiviral, antisitokin tedaviler ile kombine şekilde kullanımı ile etkinliğinde artış olabileceği ve bu konuda da yapılacak yeni çalışmalara ihtiyaç olduğu düşünülmüştür.

Anahtar kelimeler: COVID-19, remdesivir, tedavi.

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Ayşegül Seremet Keskin, M.D. Department of Clinical Microbiology and Infection Disease, Univesity of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey e-mail: aseremetkeskin@yahoo.com (https://orcid.org/0000-0002-9224-4699) (Corresponding Author)

Kübra Demir Önder, Asst. Prof. Department of Clinical Microbiology and Infection Disease, Univesity of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey e-mail:dr_kubrademir@hotmail.com (https://orcid.org/0000-0002-4164-5118)

Filiz Kızılateş, M.D. Department of Clinical Microbiology and Infection Disease, Univesity of Health Sciences Antalya Training and Research Hospital, Antalya, Turkey, e-mail:filizkizilates@gmail.com (https://orcid.org/0000-0002-8985-893X)

Introduction

On December 31, 2019, the World Health Organization (WHO) reported pneumonia cases of unknown etiology in Wuhan, China's Hubei province. On January 7, 2020, the disease was reported to be caused by a new coronavirus (2019-nCoV) which was not previously detected in humans, and this new disease was named COVID-19. In March, the WHO recognized the current situation as a pandemic due to the spread of the virus in many countries. The first case in our country was announced on March 11, 2020, and the pandemic continues at full speed in Turkey and the rest of the world [1].

Many protocols have been developed to treat COVID-19 since the first day it emerged, and many clinical studies on these treatment methods have been initiated and are ongoing. However, no effective treatment has been found yet in this regard. Antimalarial drugs such as chloroquine (CQ) and hydroxychloroquine (HCQ); antiviral drugs such as favipiravir (FAV), lopinavir/ritonavir, and remdesivir; interleukin antagonists such as tocilizumab and anakinra; recombinant human monoclonal antibodies; steroid therapies; immunoglobulin therapies; anticoagulant therapies and convalescent plasma are used in treating the disease and preventing its complications [2].

Remdesivir is an adenosine nucleotide analog antiviral drug recommended in these treatment combinations. It was originally developed to treat Ebola disease and has been effective in vitro for all coronaviruses, including 2019-nCoV [3]. It has also been used in the treatment of COVID-19 disease in Turkey and all over the world. While vaccine and drug studies are underway in the treatment of COVID-19, remdesivir is also being studied in terms of efficacy, safety, and potential side effects. Therefore, we aimed to share our experiences of patients who were diagnosed with COVID-19 and treated with remdesivir in our hospital.

Materials and methods

Patients over 18 years of age, who were diagnosed with COVID-19 in our hospital between March 15 and March 30, 2020, based on positive RT-PCR and/or thoracic computed tomography (CT) results studied from nasopharyngeal samples, were screened retrospectively. Those who had received Remdesivir treatment were included in our study. All of the patients receiving Remdesivir received the drug intravenously for 5 days in a loading dose of 1x200 mg/day and a maintenance dose of 1x100 mg/day, following the standard procedure. Supportive treatments, except for antiviral therapy, such as low molecular weight heparin, vitamin C, and steroid were applied to all patients in the same way in patients with severe pneumonia.

COVID-19 pneumonia severity

Mild to moderate pneumonia; Patients with symptoms such as fever, muscle/joint pain, cough, and sore throat who had a respiratory rate of <30/min, SpO2 level >90% in room air, and signs of mild to moderate pneumonia on chest X-ray or tomography;

Severe pneumonia; Patients with symptoms such as fever, muscle/joint pain, cough, and sore throat who had a tachypnea (≥30/min), SPO_2 level ≤90% in room air, and signs of bilateral diffuse pneumonia on chest X-ray or tomography [1]. Data about the patients were generated in the SPPS 20.0 program and statistical analysis was performed. $P<0.05$ was considered statistically significant. This study was approved by Ethics Committee of University of Health Sciences Antalya Trainning ang Research Hospital with the date 26.11.2020 and the number 18/8. All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Our study included twenty-three patients admitted in our hospital after being diagnosed with COVID-19 and treated with remdesivir. All patients were diagnosed based on the (+) result in RT-PCR and the presence of COVID-19 pneumonia signs in CT. 22 patients included in the study had RT-PCR positivity and pneumonia findings on CT. One patient was diagnosed only with pneumonia findings on CT. SPO_2 level of the patients was ≤94 when remdesivir treatment was initiated. Eighteen (79.2%) of the patients were male and 5 (20.8%) were female. The

mean age of the patients included in the study was 53.3±11.6. We reviewed their underlying diseases 34.8% of the patients had diabetes mellitus (DM), 26.1% had hypertension (HT), 21.7% had obesity, 8.7% had the chronic obstructive pulmonary disease (COPD), and 13% had asthma. 60.9% of them were smokers.

Before the remdesivir treatment, 20 patients (87%) used favipiravir (FAV), 1 (4.3%) used hydroxychloroquine (HCQ), and 2 (8.7%) used both drugs. The patients had received other treatments for an average of 5.6±2.01 days before remdesivir. Remdesivir initiation time was 8.4±2.6 days from the onset of symptoms and 6±2.6 days from the time of diagnosis.

In the follow-up period, we had to hospitalize 18 patients (78.2%) in the intensive care unit (ICU). 14 (60.8%) needed a mechanical ventilator. Post-treatment follow-up showed that 15 (65.2%) recovered, and 8 (34.8%) resulted in mortality. Table 1 shows the general characteristics of the patients. Patients were divided into two groups by days from the onset of symptoms to the initiation of remdesivir, as less than 10 days and more than 10 days. The regression analysis performed on these groups showed no significant differences in terms of mortality.

We evaluated the laboratory parameters of the patients before and at the end of the remdesivir treatment. We found that their C-reactive protein (CRP), ferritin, lactate dehydrogenase (LDH), and fibrinogen levels were significantly lower (*p*-value was 0.001, 0.005, 0.000, and 0.001, respectively). On the other hand, their Alanine aminotransferase (ALT) and blood urea nitrogen (BUN) values were higher than the pretreatment state (*p*-value was 0.004, and 0.003, respectively). Table 2 shows the other laboratory parameters.

We divided the patients included in the study into two groups as recovered and deceased and checked whether there was a difference between the two groups in the parameters followed. However, we observed no difference between the groups in the parameters checked. The characteristics of the patients by the groups are shown in Table 3.

Discussion

Since the first appearance of the disease in the Wuhan province of China in 2019 and its spread in our country in March 2019, our experience with its diagnosis and treatment has improved. However, there are still no clear treatment protocols. Many countries have different protocols for effective drugs and treatment methods. Chloroquine, HCQ, FAV, lopinavir/ritonavir, umifenovir, galidesivir, and remdesivir are thought to be effective in this respect [4].

In addition to these drugs, other treatments are also available to suppress the cytokine storm and prevent disease complications. The need to find safe, effective and rapid treatment methods for the treatment of the disease continues.

Remdesivir is an antiviral agent that inhibits RNA-dependent RNA polymerase (RdRp) that is effective in the early phase of the disease. It is known that early termination of RNA transcription decreases viral replication, reducing viral load in the lungs, ultimately improving pulmonary function [5]. It has been used in treating the Ebola, SARS-CoV, and MERS-CoV viruses. Since it has a long half-life, it offers the advantage of using a single dose per day, and the recommended dose for COVID-19 is 1x200 mg, continuing with a maintenance treatment of 1x100 mg after loading. The treatment should be completed in 5 days. In late May, it became the first drug to be licensed by the FDA for use in COVID-19 disease [6]. Although it has been the first licensed drug, its effects on the prognosis and mortality of the disease and its side effects are not fully known, and as far as we know, there are no studies published on this subject in our country.

All patients included in the study had received an average of 5.6±2.01 days of HCQ, FAV, or HCQ+FAV pre- or post-hospitalization until remdesivir was provided. The time from the onset of symptoms to the use of remdesivir was 8.4±2.6 days. In a study involving 1062 participants, the average time from the onset of symptoms to the use of remdesivir was 9 (6-12) days. Better treatment response was received when remdesivir treatment started within the first 10 days after symptom onset [7]. In another study conducted in China, remdesivir was used within an average of 9 days from the onset of

Table 1. General characteristics of the patients

	Number (n)	Percentage (%)
Gender Female	5	21.7
Male	18	78.3
Age (years)		
Underlying disease		
DM	8	34.8
HT	6	26.1
CAD	1	4.3
Asthma	3	13.0
COPD	2	8.7
Obesity	5	21.7
Malignancy	1	4.3
Smoking	14	60.9
Other antiviral treatments received before remdesivir		
Hydroxychloroquine (HCQ)	1	4.3
Favipiravir (FAV)	20	87.0
HCQ+FAV	2	8.7
Days from the onset of symptoms until the initiation of remdesivir	Avg 8.4±2.6	
Duration of other treatments received before remdesivir (days)	Avg 5.6±2.01	
Duration of hospitalization (days)	Avg 22.2±11.08	
Duration of intense care (n:18)	Avg 16.9±7.93	
Duration of using a mechanical ventilator (days) (n:14)	Avg 11.9±7.34	
Presence of ARDS at the initiation of treatment		
Yes	12	52.2
No	11	47.8
Pneumonia severity at the initiation of treatment		
Mild to moderate	2	8.7
Severe	21	91.3
Presence of ARDS at the initiation of treatment 1 patient missing		
Yes	12	8.7
No	11	91.3
Convalescent plasma treatment		
Yes	20	87.0
No	3	13.0
Cytokine apheresis application		
Yes	5	21.7
No	18	78.3
Result		
Recovery	15	65.2
Death	8	34.8
Mortality <7 days	1	4.3
Mortality 7-14 days	1	4.3
Mortality 14-28 days	3	13.0
Mortality over 28 days	3	13.0

Table 2. Laboratory values

	Initiation of remdesivir treatment (x±SD)	End of remdesivir treatment (x±SD)	*p*
Leukocyte (WBC)/mm^3	11173.9±4591.02	12739.1±4845.49	0.212
Lymphocyte	713.0±341.52	801.1±378.12	0.144
Neutrophile/Lymphocyte ratio	15.8±9.37	17.5±14.3	0.784
C-reactive protein	140.6±81.75	62.7±50.95	0.001*
Procalcitonin	0.4±0.24	0.4±0.34	0.993
Blood urea nitrogen (BUN)	19.3±7.71	25.2±11.5	0.003**
Creatinine	1.5±3.39	0.7±0.42	0.323
AST	47.5±29.1	52.4±34.4	0.223
ALT	35.8±20.87	66.6±88.99	0.004**
LDH	560.1±223.99	380.6±163.5	0.000**
D-Dimer	2040.0±241.95	813.5±842.47	0.002**
Ferritin	749.9±611.87	480.1±333.92	0.005**
Fibrinogen	548.4±241.45	372.9±133.20	0.001**
Interleukin-6	77.8±95.89	×	

*p<0.05, paired-t-test
** p<0.05, Wilcoxon test
× IL-6 values of patients were not analyzed at the end of the treatment

Table 3. Characteristics of the patients by groups

	Recovered (n:15/%)	Deceased (n:8/%)	*p*
DM	5 (33.3)	3 (37.5)	0.596
HT	3 (20)	3 (37.5)	0.334
Asthma	2 (13.3)	1 (12.5)	0.731
COPD	2 (13.3)	0	0.415
Obesity	2 (13.3)	3 (37.5)	0.208
Smokers	10 (66.7)	4 (50)	0.337
Other antiviral treatments received before remdesivir Hydroxychloroquine (HCQ) Favipiravir (FAV) HCQ+FAV	 0 14 (93) 1 (6.7)	 1 (12.5) 6 (75.0) 1 (12.5)	 0.320
Duration of other treatments received before remdesivir (days)	5.9±1.64	5.2±2.65	0.494
Days from the onset of symptoms until the initiation of remdesivir	8.2±1.65	8.7±3.95	0.720
Hospitalization in the intensive care unit	10 (66.7)	7 (87.5)	0.288
Intensive care stay	16.4±6.58	17.5±9.81	0.780
The need for a mechanical ventilator	6 (40)	8 (100)	**0.006**
Duration of using a mechanical ventilator	9.7±4.13	13.5±8.99	0.354
Pneumonia severity at the initiation of treatment Mild to moderate Severe	 2 (13.3) 13 (86.7)	 0 8 (100)	 0.415
The total duration of hospitalization	22.5±10.25	21.5±13.21	0.780

symptoms, and better clinical improvement was observed in the group who started the treatment early [8]. In another study conducted by Grein et al. [9] including 61 patients, the time to begin the treatment after the onset of symptoms was 12 days on average. Compared to the others, in our study, remdesivir treatment started in the earliest period after the onset of symptoms. We found no difference in mortality when we divided the patients into two groups by days from the onset of symptoms to the initiation of remdesivir, as less than 10 days and more than 10 days.

Although the patients who received treatment had severe pneumonia, 65.2% (15) of them recovered. In another study, 84% of the patients treated with remdesivir recovered in the 28-day follow-up [9]. Mortality rates in the placebo group and the remdesivir group were compared in the study involving 1062 patients. Although there was a lower mortality rate in the remdesivir group, it was not statistically significant [7]. Remdesivir was compared to HCQ, lopinavir, and interferon in a study conducted by the World Health Organization (WHO) including 405 hospitals and 11330 patients in 30 countries. No significant difference was found between the groups in terms of hospital stay and mortality [10]. The clinical recovery rate after treatment with favipiravir in patients with severe pneumonia was 71% in 7 days [11]. In the study conducted with lopinavir/ritonavir, no significant difference was found between its effect on clinical recovery and recovery time in the group receiving lopinavir-ritonavir and the group receiving standard care. The 28-day mortality rate was 19.2% [12].

The most important contribution of laboratory parameters in COVID-19 disease is that they guide us in identifying prognosis. Parameters such as C-Reactive protein, IL-6, ferritin, D-Dimer, fibrinogen, absolute lymphocyte count, and neutrophil-lymphocyte rate are also critical in defining the prognosis of COVID-19 disease, in addition to the factors such as the underlying disease, severity of pneumonia, and the presence of ARDS [1]. In our study, we evaluated laboratory parameters at the beginning and end of remdesivir treatment and detected a significant decrease in CRP, ferritin, LDH, and fibrinogen levels.

In the light of the data obtained from several studies, it is known that remdesivir may have some side effects such as hypotension, arrhythmia, dyspnea, pneumothorax, anemia, lymphopenia, hyperglycemia, septic shock, nausea, vomiting, diarrhea, constipation, acute renal failure, headache, rash, delirium, ALT, high levels of AST, hypernatremia and hypokalemia [7, 8, 13, 14]. In our study, we observed no side effects that would require drug discontinuation. ALT and BUN values increased at the end of the treatment. Similar to this result in our study, another study reported that 32 of 53 patients developed side effects such as an increase in liver enzymes, acute renal failure, diarrhea, and hypotension [9]. In another study, 10% of patients developed nausea, 6% hypokalemia, and 5% headache [15].

In conclusion, conducted with a small group of 23 patients followed up with severe pneumonia, our study is an observation report on remdesivir treatment. It is the first study in our country on remdesivir treatment and its results. Broader, randomized, placebo-controlled studies can provide more reliable results. Since inflammation is as critical as the replication of the virus in the pathogenesis of COVID-19 disease, the use of remdesivir in combination with other antiviral and anti-cytokine therapies may increase the effectiveness. We believe that we need new studies in this regard.

Limitations of the study

1- Absence of a control group

2- The effect of redeliver on viral load remains unanalyzed

3- A small group of patients

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

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Ethics committee approval: This study was approved by Ethics Committee of University of Health Sciences Antalya Trainning ang Research Hospital with the date 26.11.2020 and the number 18/8.

Contributions of the authors to the article

A.S.K. conceived the idea. A.S.K. collected the data. F.K. performed the calculations, data analysis and created figures. A.S.K., K.D.O. and F.K. interpreted and discussed the results. K.D.O. and F.K. provided critical feedback. A.S.K. wrote the manuscript with input from all authors. All authors discussed the results, reviewed and commented on the manuscript.

Research Article

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Risk factors of early recurrence of ischaemic stroke

İskemik inmenin erken dönem tekrarında risk faktörleri

Nevzat Uzuner, Gülnur Tekgöl Uzuner, Yasemin Tehli

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Abstract

Purpose: Despite acute and preventive treatments for ischemic stroke, it remains a cause of high mortality and morbidity due to recurrence of ischemic stroke. The generally accepted point of view is that the risk factors that caused the initial stroke are also important in the recurrence of ischemic stroke. Our study was conducted to determine the risk factors involved in early ischemic stroke recurrence.

Material and method: We selected ischemic stroke patients from our own stroke database, and among the patients included in this study, 521 patients who could be followed up for 3 months after the first stroke and had complete examinations were included in the analysis.

Results: Seventy-one patients (14%) had another stroke within 3 months of the first stroke. The mean time to early stroke recurrence is 21 days. Significant risk factors for early stroke were coronary artery disease (43%, $p<0.016$) and congestive heart failure (38%, $p<0.016$). Age, atrial fibrillation, hypertension, diabetes mellitus, hyperlipidaemia, smoking, and alcohol use were not found to be significant risk factors for stroke recurrence in the early period.

Conclusion: Despite appropriate treatments, coronary artery disease and congestive heart failure have emerged as important risk factors for stroke recurrence in the early period after stroke, indicating that more attention should be paid to this issue.

Key words: Ischemic stroke, risk factors, stroke recurrence.

Uzuner N, Tekgol Uzuner G, Tehli Y. Risk factors for early recurrence of ischaemic stroke. Pam Med J 2023;16:9-12.

Öz

Amaç: İskemik inme gelişen akut ve koruyucu tedavilere rağmen, iskemik inmenin tekrarlaması nedeniyle de yüksek ölüm ve morbidite nedeni olarak kalmaya devam etmektedir. Genellikle kabul edilen görüş, ilk inmeye neden olan risk faktörlerinin, iskemik inme tekrarında da önemli olduğudur. Bizim çalışmamız erken dönem iskemik inme tekrarında yer alan risk faktörlerini belirlemek amacıyla yapılmıştır.

Gereç ve yöntem: İskemik inme hastalarını kendi inme veri tabanımızdan seçtik ve bu çalışmaya alınan hastalar içinde ilk inmeden sonraki dönemde 3 ay takip edilebilen ve incelemeleri eksiksiz olan 521 hasta analize dahil edilmişlerdir

Bulgular: Yetmiş bir hasta (%14) ilk inmeden sonraki 3 ay içerisinde tekrar inme geçirmişlerdir. Erken inme tekrarı için geçen ortalama süre 21 gündür. Erken inme için belirgin risk faktörleri koroner arter hastalığı (%43, $p<0,016$) ve konjestif kalp yetmezliği (%38, $p<0,016$) olarak saptanmıştır. Yaş, atriyal fibrilasyon, hipertansiyon, diabetes mellitus, hiperlipidemi, sigara, alkol kullanımı erken dönemde inme tekrarı için anlamlı risk faktörü olarak bulunmamıştır.

Sonuç: Uygun tedavilere rağmen, koroner arter hastalığı ve konjestif kalp yetmezliği inmeden sonraki erken dönemde inme tekrarı için önemli risk faktörleri olarak öne çıkmıştır ve bu konuya biraz daha fazla önem verilmesi gerektiğine işaret etmektedir.

Anahtar kelimeler: İskemik inme, risk faktörleri, inme tekrarı.

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Nevzat Uzuner, Prof. Eskisehir Osmangazi University, Neurosonology Unit, Eskisehir, Turkey, e-mail: nuzuner@ogu.edu.tr (https://orcid.org/0000-0002-4961-4332)

Gülnur Tekgöl Uzuner, Assoc. Prof. Eskisehir Osmangazi University, Cerebrovascular Disease Department, Eskisehir, Turkey, e-mail: uzunergulnur@gmail.com (https://orcid.org/0000-0002-9795-4817)

Yasemin Tehli, Asst. Prof. Eskisehir Osmangazi University, Neurology Department, Eskisehir, Turkey, e-mail: yaseminden87@hotmail.com (https://orcid.org/0000-0003-0342-5939)

Introduction

Despite acute and preventive treatments for ischemic stroke, it remains a cause of high mortality and morbidity due to recurrence of ischemic stroke. The risk factors that cause ischemic stroke to recur have not been studied as thoroughly as the risk factors that cause ischemic stroke. In studies on this subject, it has been shown in hospital and population-based studies that stroke recurrence is higher in the very early and very late periods after ischemic stroke. The generally accepted point of view is that the risk factors that caused the initial stroke are also important in the recurrence of ischemic stroke. Among these, cardiovascular risk factors, hypertension, diabetes mellitus, dyslipidaemia and atrial fibrillation stand out as modifiable risk factors [1]. Our study was conducted to determine the risk factors involved in early ischemic stroke recurrence.

Materials and methods

It was approved by Eskisehir Osmangazi University, Non-Interventional Clinical Research Ethics Committee with the decision numbered 80558721/G-191 on 13 June 2017. Study data were compiled in the Stroke Data Collection Form created by the Department of Cerebrovascular Diseases. The records of patients presenting with ischemic stroke from May 2017 to October 2007 were transferred to the database. Among these patients, 521 patients who could be followed up for 3 months after the first stroke and whose examinations were complete were included in the analysis. Ischemic stroke patients were defined by demonstrating lesions with CT or MRI. Doppler ultrasonography and transcranial Doppler sonography of the patients were performed in the Neurosonology unit of the department. Stroke subtypes were made according to the Trial of ORG10172 in Acute Stroke Treatment (TOAST) classification [2] and clinical stroke types according to the Oxfordshire Community Stroke Project (OCSP) classification [3]. All information about the demographic data and risk factors of the patients were transferred to the database. Statistical analyses were performed with SPSS-24 software and categorical data were evaluated with Chi-square analysis.

Results

Seventy-one patients (14%) had another stroke within 3 months of the first stroke. The mean time to early stroke recurrence is 21 days. The mean age of patients with recurrent stroke was 73 years, while the mean age of patients without recurrent stroke was 70 years, and there was no significant difference between them.

When the clinical types of ischemic stroke were evaluated (Table 1), stroke recurrence was observed in 8 of 68 patients in the total anterior circulation infarcts (TACI) group, 49 of 316 patients in the partial anterior circulation infarcts (PACI) group, 3 of 36 patients in the lacunar infarct (LACI) group, and 11 of 99 patients in the posterior circulation infarcts (POCI) group within the first 3 months. However, no significant difference was found in stroke recurrences according to clinical classification.

When we look at the etiological classification (Table 2), stroke recurrence developed in 21 of 126 patients with large artery disease, 4 of 39 patients with small artery disease, 24 of 166 patients with cardio embolism, and 21 of 170 patients with cryptogenic causes. In contrast, stroke recurrence was not seen in any of the 5 patients with haematological causes and none of the 9 patients who were considered for ESUS.

In the analysis of risk factors, gender, alcohol and smoking, hypertension, hyperlipidaemia, diabetes mellitus, obstructive sleep apnoea, patent foramen ovale, atrial fibrillation did not differ significantly in early stroke recurrence (Table 3). Conversely, early stroke recurrence was significantly higher in patients with coronary artery disease and congestive heart failure (p<0.016).

Discussion

There has been no significant change in stroke recurrence in the last 20 years [4], and large artery disease and cardioembolic strokes have come to the fore in recurrent strokes [5]. However, there are differences between the recurrence times of stroke in studies. In our study, although the recurrence rate was higher in large vessel disease, cardioembolic strokes and cryptogenic strokes, no significant differences were found in early stroke recurrence. Similarly, although PACI showed a higher rate of recurrence among recurrent strokes, it did not make a significant difference.

Table 1. Stroke recurrence data by stroke clinical subtypes

	Recurrent stroke (n=71)	Non-recurring stroke (n=450)	*p* value
TACI (total anterior circulation infarcts)	8 (11.3%)	60 (13.3%)	0.63
PACI (partial anterior circulation infarcts)	49 (69.0%)	267 (59.3%)	0.12
LACI (lacunar infarct)	3 (5.6%)	33 (7.8%)	0.34
POCI (posterior circulation infarcts)	11 (15.5%)	88 (19.6%)	0.42

Pearson Chi-square

Table 2. Stroke subtypes by etiological classification

	Recurrent stroke (n=71)	Non-recurring stroke (n=450)	*p* value
Large artery disease	21 (29.6%)	105 (23.3%)	0.25
Small artery disease	4 (5.6%)	35 (7.8%)	0.52
Cardioembolism	24 (33.8%)	142 (31.6%)	0.71
Haematological	0 (0.0%)	5 (0.9%)	0.42
Cryptogenic	21 (29.6%)	149 (33.1%)	0.56
ESUS	0 (0.0%)	9 (2.0%)	0.23

Pearson Chi-square

Table 3. Distribution of risk factors

	Recurrent stroke (n=71)	Non-recurring stroke (n=450)	OR (95% CI)	*p* value
Gender (W/M)	33/38	203/247	0.95 (0.57-1.56)	0.83
Atrial Fibrillation	20 (28.2%)	118 (26.2%)	1.10 (0.63-1.93)	0.73
Patent Foramen Ovale	0 (0.0%)	5 (1.1%)	0.99 (0.98-1.00)	0.37
Congestive heart failure*	27 (38.0%)	110 (24.4%)	1.90 (1.12-3.20)	0.016
Coronary artery disease*	31 (43.7%)	132 (29.3%)	1.87 (1.12-3.11)	0.016
Diabetes Mellitus	27 (38.0%)	137 (30.4%)	1.40 (0.83-2.36)	0.20
Hypertension	53 (74.6%)	298 (66.2%)	1.50 (0.85-2.65)	0.16
Hyperlipidaemia	27 (38.0%)	188 (41.8%)	0.86 (0.51-1.43)	0.55
Obstructive sleep apnoea	0 (0.0%)	1 (0.2%)	0.99 (0.99-1.00)	0.69
Alcohol usage	2 (2.8%)	13 (2.9%)	0.97 (0.21-4.41)	0.97
Smoking	22 (31.0%)	154 (34.2%)	0.86 (0.50-1.48)	0.59

In the literature, especially hypertension and diabetes mellitus, atrial fibrillation, angina pectoris, ischemic heart disease, cardiomyopathy and smoking emerge as independent risk factors for recurrent strokes [5, 6]. As mentioned above, these risk factors become more prominent in long follow-up periods after stroke. The fact that the treatment and follow-up of modifiable risk factors in the early period is more intense may have led to this result. In particular, antiaggregant therapy plays an important role in the prevention of recurrence of ischemic stroke in the early period [7]. In our study, early stroke recurrence was found to be significantly higher in patients with congestive heart failure and coronary artery disease. According to the Framingham study, among the risk factors for congestive heart failure are primarily hypertension and coronary heart diseases. In addition to these, rheumatic heart valve diseases, diabetes mellitus, hyperlipidemia and even atrial fibrillation are also included. In the presence of these diseases, congestive heart failure occurs as a result [8]. In addition, the rate of congestive heart failure in our patient group was found to be higher than expected. Therefore, our results are an expected result. Despite appropriate treatments, coronary artery disease and congestive heart failure can still lead to stroke recurrence, indicating that more attention should be paid to this issue.

The most important limitation of this study is that it is a retrospective evaluation. In this process, the loss of data of many patients caused a decrease in the number of patients included in the study. Apart from this, although our unit is the most comprehensive examination and treatment centre in the region, hospital data do not reflect the whole society. Nevertheless, large differences were not found between population-based studies and hospital-based studies [1]. Though, there is a need for well-ordered population-based studies.

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

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Contributions of authors

G.T.U.; Organizing the study, projecting, evaluating the data, evaluating the statistical results, making it into a draft text Y.T.; Entering data, evaluating results, contributing to draft text N.U.; Organization of the study, Doppler analysis and evaluation of data, statistical analysis, evaluation of results, draft text writing, literature control, finalization of the manuscript.

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Educational quality of YouTube videos on external versus endoscopic dacryocystorhinostomy surgery

Eksternal ve endoskopik dakriyosistorinostomi cerrahisinde YouTube videolarının eğitim kalitesi

Nejla Tükenmez Dikmen, Burak Dikmen

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Abstract

Purpose: To evaluate whether there is a difference in surgical training quality between endoscopic and external dacryocystorhinostomy (DCR) surgery videos on YouTube with the Laparoscopic Surgery Video Training Guide (LAP-VEGaS) video evaluation tool.

Matherials and methods: A comprehensive search was carried out on YouTube, using the following terms "DCR, External Dacryocystorhinostomy, Endoscopic Dacryocystorhinostomy''. Videos with 100 or more views were recorded. The number of views, age, number of likes, number of dislikes, number of comments, length, type of surgery, view ratio, like ratio, viewer interaction, and video power index were recorded. Two researchers independently assessed the videos for surgery educational quality according to LAP-VEGaS video assessment tool.

Results: After exclusion criteria, 74 out of a total of 108 videos were included in the study (27: external DCR, 47: endoscopic DSR). After the LAP-VEGaS evaluation, 30 (40.5%) of the videos were found to be of high quality and 44 (59.5%) were of low quality. External DCR videos were statistically significantly more high-quality videos than endoscopic videos (p=0.046). The average LAP- VEGaS score of external DCR videos was 10.65±2.98, and the mean LAP-VEGaS score of endoscopic DCR videos was 8.44±3.70, and the difference between them was statistically significant (p=0.009). Videos performed by ophthalmologists are statistically significantly higher quality videos according to LAP- VEGaS video assessment tool analysis (p=0.017). Concerning the selection of low and high quality videos, there was a significant agreement between two observers (kappa score 0.775).

Conclusions: Most of the DCR videos on YouTube are significantly lacking in case presentations, treatment options, and intraoperative and postoperative complications. In the future, we think that evaluating surgical videos on open access platforms such as YouTube with standard guidelines before they are published, and going through a review process may help increase the educational value of video materials.

Key words: YouTube, external dacryocystorhinostomy, endoscopic dacryocystorhinostomy, nasolacrimal duct obstructions, LAP-VEGaS video assessment tool.

Tukenmez Dikmen N, Dikmen B. Educational quality of YouTube videos on external versus endoscopic dacryocystorhinostomy surgery. Pam Med J 2023;16:13-22.

Öz

Amaç: YouTube'daki endoskopik ve eksternal dakriyosistorinostomi (DSR) cerrahi videoları arasında cerrahi eğitim kalitesinde fark olup olmadığını Laparoskopik Cerrahi Video Eğitim Kılavuzu (LAP-VEGaS) video değerlendirme aracı ile değerlendirmek.

Gereç ve yöntem: YouTube'da "DSR, Eksternal Dakriyosistorinostomi, Endoskopik Dakriyosistorinostomi" terimleri kullanılarak kapsamlı bir arama yapıldı. 100 veya daha fazla izlenen videolar kaydedildi. Videoların izlenme sayısı, beğeni sayısı, yorum sayısı, video uzunlukları, ameliyat şekli, ameliyatı yapan cerrah, izlenme oranı, beğenme oranı, izleyici etkileşimi ve video güç indeksi kaydedildi. Dakriyosistorinostomi konusunda deneyimli iki araştırmacı, videoları LAP-VEGaS video değerlendirme kılavuzuna göre cerrahi eğitim kalitesi açısından değerlendirdi.

Bulgular: Dışlama kriterlerinden sonra toplam 108 videodan 74'ü çalışmaya dahil edildi (27: Eksternal DSR, 47: Endoskopik DSR). LAP-VEGaS değerlendirmesi sonucunda videoların 30'unun (%40,5) yüksek kaliteli, 44'ünün (%59,5) ise düşük kaliteli videolar olduğu tespit edildi. Eksternal DSR videoları, endoskopik videolardan istatistiksel olarak anlamlı derecede daha yüksek kaliteli videolar idi (p=0,046). Eksternal DSR videolarının ortalama LAP-VEGaS skoru 10,65±2,98, endoskopik DSR videolarının ortalama LAP-VEGaS skoru 8,44±3,70 idi ve aralarındaki fark istatistiksel olarak anlamlıydı (p=0,009). Oftalmologlar tarafından yayınlanan videolar, LAP-VEGaS video değerlendirme aracı analizine göre istatistiksel olarak anlamlı derecede daha kaliteli videolardı(p=0,017). Düşük ve yüksek kaliteli videoların seçimiyle ilgili olarak, iki gözlemci arasında önemli derecede uyum olduğu görüldü (kappa puanı 0,775)**.**

Nejla Tükenmez Dikmen, M.D. Department of Ophthalmology, Medical Health Sciences University, Sultan Abdulhamid Han Training and Research Hospital, Istanbul, Turkey, e-mail: nejlatukenmez@hotmail.com (https://orcid.org/0000-0001-6767-6871) (Corresponding Author)

Burak Dikmen, M.D. Department of Otorhinolaryngology, University of Health Sciences Turkey, Kartal Dr. Lutfi Kirdar Research and Training Hospital, Istanbul, Turkey, e-mail: burakdikmen@hotmail.com (https://orcid.org/0000-0003-0891-5582)

Sonuçlar: YouTube'daki popüler DSR videolarından çoğu sunum, tedavi seçenekleri, intraoperatif ve postoperatif komplikasyonlar açısından önemli ölçüde eksiktir. Gelecekte cerrahi videoların YouTube gibi açık erişim platformlarında yayınlanmadan önce hakem inceleme sürecinden geçirilmesinin videoların eğitsel değerinin artmasına yardımcı olabileceğini düşünmekteyiz.

Anahtar kelimeler: YouTube, eksternal dakriyosistorinostomi, endoskopik dakriyosistorinostomi, nazolakrimal kanal tıkanıklıkları, LAP-VEGaS video değerlendirme aracı.

Tükenmez Dikmen N, Dikmen B. Eksternal ve endoskopik dakriyosistorinostomi cerrahisinde YouTube videolarının eğitim kalitesi Pam Tıp Derg 2023;16:13-22.

Introduction

Nasolacrimal duct obstructions are characterized by epiphora and recurrent acute dacryocystitis attacks. The treatment of chronic dacryocystitis is surgical, and the main purpose of surgery is to create a permanent passage between the lacrimal sac and the nasal cavity.

Dacryocystorhinostomy(DCR) has been used for over a century for the treatment of nasolacrimal duct obstruction. External DCR, first described by Toti in 1904 [1], remains the gold standard as a highly successful surgical method [2].

Caldwell [3] first described the endonasal (non-endoscopic) approach in 1893. However, this approach fell out of favor because of the difficult visualization of endonasal anatomy with instrumentation at the time. Modern endoscopic transnasal DCR was described by McDonogh and Meiring in 1989 [4].

Endoscopic approaches for the lacrimal system are increasingly used compared to previous years. Technological advances in endoscopic devices are increasing success in intranasal endoscopic DCR, and with increasing experience, success rates have recently begun to approach external DCR [5-7].

Radical changes took place in surgical training in the last two decades due to technological innovations. There are countless education applications, e-books, journals, guidelines, and videos available online. Many surgical procedure videos, which are easily accessible on the Internet, have become a preferred educational resource for most surgeons in preparation for surgery. Senior surgeons and residents frequently watch surgical videos available on the World Wide Web to review rarely performed surgeries, review some technical details, and see how other colleagues work [8, 9]. It has been reported that YouTube is the most frequently used video source to prepare for surgery and to watch rare surgery videos [10, 11].

Especially because of the COVID-19 pandemic, not performing elective surgeries in many clinics, postponing non-emergency operations and all physicians having to deal with only COVID-19 patients outside their own branches within the scope of combating COVID-19; especially, it has greatly hampered the surgical training of surgical residents. In this sense, online videos have actually become an even more important training material for assistants in terms of surgical training.

However, surgical videos on YouTube, the most used online video resource, are uploaded without quality assessment for peer review process or content [10, 11]. The popularity rate is not based on whether the surgical steps and methods in the videos are given accurately and clearly; It is determined according to non-academic parameters such as the number of views and number of comments. The quality of YouTube surgical video content has been questioned more recently as it is more widely used for educational purposes.

Despite its widespread use and popularity among physicians, a standard method for evaluating YouTube® medical videos for accuracy and reliability has not been established [10, 12]. However, an international committee recently published the Laparoscopic Surgery Video Training Guide (LAP-VEGaS) video assessment tool, a recommended checklist for obtaining high-quality educational videos that can improve surgical training [13, 14]. Subsequently, it was used and validated in many publications analyzing surgical videos on YouTube for quality assessment and reliability [14-17].

The aim of this study is to objectively analyze the quality of the videos on YouTube as an educational tool that has grown in popularity especially during the COVID-19 pandemic in learning how to perform dacryocystorhinostomy surgery, which is an important step in eye and ear nose throat surgery assistant training. In addition, it is to evaluate whether there is a difference between surgical videos explaining the endoscopic and external DCR approach in terms of surgical training quality in regards to the LAP-VEGaS video assessment tool.

Matherials and methods

A comprehensive search was carried out on YouTube (https://www.youtube.com), using the following terms "Dacryocystorhinostomy, DCR, External dacryocystorhinostomy, Endoscopic dacryocystorhinostomy." The YouTube database was queried by clearing the entire search history and without any user login. Videos shown for all keywords as of January 24, 2021 were sorted by view count from search settings, and those with 100 or more views were recorded. Ethics committee approval was not required as the study was in an observational design using only publicly available data.

Only surgical procedure videos were evaluated, excluding patient experience, TV shows, theoretical lessons, etc. Videos using non-English language, videos shorter than 1 minute, duplicated videos, videos about revision surgery and videos not related to the subject were determined as exclusion criteria (Figure 1). After the exclusion criteria, a total of 74 out of 108 videos, 27 of which were external DCR surgery videos and 47 of them were endoscopic DCR surgery videos, were included in the study. All selected videos were evaluated by an ophthalmologist (NTD) and ear, nose and throat (ENT) doctor (BD) experienced in DCR operations independently and blindly.

Video uploader (surgeon or others), surgeon (ophthalmologist or ENT doctor), surgical technique (external DCR or endoscopic DCR), number of views, video age (days from upload to January 24, 2021), number of comments, number of likes, number of dislikes, video duration (minutes), image quality were recorded. Additionally, presence of narrator's voice, music, and subtitles were noted.

Furthermore, view ratio (number of views/number of days since upload), like ratio (number of likes x 100/[like + dislike]), viewer interaction ([number of likes - number of dislikes] / total number of views x 100) and video power index (VPI; like ratio x view ratio/100), which shows the popularity of a video, defined by Erdem and Karaca [18] were calculated.

Assessment of educational quality

An international committee recently published the LAP-VEGaS video assessment tool, a recommended checklist for obtaining high-quality educational videos that can improve surgical training. LAP- VEGaS video assessment tool includes nine line items with every item being scored from 0 (the item not present in the video) to 2 (the item extensively presented in the video), with a total marking score ranging from 0 to 18. A total score of ≥11 at the LAP-VEGaS video assessment tool has been recommended to define a high-quality video (Table 1) [14].

Each video selected in our study was scored by 2 independent surgeons using the LAP-VEGaS surgical video quality assessment tool. According to the mean scores of the two surgeons, the videos were divided into 2 groups in terms of educational quality as high quality videos (≥11 LAP-VEGaS score) and low quality videos (<11 total LAP-VEGaS score).

Statistical analysis

All statistical analyses were carried out using SPSS (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). For all tests, $p<0.05$ was considered statistically significant. Frequency, percent, mean ± SD, median, and range were used to describe the data. Compliance to normal distribution was investigated with Kolmogorov–Smirnov and Shapiro Wilk tests. Normally distributed (parametric) independent groups were compared using independent groups t-test, while independent groups not showing normal distribution (nonparametric) were compared using the Mann-Whitney U test. Inter-rater reliability between physicians was calculated using Cohen's kappa coefficient. Categorical variables were compared using a chi-square test

Table 1. LAP-VEGaS video assessment tool

Item description	Not presented (0)	Presented, partially (+ 1)	Presented, completely (+ 2)
Authors and Institution information. Title of the video including name of the procedure and pathology treated	☐	☐	☐
Formal presentation of the case, including patient details and imaging, indication for surgery, comorbidities and previous surgery. Patient anonymity is maintained	☐	☐	☐
Position of patient, access ports, extraction site and surgical team	☐	☐	☐
The surgical procedure is presented in a standardised step by step fashion	☐	☐	☐
The intraoperative findings are clearly demonstrated, with constant reference to the anatomy	☐	☐	☐
Relevant outcomes of the procedure are presented, including operating time, postoperative morbidity and histology when appropriate	☐	☐	☐
Additional graphic aid is included such as diagrams, snapshots and photos to demonstrate anatomical landmarks, relevant or unexpected finding, or to present additional educational content	☐	☐	☐
Audio/written commentary in English language is provided	☐	☐	☐
The image quality is appropriate with constant clear view of the operating field. The video is fluent with appropriate speed	☐	☐	☐

Results

After entering our keywords on YouTube and determining a minimum limit of 100 views, 108 videos appeared in the first scan. After the predefined exclusion criteria, 34 videos were eliminated, and the remaining 74 videos were analyzed in detail (Figure 1).

After the LAP-VEGaS evaluation, 30 (40.5%) of the videos were found to be of high quality and 44 (59.5%) of them were of low quality. Of the 74 dacryocystorhinostomy videos, 27 were performed with external DCR technique, and 47 were performed as endoscopic DCR.

When low and quality videos were analyzed according to the type of surgery performed, it was seen that there was a statistically significant difference between the groups. Surgical videos describing the external DCR approach were found to contain statistically significantly more high-quality videos than endoscopic DCR videos according to the LAP-VEGaS video assessment tool (p=0.046) (Table 2). Supporting this, the average LAP- VEGaS score of external DCR videos was 10.65±2.98, and the mean LAP-VEGaS score of endoscopic DCR videos was 8.44±3.70, and the difference between them was statistically significant (p=0.009) (Table 3).

41 of the cases were performed by an ophthalmologist, 28 by an ENT surgeon, and in 2 cases by both an ENT and an ophthalmologist. There was no surgeon information in 3 of the videos. Of the 41 cases performed by ophthalmologists, 18 were low and 23 high quality videos. Of the 28 cases performed by ENT doctors, 21 were found to be of low quality, and 7 of them were of high quality videos. When we compared low and high quality videos to the surgeon who performed the surgery, there was a statistically significant difference between the surgical branches (p=0.017). Videos performed by ophthalmologists are statistically significantly higher quality videos according to LAP- VEGaS video assessment tool analysis (p=0.017).

The average scores of the 9 questions in the LAP- VEGaS video assessment tool are presented in Table 4. When we considered

Table 2. Comparison of low and high quality videos in regards to video parameters investigated

n (%) / Mean±SD		Low-quality videos (n:44, 59.5%) n (%) / Mean±SD	High-quality videos (n:30, 40%)	*p* value
Uploader	*Surgeon*	34 (59.6%)	23 (40.4%)	0.95
	Others	10 (58.8%)	7 (41.2%)	
Narrator's Voice	*No*	40 (85.1%)	7 (14.9%)	**<0.001**
	Yes	4 (14.8%)	23 (85.2%)	
Music	*No*	26 (57.8%)	19 (42.2%)	0.714
	Yes	18 (62.1%)	11 (37.9%)	
Image quality	*Low quality*	6 (54.5%)	5 (45.4%)	
	Medium quality	25 (62.5%)	15 (37.5%)	0.56
	High quality	13 (56.5%)	10 (43.4%)	
Subtitles	*No*	38 (62.3%)	23 (37.7%)	
	Yes	6 (46.2%)	7 (53.8%)	0.28
Type of surgery	*External DCR*	12 (44.4%)	15 (55.5%)	
	Endoscopic DCR	32 (68%)	15 (31.9%)	**0.046**
Surgeon performing the operation	*Ophthalmologist*	18 (43.9%)	23 (56.1%)	
	Otolaryngologist	21 (75%)	7 (25%)	**0.017**
	Both	2 (100%)	0 (0%)	
Number of view		13050.70±5100.70	16994.73±5824.84	0.278
Number of like		36.30±9.78	164.63±86.89	0.186
Number of dislike		3.70±1.21	5.70±2.1	0.366
Number of comment		5.77±2.79	16.97±12.46	0.435
Video length (sec.)		460.82±68.05	506.87±70.05	0.205
Time passed since video upload (days)		1996±171.32	1643.73±166.21	0.161
View ratio		5.086±1.644	9.168±2.891	**0.019**
Like/subscriber		0.240±0.006	0.107±0.046	0.086
Like/view		0.007±0.0015	0.009±0.0017	0.053
VPI		4.88±1.45	8.40±2.83	0.280
Like ratio		85.13±4.32	86.41±5.01	0.864
Viewer Interaction		0.684±0.157	0.942±0.174	0.60

VPI: Video Power Index

Table 3. Comparison of total LAP-VEGaS scores according to the type of surgery

	Surgical Type	Mean	Std. Deviation	Std. Error Mean	*p* value
Total LAP-VEGaS score	External DCR	10.65	2.987	0.575	**0.009**
	Endoscopic DCR	8.44	3.703	0.540	

Table 4. Average score and inter-observer kappa scores for each item in the LAP-VEGaS video assessment tool

LAP-VEGaS Items	Mean ± SD	Kappa coefficient (κ)
1-Authors and Institution information	1.29±0.726	0.741
2-Formal presentation of the case, including patient details and imaging, indication for surgery, comorbidities and previous surgery	0.32±0.639	0.758
3-Position of patient, access ports, extraction site and surgical team	1.36±0.660	0.534
4-The surgical procedure is presented in a standardised step by step fashion	1.79±0.397	0.506
5-The intraoperative findings are clearly demonstrated, with constant reference to the anatomy	1.11±0.820	0.544
6-Relevant outcomes of the procedure are presented, including operating time, postoperative morbidity and histology when appropriate	0.20±0.368	0.480
7-Additional graphic aid is included such as diagrams, snapshots and photos to demonstrate anatomical landmarks, relevant or unexpected finding, or to present additional educational content	0.35±0.666	0.647
8-Audio/written commentary in English language is provided	1.16±0.887	0.804
9-The image quality is appropriate with constant clear view of the operating field. The video is fluent with appropriate speed	1.60±0.503	0.640

all the questions one by one, it was observed that there was a moderate and significant agreement among the observers (kappa score ranged from 0.48 to 0.80 and $p<0.001$). The two observers made the same decision 97.6% when specifying low quality videos and 78.1% when selecting high quality videos. It was observed that there was a significant agreement between the two observers in the selection of low and high quality videos (kappa score 0.775 and $p<0.001$).

When we analyze the people who uploaded the videos; It was observed that 57 of 74 videos were uploaded by surgeons / doctors and 17 by other groups. When we analyzed the low and high quality videos according to the uploader, there was no statistically significant difference ($p=0.95$). Considering the presence of the narrator voice, it was significantly higher in the high-quality group compared to the low-quality group (85.2% vs. 14.8%, $p<0.001$) (Table 2).

The relationship of the technical properties of videos with respect to the low and high quality videos, according to the LAP-VEGaS video evaluation tool, is presented in Table 2. In regards to the interest of the viewers and technical video analysis only the view ratio was statistically significant in terms of low and high quality videos ($p=0.019$).

The most useful videos based on the criteria set in this study are summarized in Table 5 with URLs provided.

Discussion

Online surgical training videos have become an important source of information, presenting the steps and different techniques of surgical procedures from the surgeon's perspective. In this special period, we live in, the learning curve of surgical training can be shortened more effectively with visual didactic resources compared to written sources [19, 20]. Besides, social media is an undeniably important advertising portal for professional healthcare professionals. As a result, there has been a significant increase in the number of online surgical videos recently [21].

In the present study, we wanted to evaluate the quality of DCR videos on YouTube in terms of surgical training. For this purpose, we used the LAP-VEGaS video assessment tool, a validated evaluation tool that has been used in many publications before [14-17].

Of the 74 videos we reviewed, 44 are of low quality, and 30 are of high quality. Similar to our study, it has been shown in the literature that the education quality of online videos on YouTube is low. In a study by Luu et al. [16], they evaluated neck dissection videos on YouTube with LAP-VEGaS video assessment tool from an educational point of view and found only 3 of the 34 videos to be of high quality and the others of low to medium quality. In another study evaluating the educational quality of "YouTube" videos for facelift, it was found that YouTube

Table 5. The URLs and basic characteristics of the 10 most useful videos based on the LAP-VEGaS guidelines

Video Name/ Link	Surgeon	Total LAP-VEGaS Score	Surgical Type	Likes	Dislikes	Views
1-Endoscopic dacryocystorhinostomy https://www.youtube.com/watch?v=Ov6o5l45pS8	ENT	16	Endoscopic	22	2	984
2-EXTERNAL DACRYOCYSTORHINOSTOMY (DCR): AVOIDING COMPLICATIONS IN A COMPLICATED CASE- WATERING IN EYES https://www.youtube.com/watch?v=mZmdycDDWmA	EYE	16	External	9	0	507
3-External Dacryo-Cysto-Rhinostomy (DCR) by Dr Vidushi Sharma Pandey SuVi Eye Inst. Kota India https://www.youtube.com/watch?v=Csfldpc7k4c	EYE	14.5	External	168	4	19512
4-External Dacryocystorhinostomy (DCR) Full HD - Dr Akshay G. Nair at Advanced Eye Hospital (AEHI) https://www.youtube.com/watch?v=CG02p93Lonc	EYE	14.5	External	434	3	19387
5-Endoscopic DCR, 9mm LacriCATH®, by David I. Silbert, MD FAAP https://www.youtube.com/watch?v=WuukLpmiSxM	EYE	14.5	Endoscopic	22	3	4582
6-SurgTech Endonasal DCR https://www.youtube.com/watch?v=z7cbC7lMNfg	ENT	14	Endoscopic	55	0	7856
7-Endoscopic Dacryocystorhinostomy: Made It Easy	EYE	14	Endoscopic	24	2	2422
8-Endoscopic Ultrasonic Dacryocystorhinostomy for Recurrent Dacryocystitis following Rhinoplasty https://www.youtube.com/watch?v=3A7zN5TrigY	ENT	14	Endoscopic	5	0	1903
9-Bloodless Dacryocystorhinostomy (DCR) Surgery https://www.youtube.com/watch?v=_7qQLGpW9ro	EYE	13.5	External	2548	59	151745
10-External DCR - How to Get it Right? https://www.youtube.com/watch?v=mxEvnZvxYyM	EYE	13.5	External	533	30	60652

videos were insufficient in discussing the basic criteria, especially in terms of preoperative / postoperative points such as indications, patient selection and possible complications [22]. Chapman et al. [17] evaluated laparoscopic sleeve gastrectomy online videos using LAP-VEGaS guidelines, showing that 89% of the videos met less than half of all criteria.

Compared to the type of surgery performed, the proportion of high quality videos in external DCR videos was statistically significantly higher. When we compare low and high quality videos with the operating surgeon, the videos containing the surgeries performed by the ophthalmologists are statistically significantly higher quality videos compared to the videos

made by otolaryngologists compared to LAP-VEGaS video assessment tool. When we look at the comparative publications on DCR, ophthalmologists mostly prefer external DCR for nasolacrimal duct occlusions, while otolaryngologists prefer the endoscopic approach because they are more familiar with endoscopic instruments [23, 24]. According to the result of our study, we can say that external DCR videos on YouTube are better in terms of surgical training. As a matter of fact, when we look at the most useful links according to LAP-VEGAS criteria, we can see that there are more external DCR surgery videos (Table 5).

LAP-VEGaS video assessment tool takes 9 items into consideration while evaluating videos educationally. When we look at the ratio of the videos to present these titles sufficiently, it was observed that the videos mostly cover the 4th and 9th items (average score: 1.79±0.39, 1.60±0.50 respectively) The videos included the least information for the 6th and 2nd items (0.20±0.36 and 0.32±0.63, respectively). In the second question of the LAP-VEGaS video evaluation tool, the detailed presentation of the patient such as surgery indication, accompanying comorbidities, imaging results of the case, if any, are questioned. In the 6th item, the duration of the operation, postoperative morbidity and the relevant results of the procedure are expected. This is where the surgical videos on YouTube are lacking in surgical training. It is important not only the operation part, but to make the diagnosis correctly and to evaluate the results correctly, that is, to give pre-operative and post-operative processes as a whole. In literature, it has been emphasized that the same points are missing in the videos on YouTube [22, 25].

The presence of narrators' voice in videos was found to be significantly higher in high quality videos. The accompaniment of the narrator's voice in the surgery videos increases the training quality of the videos as it provides the audience with the opportunity to provide additional information about the surgery.

When we compared low and high quality videos according to their technical features, there was only a significant difference in the viewer ratio. There was no significant difference between the two groups in terms of the number of views, likes, dislikes, comments, video duration, video age, VPI, etc. Similarly, Deal et al. [26] evaluated 160 videos of cholecystectomy surgery, they could not find a relationship between high quality videos and the number of views or likes.

In studies conducted by different disciplines, there was no correlation between the educational quality of the videos and the popularity parameters in YouTube such as the number of views and the number of likes [14, 27, 28]. The fact that a video is watched too many times on YouTube or gets a lot of likes does not relate to the usefulness of the video or the objective quality. Especially for residents who are new to the subject, this situation should not be ignored as it causes incomplete and incorrect learning.

We have some limitations in this study. First, the video evaluation process is subjective. However, 2 different observers evaluated all the videos blindly and independently. This weak point was tried to be minimized by achieving a significant level of agreement among the observers. This study analyzed videos that were available on YouTube at a single time point, but due to the nature of YouTube content may change over time. Although the LAP-VEGaS video evaluation tool we used lastly was prepared primarily for laparoscopic surgeries as understood from its name; Afterwards, it was also preferred in publications examining the education quality of endoscopic and open surgeries and its validity was approved [15-17]. For this reason, we did not see any problem in using this scale in this study. Finally, while YouTube is not the primary surgical training platform for physicians, it is the most frequently referenced online video platform given its popularity and ease of access.

The LAP-VEGaS guidelines have been created to help standardize and validate surgical videos. In our study, we found that popular YouTube videos on DCR surgeries were significantly lacking in terms of case presentation, treatment options, intraoperative and postoperative complications, and all information about the healing process. However, we found that external DCR videos are more instructive than endoscopic videos in terms of training quality.

These videos, which are used as a source of information, should be recorded by more qualified professionals and their contents should

be presented objectively with all information about all treatment options, complications, and the healing process. In the future, we think that evaluating surgical videos on open access platforms such as YouTube with these guidelines before they are published and going through a standard review process may help increase the educational value of the video materials.

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Compliance with ethical standards: Ethics committee approval was not required as the study was in an observational design using only publicly available data.

Contributions of the authors to the article

N.T.D. and B.D. constructed the main idea and hypothesis of the study. N.T.D. and B.D. developed the theory and edited the material method section. N.T.D. and B.D. jointly evaluated the data in the results section. The discussion section of the article was written by N.T.D., which was reviewed, corrected and approved by B.D. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Surgery of head, neck, and skull base tumours during the COVID-19 pandemic: single center experience

COVID-19 pandemi sürecinde baş boyun ve kafa tabanı bölgesinde tümör cerrahisi: tek merkez deneyimi

Ergin Bilgin, Deniz Baklacı, Mustafa Dalgıç, Emrah Keskin

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Abstract

Purpose: The purpose of this study is to provide usable instructions on how to avoid delays in the diagnosis and treatment of head and neck tumors during COVID-19 pandemic.

Material and methods: Major head and neck surgeries performed in our clinic between March 11, 2020 and March 11, 2022 were included in the study. All patients underwent polymerase chain reaction testing for COVID-19 24-48 hours before surgery. A total of 134 patients (110 men, 24 women) were operated. While malignant diagnosis was made in the pathological examination in 79 patients, the diagnosis of benign tumor was made in 55 of our patients. A total of 167 procedures were applied.

Results: No COVID-19 related postoperative complications developed. Neck dissection was mostly performed in addition to the excision of the primary malignancy. Primary neck dissection was undertaken in six patients. Although most of the parotidectomy operations were performed for primary parotid masses, parotidectomy was required in addition to surgical excision in six patients due to primary skin tumors. Reconstruction was undertaken using free flaps in three patients. Local flaps were used for defect repair in other head and neck operations.

Conclusions: With rigorous preoperative COVID-19 screening and isolation, head and neck surgical procedures can be continued to avoid delay in diagnosis and treatment without compromising the risk of transmission of COVID-19 to patients or healthcare workers.

Key words: Pandemic, head and neck surgery, skull base surgery.

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Öz

Amaç: Bu çalışmanın amacı baş boyun tümörü tanılı hastalarda COVID-19 pandemisi sürecinde tanı ve tedavi gecikmelerini azaltmak amacıyla tecrübelerimizi ve önerilerimizi sunmaktır.

Gereç ve yöntem: Çalışmaya 11 Mart 2020 tarihi ile 11 Mart 2022 tarihleri arasında kliniğimizde gerçekleştirilen major baş boyun cerrahileri dahil edildi. Tüm hastalara ameliyattan 24-48 saat önce COVID-19 için polimeraz zincir reaksiyon testi yapıldı. Toplamda 134 hasta (110 erkek, 24 kadın) opere edilmiştir. 79 hastada patolojik incelemede malign tanı koyulmuşken, 55 hastamızda bening tümör tanısı koyulmuştur. Toplamda 167 işlem uygulandı.

Bulgular: COVID-19 ilişkili postoperatif komplikasyon gelişmedi. Boyun diseksiyonu en sık primer malignitenin eksizyonuna ek olarak yapıldı. Primer boyun diseksiyonu ise altı hastada yapıldı. Parotidektomi cerrahisi daha çok primer parotis kitlelerine yönelik yapıldı ancak altı hastada primer cilt tümörüne ek olarak yapıldı. Üç hastada serbest flap ile rekonstrüksiyon yapılırken diğer tüm hastalarda lokal flapler kullanıldı.

Sonuç: Titiz preoperatif COVID-19 taraması ve izolasyonu ile COVID-19'un hastalara veya sağlık çalışanlarına bulaşma riskini tehlikeye atmadan tanı ve tedavide gecikmeyi önlemek için baş ve boyun cerrahi prosedürlerine devam edilebilir.

Anahtar kelimeler: Pandemi, baş boyun cerrahisi, kafa tabanı cerrahisi.

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Ergin Bilgin, Asst. Prof. Bulent Ecevit University, Otorhinolaryngology and Head and Neck Surgery Clinic, Zonguldak, Turkey, e-mail: erginbilgin67@hotmail.com (https://orcid.org/0000-0001-7191-6209)

Deniz Baklacı, Assoc. Prof. Bulent Ecevit University, Otorhinolaryngology and Head and Neck Surgery Clinic, Zonguldak, Turkey, e-mail: doktorent@gmail.com (https://orcid.org/0000-0001-8449-4965)

Mustafa Dalgıç, M.D. Bulent Ecevit University, Otorhinolaryngology and Head and Neck Surgery Clinic, Zonguldak, Turkey, e-mail: dalgic_816@hotmail.com (https://orcid.org/0000-0003-1886-8994) (Corresponding Author)

Emrah Keskin, Asst. Prof. Bulent Ecevit University, Brain and Nerve Surgery Clinic, Zonguldak, Turkey, e-mail: drkeskinemrah@gmail.com (https://orcid.org/0000-0001-5326-741X)

Introduction

The COVID-19 outbreak was declared a pandemic in March 2020 [1]. The rapid progress of the COVID-19 pandemic and the disease becoming a healthcare priority have resulted in changes in the health systems of countries. This situation has adversely affected patients with head and neck tumors. In this process, delays have occurred the diagnosis and treatment of patients with cancer. Due to these delays, the disease has progressed to further stages and the treatment process has been interrupted in some patients [2]. The high risk of airborne transmission of COVID-19 through aerosols also poses a challenge in the surgery of patients with head and neck tumors [3]. In the early days of the pandemic, when The polymerase chain reaction (PCR) testing opportunities were limited and there was no vaccine available, some authors suggested applying chemoradiotherapy in cases where surgery and chemoradiotherapy would have had similar benefits [4]. In the current study, we share our experience in major head and neck surgical operations performed at our clinic during the pandemic and how the surgical team was protected from contracting COVID-19.

Material and methods

This retrospective study was conducted in a single center and covered major head and neck surgical operations performed at the Otorhinolaryngology Clinic of Zonguldak Bulent Ecevit University between March 11, 2020, and March 11, 2022. Patients who received only chemotherapy or radiotherapy were not included in the study. This study was approved by the Bulent Ecevit University Clinical Research Ethics Committee.

A total of 134 patients aged over 18 years, who underwent major head and neck surgery for therapeutic purposes, were included in the sample. Procedures such as direct laryngoscopy, lymph node excision, and biopsy were not included in the study. The polymerase chain reaction PCR test for COVID-19 was performed on all the patients at 24-48 hours before surgery. The operations were performed by the same surgical team using second-level personal protective equipment (N95 masks, safety glasses, visors, gowns, and double gloves).

The patients were questioned for signs of fever, cough, shortness of breath, or upper respiratory tract infection at the time of first presentation. Patients who did not require emergency surgery and those with COVID-19 symptoms were re-evaluated after the PCR test was performed in accordance with the infection protocols and the isolation process was completed. One day before surgery, the PCR test was applied to the patients who did not have any COVID-19 symptoms, and surgery was performed if the test result was negative.

The patients with head and neck malignancies who were positive for COVID-19 according to the PCR test and did not require emergency surgery were scheduled for surgery within four weeks at the latest.

Results

A total of 134 patients, 110 (81.9%) males and 24 (17.9%) females were included in the study. The mean ages males and females were 47.14±9.88 and 53.45±9.57 years, respectively. 79 of the pathologies (58.9%) were malignant while remaining 55 (41.1%) were benign. A total of 167 procedures were applied. Distribution of benign and malign pathologies in each group were given in Table 1.

Neck dissection was mostly performed in addition to the excision of the primary malignancy. Primary neck dissection was undertaken in six patients. Although most of the parotidectomy operations were performed for primary parotid masses, parotidectomy was required in addition to surgical excision in six patients due to primary skin tumors. Reconstruction was undertaken using free flaps in three patients; one with the carcinoma of the floor of the mouth and two with skin carcinoma in the preauricular region. Local flaps were used for defect repair in other head and neck operations.

Among the five patients who underwent maxillectomy, subtotal maxillectomy was performed with the open technique in one patient, inferior maxillectomy with the open technique in two patients, and endoscopic medial maxillectomy in the remaining two patients.

During the 30-day postoperative period one patient who had undergone total laryngectomy died due to a pulmonary hemorrhage.

Table 1. Distribution of major head, neck, and skull base operations performed at our clinic between March 2020 and March 2022

Surgery	Number
Neck dissection	38
- Bilateral	22
- Unilateral	16
Parotidectomy	32
- Superficial	20
Pleomorphic adenoma	15
Warthin tumor	5
- Total	12
Mucoepidermoid carcinoma	4
Malign melanoma (metastasis of skin melanoma)	4
Adenoid cystic carcinoma	2
Squamous cell carcinoma	2
Total thyroidectomy	12
Papillary carcinoma	6
Hurtle Cell Carcinoma	3
Multinodular Goiter	3
Laser cordectomy Glottic larynx carcinoma	12
Lip cancer surgery Lower Lip Carcinoma	9
Submandibular gland excision	9
Sialolithiasis	7
Adenoid cystic carcinoma	2
Skin cancer excision	8
Squamous cell carcinoma	5
Basal cell carcinoma	2
Malign melanoma	1
Total laryngectomy Larynx carcinoma	6
Maxillectomy	5
Squmaous cell carcinoma	4
Adenoid cystic carcinoma	1
Cordectomy with cold dissection Glottic larynx carcinoma	4
Auricular cancer excision	4
Squamous cell carcinoma	3
Basal cell carcinoma	1
Thyroid lobectomy Benign follicular neoplasm	3
Floor of the mouth cancer surgery Squamous cell carcinoma	3
Paranasal tumors surgery Inverted papilloma	3
Tongue cancer surgery Squamous cell carcinoma	3
Schwannoma excision from the neck	3
Buccal carcinoma excision	3
Thyroglossal cyst excision	3
Cerebellopontine angle tumor excision Acoustic neurinoma	2
Glomus tympanicum excision	2
Neck sarcoma excision	1
Glomus caroticum excision	1
Facial hemangioma excision	1
Total	**167**

In another patient who underwent glomus caroticum surgery, a cerebrovascular event due to thromboembolism was observed in the postoperative period. Reoperation was planned in one patient due to free flap dehiscence in the postoperative period. Another patient that underwent total thyroidectomy required urgent surgery again in the postoperative period due to a life-threatening massive hematoma in the neck. No significant morbidity was observed in the remaining patients during the postoperative 30-day period.

Discussion

As in other surgical fields, the pandemic has had some effects on head and neck surgery. In most centers, there has been a decrease in the number of operations due to the lack of beds and operating rooms, concerns about the risk of transmission, and lack of healthcare personnel [5, 6]. This has caused delays in the diagnosis and treatment of many patients.

During the pandemic, there have also been some changes in the choice of treatment options in head and neck malignancies. Non-surgical options have come to the fore in cases where chemotherapy or radiotherapy is possible. In a study conducted with 1,137 patients with a recent diagnosis of head and neck malignancies, it was stated that more non-surgical treatments were undertaken, especially in the presence of oropharynx and larynx malignancies [7]. However, we consider that with the widespread use of vaccines and infection control, surgery can be safely performed for head and neck malignancies during the pandemic, although it is a longer and more complex process compared to the pre-pandemic period.

Some guidelines recommend two separate PCR tests in surgical patients in the preoperative period [8-10], while others emphasize that a single PCR test should be performed in patients 24 hours before surgery [11, 12]. In our clinic, surgical procedures were planned by taking a single PCR sample from all the patients 24 hours before surgery.

Except in cases requiring emergency surgery, such as dyspnea and hemorrhage, it is recommended to perform surgery within four to six weeks after diagnosis in patients with high-grade squamous cell carcinomas (oral cavity, oropharynx, larynx, hypopharynx, and nasopharynx), tumors that may threaten the airway, high-grade and progressive salivary gland tumors, T3 and T4 stage malignant melanomas, locally advanced skin cancers, and thyroid malignancies invading the airway [13-15]. According to some guidelines, surgery planned to be performed for reasons such as low-grade aerodigestive system squamous cell carcinomas, low-grade and non-progressive salivary gland malignancies, skin malignancies without progression and metastasis, well-differentiated thyroid malignancies (papillary cell carcinoma and follicular cell carcinoma), and superficial larynx malignancies can be delayed for more than six weeks [16-18]. In our clinic, the patients diagnosed with head and neck malignancies that did not require emergency surgical intervention were scheduled within a maximum four weeks of diagnosis.

In patients scheduled for surgery that may lead to aerosol formation, it is recommended that the surgical team use PPAR or N95 masks, safety glasses, gowns, foot protection, and gloves [12, 19]. In our clinic, all the surgical operations were performed by the same surgical team using second-level personal protective equipment (N95 masks, safety glasses, visors, gowns, and double gloves).

In conclusion head and neck malignancies are diseases that may require emergency intervention in some cases, and timing is essential in the course of the disease. The surgical team is at high risk of transmission due to their proximity to the respiratory tract during the operation. Therefore, the examination and treatment of patients should be undertaken by taking the necessary precautions required by the pandemic conditions. The treatment of high-grade malignancies should not be delayed. Performing a preoperative PCR test for COVID-19, use of personal protective equipment, and vaccination are recommended for infection control.

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

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This study has previously been presented at 16th Turkish Rhinology Congress, 4th National Head and Neck Surgery Congress and 1st Pediatric otorhinolaryngology congress in 13th May 2022.

Ethics committee approval: This study was approved by the Bulent Ecevit University Clinical Research Ethics Committee (date: 2021 and number: 11).

Authors' contributions to the article

D.B. has constructed the main idea and hypothesis of the study. M.D. has developed the theory and arranged/edited the material and method section. E.B. and E.K. have done the evaluation of the data in the Results section. Discussion section of the article. Written by M.D. and D.B. has reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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The Effect of gluteus medius and minimus muscle thickness on developmental hip dysplasia up to three months of age.

Gluteus medius ve minimus kas kalınlığının üç aya kadar gelişimsel kalça displazisi üzerine etkisi.

Aydan Arslan, Bahadır Balkanlı

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Abstract

Purpose: To investigate whether there is a difference in the gluteus medius and minimus muscle thicknesses between the cases with Graf method type IIa and normal subjects.

Material and methods: A total of 200 cases, 1-3 months old infants, who applied to our hospital for developmental hip dysplasia ultrasound scanning between January 2021 and March 2021 were included in our study. The cases were evaluated with a standard coronal plane with a 9-12 Mhz linear array probe according to the Graf method at the level of the triradiate cartilage by the same radiologist. The largest gluteus medius and minimus muscle thickness were measured.

Results: The female to male ratio was 0.9. and the mean age was 45.9±13.7 days. The present study had 159 (79.5%) Graf type I (Group A) and 41 newborns (20.5%) with Graf type IIa (Group B). Demographic and clinical characteristics were similar in both groups (p>0.05). The mean lengths of the gluteus medius and minimus muscles were similar in newborns with Graf type I and IIa (p=0.975 and p=0.069, respectively). A significant difference was found in the mean length of the gluteus minimus muscle between male and female newborns (p=0.001). The muscle length was statistically shorter in the female newborns than the male newborns (3.4±0.5 mm vs. 3.6±0.5 mm).

Conclusion: Since there was no difference in gluteal muscle thickness between mature and immature hips; Gluteal muscle lengths are not a diagnostic landmark in the hip ultrasound scan.

Key words: Developmental dysplasia of hip, hip ultrasound, gluteus medius muscle, gluteus minimus muscle, Graf method.

Arslan A, Balkanli B. The Effect of gluteus medius and minimus muscle thickness on developmental hip dysplasia up to three months of age. Pam Med J 2023;16:29-36.

Öz

Amaç: Graf yöntemi tip IIa olguları ile normal olgular arasında gluteus medius ve minimus kas kalınlıkları açısından fark olup olmadığını araştırmaktır.

Gereç ve yöntem: Ocak 2021-Mart 2021 tarihleri arasında gelişimsel kalça displazisi ultrason taraması için hastanemize başvuran, yaş aralığı 1-3 aylık arası olan, toplam 200 olgu çalışmamıza dahil edildi. Olgular aynı radyolog tarafından, Graf yöntemine göre 9-12 Mhz lineer array prob ile standart koronal düzlemde triradiat kıkırdak seviyesinde değerlendirildi. En geniş gluteus medius ve minimus kas kalınlığı ölçüldü.

Bulgular: Kadın erkek oranı 0,9'du ve ortalama yaş 45,9±13,7 gündü. Bu çalışmada 159 (%79,5) Graf tip I (Grup A) ve 41 (%20,5) Graf tip IIa (Grup B) yenidoğan vardı. Demografik ve klinik özellikler her iki grupta benzerdi (p>0,05). Graf tip I ve IIa olan yenidoğanlarda gluteus medius ve minimus kaslarının ortalama kalınlıkları benzerdi (sırasıyla p=0,975 ve p=0,069). Erkek ve kız yenidoğanlar arasında gluteus minimus kasının ortalama kalınlığında anlamlı bir fark bulundu (p=0,001). Kas kalınlığı, kız yenidoğanlarda erkek yenidoğanlara göre istatistiksel olarak daha kısaydı (3,4±0,5 mm'ye karşı 3,6±0,5 mm).

Sonuç: Matür ve immatür kalçalar arasında gluteal kas kalınlıkları açısından fark olmadığı için; gluteal kas uzunlukları, kalça ultrason taramasında tanısal bir nirengi noktası değildir.

Anahtar kelimeler: Gelişimsel kalça displazisi, kalça ultrasonu, gluteus medius kası, gluteus minimus kası, Graf metod.

Arslan A, Balkanlı B. Gluteus medius ve minimus kas kalınlığının üç aya kadar gelişimsel kalça displazisi üzerine etkisi. Pam Tıp Derg 2023;16:29-36.

Aydan Arslan, M.D. University of Health Sciences İstanbul Ümraniye Training and Research Hospital, Department of Radiology, Istanbul, Turkey, e-mail: arslanaydan@gmail.com (https://orcid.org/0000-0002-6073-1927) (Correspondence Author)

Bahadır Balkanlı, Specialist, Zonguldak Atatürk State Hospital, Department of Orthopedics and Traumatology, Zonguldak, Turkey, e-mail: balkanlibahadir@gmail.com (https://orcid.org/0000-0003-4501-9090)

Introduction

Developmental dysplasia of the hip (DDH) also known as anatomically abnormal development of the femoral head and acetabulum varies in severity from mild dysplasia to complete hip dislocation [1]. DDH includes not only congenital malformations but also disruptions in development.

Developmental hip dysplasia is usually in the early neonatal period with some positive physical examination findings (including the Ortolani test, Barlow maneuvers, and Galeazzi sign) and clinical history (female sex, gestational age, firstborn baby, family history, breech presentation, oligohydramnios, limitation in abduction, foot anomaly) and a definitive diagnosis is made by hip ultrasound in the first 6 months. The Graf method is an ultrasound classification that objectively evaluates hip morphology worldwide, including the alpha and beta angles. This method, described by Graf R. [2] in 1980, is used to distinguish between normal and luxated joints in ultrasound. The neonatal hip is evaluated by measuring two angles formed by three lines drawn from three points, namely the lower limb of the os ilium, the bottom of the acetabulum, and the center of the labrum. As a rule, the angle formed by the acetabular bony roof to the vertical cortex of the iliac bone is the alpha angle, which mainly determines the hip type. The beta angle, also known as cartilaginous roof angle, determines hip subtype.

The incidence of DDH varies from 1.5 to 25 per 1000 live births, although it differs between populations [3]. In studies conducted with neonatal hip ultrasound in Turkey, the incidence was reported to be between 0.5% and 15% [4]. Differences between countries are attributed to genetic, cultural and lifestyle factors.

In Turkey, selective imaging screening of infants with risk factors or physical examination findings (positive or equivocal) is recommended in the first 3-6 weeks of their life by the Ministry of Health. For this purpose, in cases where treatment is required, initiating early and appropriate treatments reduces the number of surgical treatments for hip dislocation and minimizes possible complications [5]. In addition, hip ultrasonography was performed on all infants as a routine screening program at our hospital.

The gluteal muscles are stabilizers of the hip joint and play an important role in knee and pelvic stability [6]. The changes that occur in the gluteus medius-minimus muscles in patients with developmental dysplasia of the hip (DDH) are not fully understood. The aim of our study was to examine whether there is a difference in the gluteus medius and minimus muscle thicknesses between the cases with type IIa developmental dysplasia according to the Graf method and normal cases in the ultrasound imaging performed for screening in the first 3 months.

Material and methods

Infants aged 1-3 months, who were admitted to our hospital for developmental dysplasia ultrasound screening between January 2021 and March 2021, were included in our study. A total of 400 hip assessments were performed in 200 cases. Demographic information of the patients, number of children, family history, type of delivery and birth weight were collected.

The cases were evaluated using ultrasound (Siemens Healthineers, Acuson S3000, Erlangen, Germany) by the same radiologist who has seven years of general ultrasound and hip ultrasound experience. The cases detected as type IIa according to the Graf method were called for ultrasound control one month later.

The cases were evaluated with a standard coronal plane with a 9-12 Mhz linear array probe according to the Graf method. Ultrasound examination was performed in the transverse view with the hip flexed at 90°. Important anatomical structures (center of labrum, lower extremity of iliac bone, bony edge of acetabulum, femoral head, and neck) were identified. Parents were allowed to stay with their babies to calm them down. The alpha (α) and beta (β) angles were calculated according to the Graf method.

The alpha angle greater than 60° and the beta-angle below 55° are classified as normal hip (type I); these patients require no treatment. The alpha-angle 50-60° is classified as an immature hip (type IIa) up to the age of 3 months (13 weeks); these patients require follow-up. The

largest gluteus medius and minimus muscle thicknesses were identified in the coronal plane at the level of the triradiate cartilage (Figure 1).

This study was approved by the Zonguldak Bülent Ecevit University Ethics Committee.

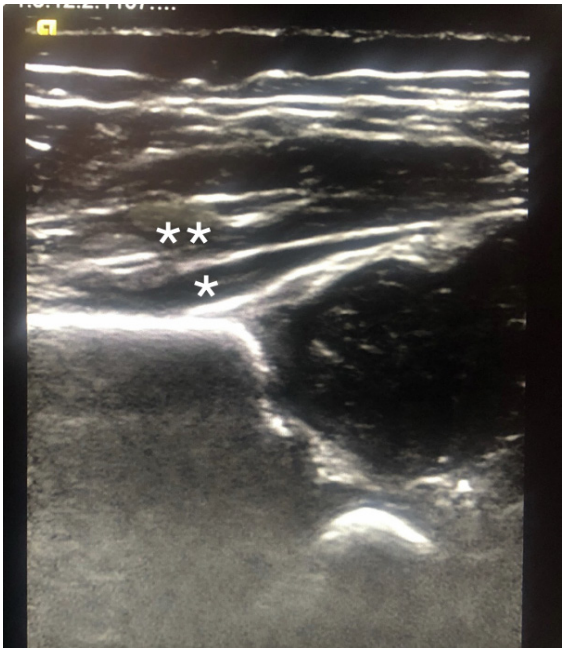

Figure 1. The view of gluteus medius (**) and minimus (*) muscle in hip ultrasound examination at coronal plane

Statistical analysis

Descriptive statistics were given as mean ± standard deviation and median with minimum-maximum values for continuous variables depending on their distribution. Numbers and percentages were used for categorical variables. The normal distribution of the numerical variables was analyzed by the Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests.

The Independent Samples t-test was used in comparing two independent groups where numerical variables had a normal distribution. The power analysis was calculated using G*Power version 3 based on independent two samples (alpha: 0.05, power: 80%). The Mann-Whitney U test was applied for variables without normal distribution.

Pearson Chi-Square and Fisher's Exact tests were used in 2x2 tables to compare the differences between categorical variables.

For statistical analysis, "Jamovi project (2020), Jamovi (Version 1.8.2) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.14.1.0) (Retrieved from https://jasp-stats.org) were used. The significance level (p-value) was set at 0.05 in all statistical analyses.

Results

There were 200 newborns in the study with a female-to-male ratio of 0.9. The mean age at the diagnosis was 43.9±13.7 days. We detected a positive family history in 3.0% of the cases. The demographic and clinical characteristics of the newborns are given in Table 1. In the study group, there were 159 (79.5%) and 41 newborns (20.5%) with Graf types I (Group A) and IIa (Group B). The mean age at the diagnosis was 47.2±13.5 days in Group A and 40.8±13.5 days in Group B. The difference in mean age at the diagnosis was significant (p=0.008). Other demographic and clinical characteristics were similar (p>0.05) (Table 1) (Figure 2, 3).

Calculating each side of the thicknesses separately, the mean length of the gluteus medius and minimus muscles were similar in newborns with Graf type I and IIa (p=0.975 and p=0.069). The mean alpha angle of the hips (each side counted separately) within Group A was 65.9±2.7°. The mean alpha-angle in Group B was 58.4±1.0°. The difference was statistically significant (p<0.001). We also detected a significant difference in the mean beta angle of the hips between the groups (p<0.001) (Table 2).

By calculating each side of the lengths separately, the mean length of the gluteus medius muscle was 4.6±0.8 mm in the male newborns and 4.4±0.8 mm in the female newborns (p=0.089). We detected a significant difference in the mean length of the gluteus minimus muscle between the male and female newborns (p=0.001). The muscle length was statistically shorter in the female newborns than the male newborns (3.4±0.5 mm vs. 3.6±0.5 mm) (Table 3).

Although there was no difference in the mean alpha angle of the hips (each side counted separately) between the male and

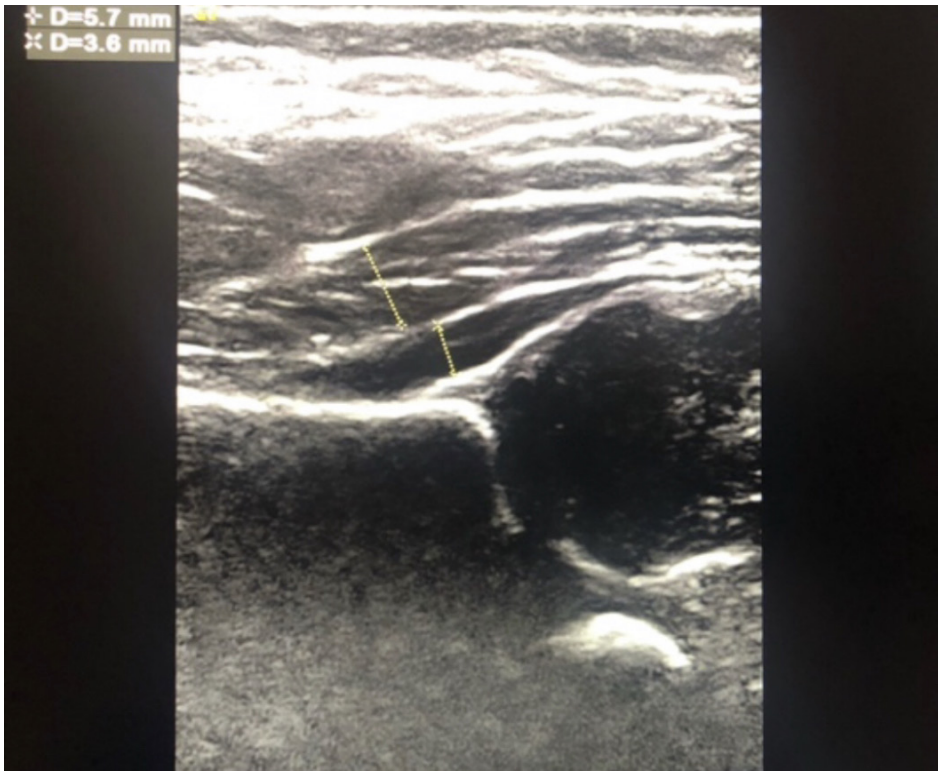

Figure 2. A 37-day age-old girl, Graf method type 1 (mature) hip ultrasound image
alpha angle: 67° beta angle: 48°
gluteus medius muscle thickness: 5.7 mm
gluteus minimus muscle thickness: 3.6 mm

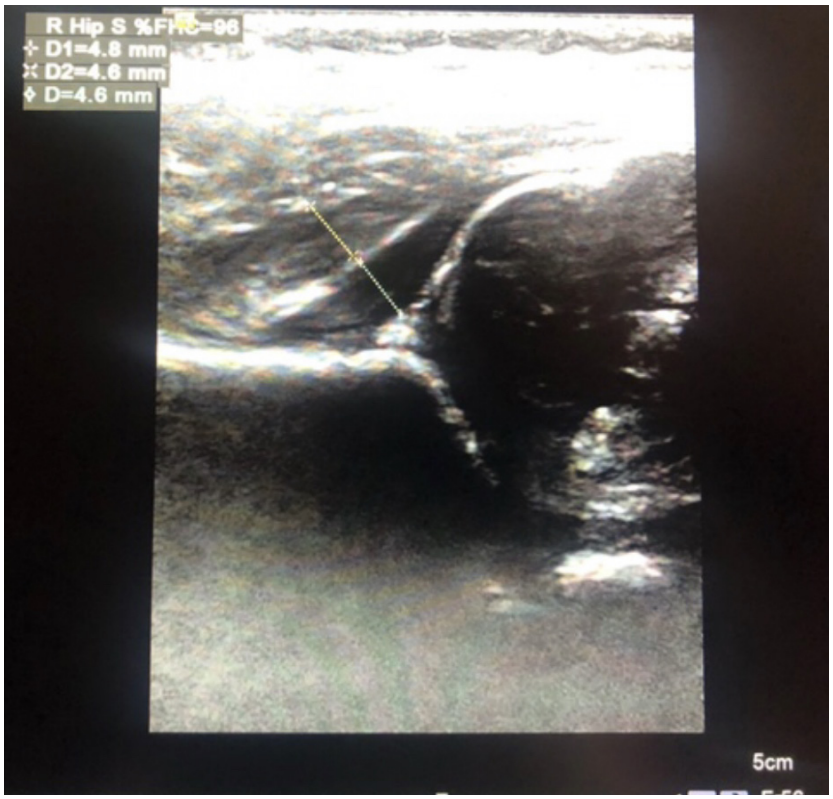

Figure 3. A 45-day age-old girl, Graf method type 2a (immature) hip ultrasound image
alpha angle:56° beta angle: 54°
gluteus medius muscle thickness: 4.8 mm
gluteus minimus muscle thickness: 4.6 mm

Table 1. Demographic and clinical characteristics of the newborns with developmental dysplasia of the hip (n=200)

		Graf type		
	Overall	**Group A (Type I) (n=159)**	**Group B (Type IIa) (n=41)**	***p*-value**
Age at the diagnosis (day) †	45.9±13.7	47.2±13.5	40.8±13.5	**0.008***
Sex ‡				
Male	105 (52.5)	85 (53.5)	20 (48.8)	0.719***
Female	95 (47.5)	74 (46.5)	21 (51.2)	
Birth order §	2.0 [1.0-8.0]	2.0 [1.0-8.0]	2.0 [1.0-5.0]	0.997**
Positive family history ‡	6 (3.0)	4 (2.5)	2 (4.9)	0.605***
Birth weight (g) †	3,238.4±431.8	3,244.1±447.2	3,216.0±370.3	0.680*
Birth weight groups ‡				
<4000 g	193 (96.5)	152 (95.6)	41 (100.0)	0.348***
≥4000 g	7 (3.5)	7 (4.4)	0 (0.0)	
Type of delivery ‡				
0 Cesarean section	48 (24.0)	36 (22.6)	12 (29.3)	0.496***
1 Spontaneous vaginal delivery	152 (76.0)	123 (77.4)	29 (70.7)	

†: mean ± standard deviation, ‡: n (%), §: median [min-max]
US: ultrasound
*. Independent samples t-test
**. Mann Whitney U test
***. Pearson Chi-square test / Fisher exact test

Table 2. Morphometric features of the bilateral hips in the newborns with Graf type 1a and 2a

	Graf method type		
	1a (n=159)	**2a (n=41)**	***p*-value**
Length of gluteus medius muscle (mm) †	4.5±0.8	4.5±0.8	0.975
Length of gluteus minimus muscle (mm) †	3.5±0.5	3.6±0.6	0.069
Alpha angle (°) †	65.9±2.7	58.4±1.0	<0.001
Beta angle (°) †	44.5±4.4	47.0±4.9	<0.001

†: mean ± standard deviation
Independent samples t-test

Table 3. Comparison of the morphometric features of the bilateral hips based on the sex distribution

	Bilateral hips		
	Male newborn (n=105)	**Female (n=95)**	***p*-value**
Length of gluteus medius muscle (mm) †	4.6±0.8	4.4±0.8	0.089
Length of gluteus minimus muscle (mm) †	3.6±0.5	3.4±0.5	0.001
Alpha angle (°) †	64.7±4.0	64.1±3.8	0.097
Beta angle (°) †	44.5±4.7	45.7±4.3	0.008

†: mean ± standard deviation
Independent samples t-test

female newborns (p=0.097), the beta angle was significantly lower in the male newborns than the female newborns (44.5±4.7° vs. 45.7±4.3°, p=0.008).

By calculating each side of the lengths separately, we detected no significant difference in the mean lengths of the gluteus medius and minimus muscles between the newborns with ≤42 days and >42 days (p=0.627 and p=0.119) (Table 4).

The mean alpha angle of the hips (each side counted separately) within newborns with ≤42 days was 63.6±3.9°. The mean alpha angle in newborns with >42 days was 65.1±3.8°. The difference was statistically significant (p<0.001) (Table 4). There was no significant difference in the mean beta angle of the hips between the newborns (p=0.065).

Post hoc power analysis was done using G*Power version 3, to interpret the generalization of results. Effect size and power values were determined based on independent two samples t-test (alpha: 0.05, sample sizes 159 and 41). Comparison of length of gluteus minimus muscle has 0.181, 0.06, comparison of alpha angle has 3.683, 1, comparison of beta angle has 0.536, 0.678 as effect size and power values correspondingly.

Table 4. Comparison of the morphometric features of the bilateral hips based on the age of the newborns as ≤42 and >42 days

	Age		
	Newborns with ≤42 days (n=94)	**Newborns with >42 days (n=106)**	**p-value**
Length of gluteus medius muscle (mm) †	4.5±0.8	4.5±0.8	0.607
Length of gluteus minimus muscle (mm) †	3.6±0.5	3.5±0.5	0.119
Alpha angle (°) †	63.6±3.9	65.1±3.8	<0.001
Beta angle (°) †	45.5±4.2	44.6±4.9	0.065

†: mean ± standard deviation
Independent samples t-test

Discussion

The analysis of the data collected demonstrated the mean diameters of the gluteus medius and minimus muscles were similar in newborns with Graf type I and IIa in our study sample. Since there is no similar study in the literature; considering our data, we observed the gluteus muscle lengths are not a diagnostic landmark in the first 3 months of hip ultrasound screening. In a study conducted by Liu et al. [7] in 2012, it was observed that the length of the gluteus medius muscle decreased by 8-11% in a total of 19 adult patients aged 35-61 years with unilateral developmental dysplasia of the hip. The causes of gluteus medius muscle atrophy includes late-stage joint pathology, and the femur is displaced proximally. Unlike our study, the CT diagnostic method was used, and we had an adult patient sample group.

The US is the primary imaging tool for the evaluation of DDH in infants. Some type IIa, immature hips improved to type I during follow-up. Graf type IIa hips often have the potential to mature until 12 weeks of age. However, studies have shown that newborn girls with type IIa immature hips have a higher rate of treatment than boys [8]. In our study, only the cases with the first examination were included in the study; follow-up studies were excluded from the study.

Female gender, normal birth, first birth order, positive family history and birth weight were not found to correlate statistically associated with increased risk of hip immaturity in the present study, in a prospective, randomized study of 15529 newborn infants; There was no statistically significant difference between the two groups all neonates-neonates belonging to the risk groups) in terms of late diagnosis (follow-up period between 6-11 years) [9].

Gluteal muscles originate from the gluteal surface of the ilium. The gluteal muscles provide abduction of the femur and prevent pelvic drop on the opposite side during walking. The gluteal muscles have an important place in lateral hip stability and lower extremity function. The thickness of gluteal muscles can be reliably evaluated using US [10, 11]. In our study, the mean gluteus medius muscle diameter was 4.5±0.8 mm, and the minimus diameter was 3.6-3.5±0.5 mm. Furthermore, gluteus minimus was statistically shorter in female newborns than the male newborns.

Our study had some limitations. Firstly, our study includes a relatively small number of patients (200 cases) and the presence of Graf type II patients whose follow-up information was not available. Some of these immature Graff type II cases highly likely have the potential to mature.

Ultrasound is an operator-dependent imaging method. However, all examinations were evaluated by the same radiologist under similar conditions. The interobserver and intraobserver reproducibility could not be evaluated. One of the limitations was that it was a single-center study. Our results should be supported by multicenter prospective studies with a large patient population.

The strengths of our work; It is the first study in the literature to give average gluteus muscle lengths in infants up to the first 3 months; It also emphasizes that it is not necessary to use the gluteus muscle thickness as a landmark in routine DDH screening program.

In conclusion, this study provides preliminary data on the mean gluteus muscle lengths and the absence of differences in the gluteus medius and minimus muscle thicknesses between mature and immature hips.

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Authors contribuitions

Planning methodology to reach the conclusion: A.A.

Organising and supervising the course of the project or the article and taking the responsibility: A.A. and B.B.

Reviewing the article before submission not only for spelling and grammar but also for its intellectual content: A.A. and B.B.

Research Article

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Scimitar syndrome with different features in pediatric patients: a single-center experience

Çocuk hastalarda farklı özellikleriyle Scimitar sendromu: tek merkez deneyimi

Ali Orgun, Birgül Varan, İlkay Erdoğan, N.Kürşad Tokel, Hazım Alper Gürsu, Murat Özkan, Sait Aşlamacı

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Abstract

Purpose: Scimitar syndrome is a rare congenital cardiac anomaly in which pulmonary veins are drained to the inferior vena cava (IVC) instead of the left atrium and it is often associated with additional cardiac and pulmonary anomalies. In this article, the different clinical features of pediatric patients with Scimitar syndrome are reported.

Material and methods: All patients with scimitar syndrome were diagnosed in our hospital between 2000 and 2020. The clinical findings, angiographic and surgical procedures, and follow-up of the patients are evaluated.

Results: Five pediatric patients aged between 1.5 months and 10 years were diagnosed as Scimitar syndrome. All patients were symptomatic. One patient had cor triatriatum and pulmonary venous stenosis, one patient had left atrial isomerism and absence of the IVC (azygous continuity), and another patient had coarctation of the aorta. One patient had dual drainage: the IVC and left atrium with meandering pulmonary veins, which we determined as a Scimitar variant. One infant patient with pulmonary hypertension and two patients with pulmonary to systemic flow ratio (Qp/Qs)>1.5 were treated surgically with the reanastomosis technique. Vascular embolization of the aortopulmonary collaterals was performed in two patients using vascular plugs, coils, and onyx.

Conclusion: Treatment should be planned individually in this syndrome due to Scimitar syndrome has a wide range of anatomic and clinical variations.

Key words: Aortopulmonary collateral, children, meandering pulmonary veins, Scimitar syndrome.

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Öz

Amaç: Scimitar sendromu, pulmoner venlerin sol atriyum yerine inferior vena kavaya (IVC) açıldığı ve sıklıkla ek kardiyak ve pulmoner anomalilerle ilişkili olduğu nadir görülen bir doğuştan kalp anomalisidir. Bu yazıda farklı klinik özellikleri olan Scimitar sendromlu pediyatrik hastalar tartışılmıştır.

Gereç ve yöntem: Hastanemizde 2000-2020 yılları arasında Scimitar sendromlu tanısı alan olgular çalışmaya alındı. Hastaların klinik bulguları, anjiyografik ve cerrahi işlemler ve takipleri değerlendirildi.

Bulgular: Çalışma süresi içinde yaşları 1,5 ay ile 10 yaş arasında Scimitar sendromu tanısı olan beş hasta değerlendirildi. Tüm hastalar semptomatikti. Bir hastada kor triatriatum ve pulmoner venöz stenoz, bir hastada sol atriyal izomerizm ve IVC yokluğu (azigos ven devamlılığı) ve diğer hastada aort koarktasyonu vardı. Diğer bir hastada ise çift drenaj saptandı. Bu hastada İVC'nin meandering pulmoner venler aracılığıyla sol atriyum ile olan bağlantısı Scimitar varyantı olarak değerlendirildi. Pulmoner hipertansiyonlu infantil bir hasta ve pulmoner / sistemik akım oranı (Qp/Qs)>1,5 olan iki hasta reanastomoz tekniği ile cerrahi olarak tedavi edildi. İki hastada ise aortopulmoner kollateraller saptanarak bu olgulara vasküler embolizasyon (vasküler plug, koil ve onyx kullanılarak) yapıldı.

Sonuç: Scimitar sendromunun çok çeşitli anatomik ve klinik varyasyonları olması nedeniyle tedavi ve takip kişiye özel olarak planlanmalıdır.

Anahtar kelimeler: Aortopulmoner kollateral, çocuk, meandering pulmoner venler, Scimitar sendromu.

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Ali Orgun, M.D. Department of Pediatric Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: draliorgun@hotmail.com (https://orcid.org/0000-0003-1604-270X) (Corresponding Author)

Birgül Varan, Prof. Department of Pediatric Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: birgulv@hotmail.com (https://orcid.org/0000-0002-6719-8563)

İlkay Erdoğan, Prof. Department of Pediatric Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: ilkayoerdogan@hotmail.com (https://orcid.org/0000-0002-3770-9973)

N.Kürşad Tokel, Prof. Department of Pediatric Cardiology, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: kursatt80@gmail.com (https://orcid.org/0000-0002-6759-1795)

Hazım Alper Gürsu, Assoc. Prof. Department of Pediatric Cardiology, University of Health Sciences, Ankara City Hospital, Ankara, Turkey, e-mail: hagursu@yahoo.com.tr (https://orcid.org/0000-0003-4795-4066)

Murat Özkan, Assoc. Prof. Department of Cardiovascular Surgery, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: ozkan.mrt@gmail.com (https://orcid.org/0000-0003-3991-8479)

Sait Aşlamacı, Prof. Department of Cardiovascular Surgery, Başkent University Faculty of Medicine, Ankara, Turkey, e-mail: saitaslamaci@hotmail.com (https://orcid.org/0000-0002-9372-2277)

Introduction

Scimitar syndrome is a rare congenital heart anomaly in which the pulmonary veins drain into the inferior vena cava (IVC) instead of the left atrium and is often associated with additional anomalies such as aortopulmonary collaterals (APCs), right lung hypoplasia, right pulmonary artery hypoplasia, atrial septal defect (ASD), pulmonary sequestration, and dextrocardia [1, 2]. Treatment and follow-up of the Scimitar syndrome should be planned individually according to patient because of its wide range of presenting age, anatomic, and clinical variations [3]. In this article, the clinical findings, angiographic and surgical procedures, and follow-up of pediatric patients with Scimitar syndrome with different presentations are reported.

Material and methods

All cases with Scimitar syndrome were diagnosed in our hospital between 2000 and 2020. One of the patients was reported previously from our clinic [4]. The research protocol was approved by the local ethics committee of Baskent University(Project No: KA20/344). Informed consent was obtained from all patients. The study was conducted in accordance with the principles of the Declaration of Helsinki. The clinical findings, angiographic and surgical procedures, and follow-up of the patients with Scimitar syndrome are evaluated.

Results

Five pediatric patients (2 female,3 male) with Scimitar syndrome diagnosis, were evaluated. Diagnosis age of patients was between 20 days and 9 years. All patients were symptomatic. Their symptoms were sweating, fatigue during feeding, cyanosis, cough and restlessness. One infant patient had a history of recurrent respiratory infections. The clinical features, angiographic and surgical procedures of the patients were given in Table 1.

Table 1. The demographic, clinical, and laboratory features of the patients with Scimitar syndrome

Case	1	2	3	4	5
Age	17 years	66 days	6 years	6.5 years	10 years
Age of diagnosis	1.5 month	20 days	4.5 years	5 years	9 years
Gender	Female	Male	Male	Female	Male
Complaint	Sweating, fatigue	Cyanosis	Sweating, weakness	Cough	Fatigue, fainting
Concomitant congenital heart disease	Collateral artery Pulmonary sequestration Right pulmonary artery hypoplasia Coarctation of the aorta	Cor triatriatum Hypoplastic pulmonary veins Pulmonary hypertension ASD	Collateral artery Pulmonary sequestration ASD	Meandering light pulmonary veins	Left atrial isomerism Total abnormal hepatic venous connection
mPAP(mmHg)*	19	32	31	22	18
Qp/Qs	1.59		4.6	1	2.21
Interventional	Collateral occlusion(coil, onyx) CoA balloon angioplasty	No collateral	Collateral occlusion (vascular plug)	No collateral	No collateral
Surgery	No	Pulmonary vein repair Cor triatriatum	Pulmonary vein repair ASD	No (Qp/Qs:1)	Pulmonary vein repair
Surgery time	No	42 days	5 years	No	9.2 years
Follow up time (years)	17	Exitus at 2.5 months old (Hypoplastic pulmonary veins)	1.5	1.5	1

* mPAP: Mean pulmonary arterial pressure

A pulmonary venous return anomaly was suspected in echocardiography in two patients. In the echocardiography findings of the other three patients, concomitant congenital anomalies were detected. Concomitant congenital heart disease(CHD) is described in Table 1. Coarctation of the aorta in the first patient; cor triatriatum, hypoplastic pulmonary veins, pulmonary hypertension and ASD in the second patient; left atrial isomerism, absence of the infrahepatic segment of the IVC (azygos vein connected to the right superior vena cava), total abnormal hepatic venous connection, and foramen ovale were diagnosed in the fifth patient.

Angiography was performed in four patients. Pulmonary-systemic flow ratio (Qp/Qs) was calculated range 1-4.6. In addition to the scimitar vein, collateral artery was seen in two patients. Collateral arteries were closed interventionally in two patients. Angiography of the first patient showed a large and three feeding artery branches arising from the aorta and another feeding artery arising from the celiac trunk. (Figure 1a) We performed occlusion of arteries and branches with microcoils (Figure 1b) Post-closure control angiography revealed incomplete occlusion. An embolic agent for occlusion of the all feeding arteries was used. Ultraflow microcatheter (Covidien, USA) was used during Onyx embolization, dimethyl sulfoxide (DMSO) was injected in the ultraflow microcatheter to fill the feeding arteries and then Onyx (ev3, USA) was injected slowly under fluoroscopy (Figure 1c). In the third patient, two collateral arteries with diameters of 5.3 mm and 3.2 mm originating from the descending aorta were supplying blood to the lower zone of the right hypoplastic lung segment. Both collaterals were closed respectively by inserting 8-mm and 6-mm vascular plugs (Lifetech Cera).

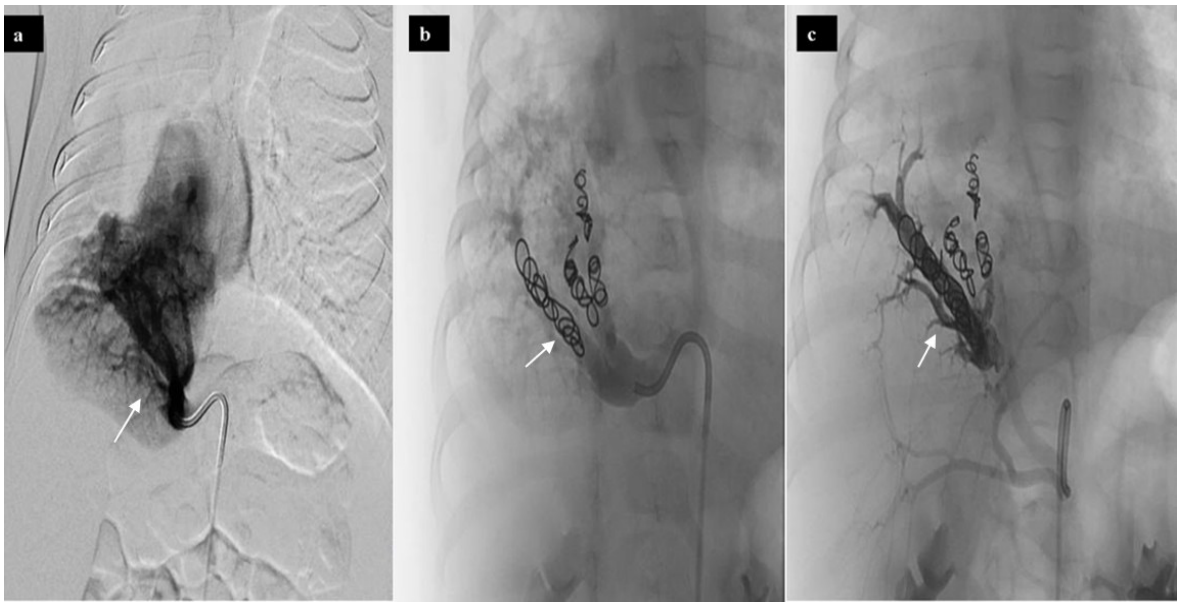

Figure 1. The angiogram images of case 1. The images show; a) the arterial collaterals were taking origin from the aorta, b) the three feeding artery branches after occlusion with micro-coils, c) a large artery embolization with onyx

Meandering right pulmonary veins were detected in the fourth patient. The right pulmonary veins connected with the IVC via the right vertical descending vein. (Figure 2a, 2b) The right lower lung segmental vein drained to the IVC via the right descending vertical vein. The right upper and middle pulmonary veins connected to the left atrium and the vertical vein via meandering pulmonary veins (Figure 3a, 3b). In the fifth patient the angiogram showed that the left pulmonary veins drained to the left atrium, and the right pulmonary veins drained into the hepatic vein via the right lateral vertical vein. The scimitar sign was present.

Surgery was performed in three patients. The surgery age was 42 days-9.2 years. The decision of surgery was made in one infant patient (case 2) due to pulmonary hypoplastic veins and in the other two patients (case 3 and 5) due to pulmonary to systemic flow ratio (Qp/Qs)>1.5. In the second patient during surgery, two separate right pulmonary veins

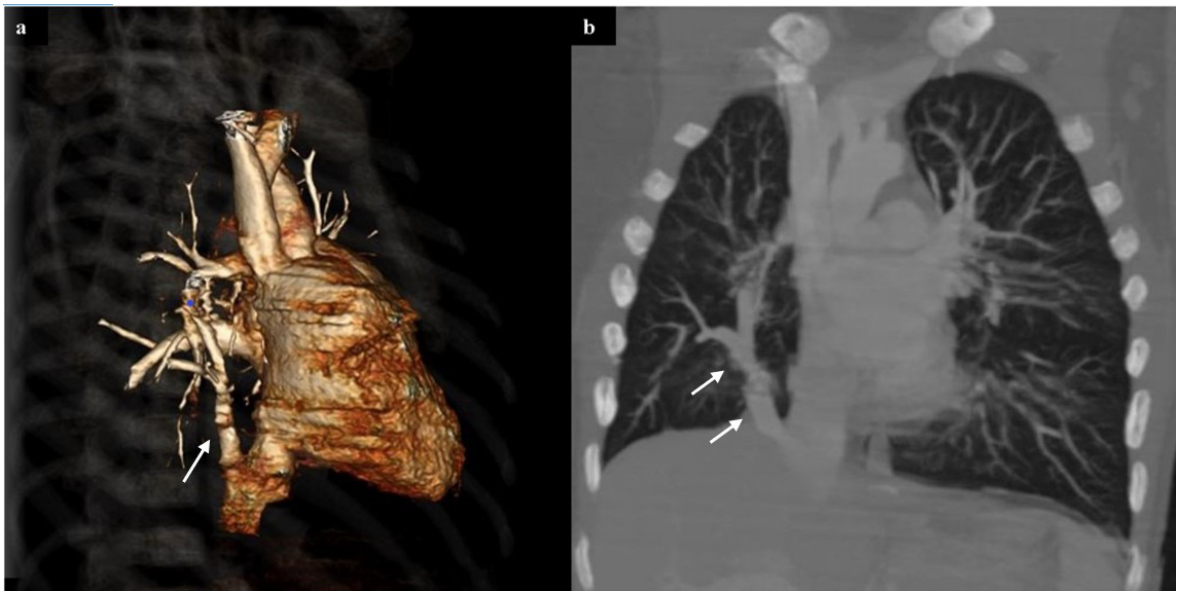

Figure 2. The images of case 4. The images show, a) Scimitar vein 3D Image, b) Scimitar vein coronal plane computed tomography image

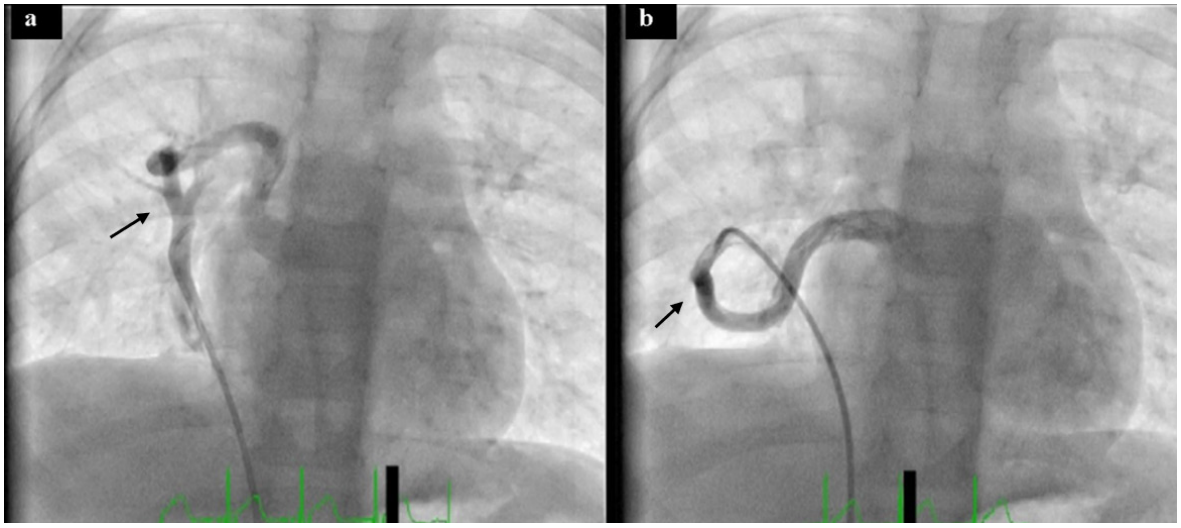

Figure 3. The angiogram images of case 4. The images show a) dual drainage angiography image between the Scimitar vein and the left atrium, b) an angiography image of meandering veins

of 4 mm and 2.5 mm were observed under the diaphragm, which drained to the IVC instead of opening to the left atrium. The left pulmonary veins were connected to the left atrium with a 4-mm diameter tunnel. In addition, sequestered lung segment and large secundum ASD were observed. The left atrium cavity was small. The large right pulmonary vein was anastomosed with the left atrium. The small right pulmonary vein was not anastomosed. The general underdevelopment of the pulmonary veins was not considered appropriate for correction. The ASD was left open. In the other two patients, repair of the anomalous pulmonary venous return was performed by surgery.

The patient with hypoplastic pulmonary vein stenosis died after a postoperative 24th day. The follow-up period of the other 4 patients ranged from 1 year to 17 years with good clinical conditions.

Discussion

Scimitar syndrome is a very rare congenital heart anomaly comprising a partial anomalous pulmonary venous connection to the IVC, lung hypoplasia, hypoplasia in the right pulmonary artery and APCs, and pulmonary sequestration [5, 6]. Scimitar syndrome has a wide range of anatomic and clinic variations and has high morbidity and mortality rates.

In early childhood, patients with Scimitar syndrome are mostly symptomatic with heart failure and recurrent lung infections, but are usually diagnosed incidentally in adult age [6-8]. Scimitar syndrome patients are divided into two groups as infantile under 1 year old and older group over 1 year old [7, 9, 10]. The presence of additional cardiac anomalies and pulmonary hypertension causes patients to be symptomatic earlier and affect prognosis [1, 7]. For these reasons, the prognosis in infants with Scimitar syndrome has been reported to be worse than in the older group [6]. The diagnosis ages of our patients, two of which were infants, ranged between 20 days and 9 years, and all were symptomatic. Different clinical symptoms that reflect heart failure were seen in our patients, and one patient had a history of recurrent lung infections. A two-month old patient died on the 24th day of the post operation due to pulmonary hypertension and severe left pulmonary vein stenosis. There was no reanastomosis stenosis in this patient. Severe left pulmonary vein stenosis was considered as the primary cause of death. In publications, pulmonary vein stenosis is accepted as an independent risk factor for poor prognosis in Scimitar syndrome [2, 9].

Scimitar syndrome can be seen with many congenital heart diseases and the most common association is secundum ASD. Consistent with the literature, secundum ASD was the most common CHD in our patients [3]. In addition, one patient had cor triatriatum and pulmonary venous stenosis, one patient had left atrial isomerism and absence of IVC (azygous continuity), and another patient had coarctation of the aorta.

The term Scimitar variant is used for patients who do not show all the features of Scimitar syndrome and sometimes show additional features. Meandering pulmonary veins with a dual-drain to IVC and left atrium are described as the 'Scimitar variant' [11]. In the literature, Goodman et al. [11] described the presence of the Scimitar sign and an anomalous right pulmonary vein draining to the left atrium [12]. Only the presence of a meandering pulmonary vein does not cause a left to right shunt, whereas a bilateral connection leads to a left to right shunt, which requires treatment [13]. We considered our fourth patient as having a Scimitar variant because of the presence of the dual-drainage to IVC and left atrium with meandering pulmonary veins. However, she was mildly symptomatic and her Qp/Qs was 1 at catheterization, thus an intervention was not considered. There were no problems in the follow-up.

Treatment planning in Scimitar syndrome is determined by the presence of the accompanying anomalies and the patient's symptoms. Patients who are asymptomatic or have mild symptoms do not require surgery. The presence of pulmonary hypertension and additional anomalies may require early surgery and these additional anomalies increase the risk of morbidity and mortality. Patients with pulmonary hypertension who have a Qp/Qs>1.5 in catheterization should undergo surgery [1, 6, 7, 9]. Two surgical techniques, either baffle or reanastomosis, are performed according to the choice of the surgeon [6, 14]. One infant patient with pulmonary hypertension and two patients with Qp/Qs>1.5 were treated surgically with the reanastomosis technique. In addition, the ASD was closed. No postoperative anastomotic stenosis was observed. However, in an infant with pulmonary hypertension, no intervention could be made to his narrow left pulmonary veins. In our first patient with a Qp/Qs of 1.59, firstly, the APCs were closed, after which the Qp/Qs were calculated as 1.5, and the decision was follow-up without intervention.

Two of our patients had pulmonary sequestration, which is a feature of Scimitar syndrome [15]. The treatment of pulmonary sequestration was previously surgical removal of abnormal tissue. Transcatheter occlusion of abnormal arteries is less invasive and has fewer complications than surgery [14, 16]. Coil and vascular plugs are effectively used for transcatheter occlusion of APCs in pediatric patients with CHD. Transcatheter occlusion of APCs was performed in two of our patients. Embolization of the feeding arteries, which originated from the celiac trunk and ascending aorta and their branches, was performed using microcoils in the first patient. Residual flow was managed with onyx. The embolization was performed successfully, and APCs were completely occluded. The third patient had two collateral arteries and two collaterals were closed by a vascular plug.

The limitations of our study are the low number of patients and retrospective evaluation of the patients from a single center. Because Scimitar syndrome is a rare congenital

abnormality, multicentric prospective studies with more number of patients would increase the information about the patients with Scimitar syndrome.

In conclusion, Scimitar syndrome carries an increased risk of morbidity and mortality in the presence of pulmonary hypertension and additional anomalies, are more common in infants than in adults and they may require early surgery. Treatment planning in Scimitar syndrome is determined by the presence of the accompanying anomalies and the patient's symptoms.

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Ethics committee approval: This study was approved by Başkent University Institutional Review Board (project no: KA20/344).

Author contributions

A.O. designed the study, performed the data collection, wrote the draft, and created the tables and figures for the manuscript. B.V., İ.E. and H.A.G. designed the study, designed data collection tools, performed data collection and analysis, and wrote the initial article. M.Ö. performed data collection, analyzed data, created tables and figures N.K.T. and S.A. conceptualized and designed the study, revised the article. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Research Article

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Parameters predicting the number of recurrences, strictural length and localization in urethral strictures

Üretra darlıklarında nüks sayısı, darlık uzunluğu ve lokalizasyonu öngören parametreler

Muhammed Cihan Temel, Sezgin Okçelik

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Abstract

Purpose: In addition to the known etiological and predisposing factors of urethral stricture, we aimed to examine unknown and not clearly defined factors.

Materials and methods: Medical records of 317 patients who underwent visual internal urethrotome (VIU) surgery in our clinic between 2017 and 2022 were retrospectively reviewed. The parameters affecting the total number of VIU operations were investigated. In addition, the factors affecting the total length and localization of the stricture were investigated.

Results: The presence of history of endourological surgery and history of cardiovascular disease were independently associated with a higher number of VIU operations (p<0.05). The age was independently associated with a longer total segment of urethral stricture (p<0.05). The history of previous endourological intervention or the presence of cardiovascular disease are significantly increased the rate of distally localized strictures (p<0.05).

Conclusion: Endourological interventions and urethral catheter procedures should be avoided as much as possible for people with cardiovascular disease. It will be a useful approach to investigate the status of cardiovascular disease of patients with anterior urethral stricture, as it is done in erectile disfunction.

Key words: Urethral stricture, visual internal urethrotome, cardiovascular arrest, coronary artery bypass.

Temel MC, Okcelik S. Parameters predicting the number of recurrences, strictural length and localization in urethral strictures. Pam Med J 2023;16:43-49.

Öz

Amaç: Bu çalışmada üretral darlıkların bilinen etiyolojik ve predispozan faktörlerine ek olarak, bilinmeyen ve net olarak tanımlanmamış faktörler incelendi.

Gereç ve yöntem: Merkezimizde 2017-2022 yılları arasında Vizüel internal üretrotom (VIU) operasyonu geçiren 317 hastanın tıbbi kayıtları geriye dönük olarak incelendi. Total VIU operasyon sayısı üzerinde etkili olan parametreler araştırıldı. Ek olarak total dar segment uzunluğu ve darlık lokalizasyonuna etki eden faktörler araştırıldı.

Bulgular: Geçirilmiş endoürolojik cerrahi öyküsü ve kardiyovasküler hastalık öyküsünün, daha fazla VIU operasyonu sayısı ile ilişkili olduğu görüldü (p<0,05). Yaş, daha uzun total üretral darlık segmentiyle ilişkiliydi (p<0,05). Daha önce geçirilmiş endoürolojik müdahale öyküsü ve kardiyovasküler hastalık hikâyesi, darlığın daha distalde olma oranını istatistiksel anlamlı şekilde arttırmaktaydı (p<0,05).

Sonuç: Kardiyovasküler hastalık hikâyesi olan kişilerde endoürolojik girişim ve üretral kateter yerleştirilmesi işlemlerinden mümkün olduğunca kaçınılmalıdır. Erektil disfonksiyon hastalarında yapıldığı gibi, anterior üretral darlığı olan hastalarda da kardiyovasküler hastalık araştırmasının yapılması faydalı bir yaklaşım olacaktır.

Anahtar kelimeler: Üretral striktür, vizüel internal üretrotomi, kardiyovasküler arrest, koroner arter bypass.

Temel MC, Okçelik S. Üretra darlıklarında nüks sayısı, darlık uzunluğu ve lokalizasyonu öngören parametreler. Pam Tıp Derg 2023;16:43-49.

Muhammed Cihan Temel, Department of Urology, Nevsehir State Hospital, Nevsehir, Turkey, e-mail: dr.cihantemel@gmail.com (https://orcid.org/0000-0002-8677-8504) (Corresponding Author)

Sezgin Okçelik, Department of Urology, Afyonkarahisar State Hospital, Afyonkarahisar, Turkey, e-mail: drsezginokcelik@hotmail.com (https://orcid.org/0000-0001-6479-9913)

Introduction

Urethral stricture is a disease that can develop throughout the entire male urethra and has many etiologies. Overall, its incidence is estimated to be 229-627 per 100,000 men [1]. This disease, which is common and frequently recurring worldwide, seriously affects human health and can significantly reduce the quality of life [2]. Urethral stricture, which has many etiologies, imposes serious burdens on the health system and patients [3]. A thorough understanding of the etiology and pathophysiology of urethral stricture may play an active role in preventing this disease and finding new treatment methods. Many predisposing factors related to urethral stricture have been reported in the guidelines of European Association of Urology and American Urological Association [4, 5]. The most common etiology is iatrogenic causes, however idiopathic strictures still constitute a substantial portion of 34% [6]. Based on these informations, it can be concluded that there are still many unknown factors about the etiology of urethral stricture. Mundy and Andrich [7] reported that one of the possible causes of idiopathic urethral strictures in elderly patients may be urethral ischemia, in a review. Yildiz et al. [8] reported that the severity of coronary artery disease is an independent predictive factor in the occurrence of urethral stricture, in a study which they compared patients with and without urethral stricture after urethral catheterization. In this study, we aimed to investigate also the not yet clearly defined etiological factors such as cardiovascular arrest, bypass and patient's age, in addition to well defined etiological and predisposing factors of urethral stricture. New informations related to these factors will be scientifically valuable due to they have the potential to provide a new and different approach to this disease in the literature and guidelines. Our study is one of the limited number of studies examining these new potential etiological factors.

Material and methods

After the ethical approval from local institute's committee on human research obtained on 28.03.2022, medical records of 381 patients who underwent internal urethrotome (VIU) surgery in our clinic between 2017 and 2022 were reviewed retrospectively. All the patients were underwent VIU operation due to urethral stricture disease which had diagnosed with uroflowmetry and cystourethroscopy. A 20 Fr urethral catheter was inserted after the procedure to all patients. The durations of catheterizations were determined according to the surgeon's foresight. All patients who had a second VIU operation were offered to the option of open urethroplasty operation. Patients who accepted open urethroplasty were excluded the study. Patients younger than 18 years old, with congenital urethral/penile anatomical anomalies (Hipospadias, Epispadias, Posterior urethral valve exc.) or who were operated for these reasons (TIPU, Magpi, Other urethroplasties exc.), with Balanitis xerotica obliterans or lichen sclerosus et atrophicus of the penis, with previous pelvic fracture and postradiation urethral strictures were excluded from the study. Patients older than 18 years, who had undergone VIU surgery and had congenital normal urethral anatomy were included in the study. Patients who wanted to continue their treatment with VIU operation and did not accept urethroplasty after second VIU were included in the study. A total of 381 patients' data were obtained and 317 patients, who met the study criteria were included in the study. Informed consent was obtained from all patients included in the study. The patients' age, number of total VIU operations, history of previous endourological intervention, history of cardiovascular disease, history of cardiovascular arrest/bypass, length of the total strictural segment and stricture localization (Anterior or Posterior urethra) were recorded. Patients who had previously undergone any type of transurethral resection (TUR), cystoscopy, ureterorenoscopy (URS) or percutaneous nephrolithotomy (PNL) surgery were considered as patients with endourological intervention. Patients with chronic hypertension, coronary artery disease affecting cardiac function, previous myocardial ischemia, cardiac arrhythmia, cardiomegaly, chronic heart failure, cardiac thrombus, low ejection fraction, chronic valve diseases, aortic aneurysm and varicose diseases were considered as patients with cardiovascular disease. Cold knife visual internal urethrotomy technique was applied to all patients at 12 o'clock position. The length of the urethral stricture was measured by calculating the ratio of the stricted segments' length to the cold knife length, after the stricture/strictures was incised with the urethrotome. In patients with more than one urethral stricture, the stricture length was calculated as the sum

of the length of all stricture segments. The effect of other parameters on the total number of VIU operations performed on the patients was investigated. In addition, the factors affecting the stricture length and localization were investigated.

The statistical analysis of the data was performed using the SPSS version 22.0 (IBM, New York, USA). Shapiro-Wilk test was used to determine whether the data was normally distributed or not. Qualitative data was expressed as frequencies and percentages. Because the quantitative data in the study was distributed nonparametrically, the results were reported as Median (IQR). Linear regression analysis was applied to investigate which parameters affected the number of total VIU operations and the strictural length. Binary regression analysis was used to assess the relation between the localization of urethral stricture and other parameters. Values of $p<0.05$ were considered statistically significant.

Results

A total of 317 patients were included in the study. The age range of the patients included in the study was 18-93, and the median (IQR) age was 68 (17.50). The urethral stricture lengths of the patients ranged from 2 to 100 mm, and the median (IQR) value was 10 (5) mm. The total number of VIU operations performed to the patients ranged from 1 to 23, and the median (IQR) value was 1 (1). The mean VIU values, the number of cardiovasculary disease, the number of cardiovasculary arrest/surgery history according to age decade of the patients are given in Table 1. Of 317 patients, 162 (51.1%) had a history of previous endourological procedure, 97 (30.6%) had a history of cardiovascular disease, and 28 (8.8%) had a history of cardiovascular arrest or bypass. The stricture was in the posterior urethra in 48 (15.14%) patients and in the anterior urethra in 269 (84.86%) patients. Anterior urethral strictures were localized in the bulber urethra in 176 (55.52%) patients and in the penile urethra in 93 (29.34%) patients.

The presence of history of endourological surgery and history of cardiovascular disease were independently associated with a higher total number of VIU operations in lineer regression analysis ($p<0.05$), (Table 2). The age was independently associated with a longer total segment of urethral stricture in regression analysis ($p<0.05$), (Table 3). In addition, it was observed that the presence of a previous endourological intervention or cardiovascular disease significantly increased the probability of the stricture being at more distal (anterior urethra) ($p<0.05$), (Table 4).

Table 1. The mean VIU values, the number of cardiovasculary disease, the number of cardiovasculary arrest/surgery history according to age decade of the patients

Decade of Age	Frequency (number of patients)	Mean number of VIU operations	Presence of history of cardiovasculary disease (Ratio to decade population)	Presence of history of cardiovasculary arrest/ surgery (Ratio to decade population)
18-20	2	1.00	0 (0.00 %)	0 (0.00 %)
21-30	10	1.40	0 (0.00 %)	0 (0.00 %)
31-40	14	1.42	0 (0.00 %)	0 (0.00 %)
41-50	23	1.60	5 (21.73 %)	3 (13.04 %)
51-60	49	1.95	11 (22.44 %)	0 (0.00 %)
61-70	87	1.93	24 (27.58 %)	7 (8.04 %)
71-80	97	2.28	40 (41.23 %)	13 (13.40 %)
81-90	33	1.66	16 (48.48 %)	5 (15.15 %)
91-93	2	2.50	1 (50.00 %)	0 (0.00 %)
Total	**317**		**97**	**28**

Table 2. Linear regression analysis results in which total IUT number was assumed as independent variable and other factors as dependent variable (p<0.05)

	B			*p*	95% Confidence Interval	
	value	Standard Error	Beta(β) value	value	Min	Max
Age	0.003	0.008	0.024	0.664	-0.012	0.018
History of previous endourological surgery	1.148	0.225	0.275	**0.000**	0.706	1.590
History of cardiovascular disease	1.081	0.282	0.239	**0.000**	0.526	1.635
History of cardiovascular arrest/ bypass	-0.371	0.439	-0.050	0.399	-1.235	0.493

Table 3. The age was independently associated with a longer total segment of urethral stricture (p<0.05)

	B			*p*	95% Confidence Interval	
	value	Standard Error	Beta(β) value	value	Min	Max
Age	0.138	0.053	0.150	**0.010**	0.033	0.243
History of previous endourological surgery	-2.253	1.558	-0.083	0.149	-5.319	0.813
History of cardiovascular disease	-1.486	1.956	-0.051	0.448	-5.334	2.362
History of cardiovascular arrest/bypass	0.017	3.048	0.000	0.995	-5.980	6.015

Table 4. Binary regression analysis with the localization of urethral stricture as the dependent variable and the other parameters as the independent variables (p<0.05)

	β	*p*	Odds	95% Confidence Interval for β	
	value	value	ratio	Min	Max
Age	0.010	0.450	1.010	0.985	1.035
History of previous endourological surgery	0.938	**0.012**	2.555	1.230	5.308
History of cardiovascular disease	1.600	**0.000**	4.951	2.297	10.668
History of cardiovascular arrest/bypass	0.294	0.560	1.341	0.500	3.597

Discussion

Urethral stricture is a common disease that can affect men of all ages and seriously reduce the quality of life all over the world [2]. The mean age at diagnosis of urethral stricture in men is 45.1, with a significant increase in incidence after 55 years of age [1, 9]. Many etiological factors have been reported about urethral stricture, which is known to impose serious burdens on the patient and the health system, and all causes are still not fully clarified [3, 5]. Obtaining more clear data about the etiological and predisposing factors will play an active role in the management of this disease and in the prevention of its recurrence. Therefore, in addition to the identified etiological factors of urethral stricture, we aimed to investigate the factors that have not yet been defined or for which sufficient data has not been obtained in the literature. Therefore, we collected the data of all our patients who had VIU operation in our clinic in the last 6 years, and we investigated how these factors are effective on urethral stenosis.

It is stated in the EAU and AUA guidelines that previous endourological interventions and iatrogenic causes are serious predisposing factors for urethral stricture [4, 5]. However, there is no detailed data about the factors that are affecting the recurrence and re-VIU operation requirement. Based on these lack of data, we tried to find out which parameters affect the recurrence of urethral stricture and the need for re-VIU. According to our study results, it was observed that the history of previous endourological interventions increased the total number of VIUs performed and urethral stricture recurrences significantly (p<0.05), (Table 2). In a retrospective study of 224 patients by Kizilay et al. [10], it was observed that the rate of recurrence of urethral stenosis increased statistically significantly in patients with a previous history of endourological intervention.

The studies investigating the relationship between cardiovascular diseases and urethral stenosis are limited. However, urethral catheterization and poor tissue perfusion due to cardiovascular pathologies are said to be the cause of urethral stenosis, which occurs frequently in patients with hemodynamic instability due to acute coronary syndrome or other cardiovascular pathologies [7, 11-13]. In a retrospective study of 306 patients, Yildiz et al. [8] reported that; There is a positive correlation between the SYNTAX score, which indicates the severity of coronary artery disease, and the risk of urethral stenosis in patients with urethral catheterized acute coronary syndrome. According to the results of this study; It was observed that the SYNTAX score was statistically significantly higher in the group of patients who were hospitalized for acute coronary syndrome and developed urethral stenosis during the follow-up period, compared to those who did not develop urethral stenosis. In addition, it was also reported in the same study that the SYNTAX score and severity of coronary artery disease are independent predictors for urethral stricture development (p<0.001). In our study, the presence of cardiovascular disease was found to be an independent risk factor for increased number of previous VIUs and recurrence of urethral stenosis (p<0.05) (Table 2). There is no detailed information about the effects of cardiovascular diseases on urethral strictures in the actual urology guidelines we use. Avoiding endourological interventions or urethral catheter procedures in people with cardiovascular disease may have a potential role in the prevention of this disease. Condom catheters may be used as an alternative method in such patients. If invasive urinary diversion is absolutely necessary, using percutaneous cystostomy may be more appropriate to reduce the risk of urethral stricture [14].

It is known that the risk of urethral stricture increases with age [1, 2, 9, 15]. In a comprehensive demographic study of Santucci et al. [16]; It has been reported that the incidence of urethral stenosis increases significantly especially after the age of 55, and the prevalence of urethral stenosis increases in correlation with increasing age. There is no study primarily investigated the relationship between age and the length of the urethral stricture. However, in a study by Levy et al. [17]; It has been reported that the mean urethral stricture length in patients over 60 years of age is higher than under 60 years of age, although not statistically significant. In our study, age was found to be the only independent factor that had a statistically significant increase effect in urethral stricture length (p<0.05) (Table 3). We think that avoiding endourological interventions or urethral catheterization as much as possible especially in elderly patients will be a serious

prevention in terms of reducing the risk of urethral stricture developement [11].

In a retrospective cohort study in which Stein et al. [3] compared two different urethral stricture groups; It was reported that in the patient group with a higher rate of iatrogenic stenosis, the rate of the urethral stricture segment being more distally was statistically significantly higher. Also in our study, the probability of the urethral stricture segment being more distally (anterior urethra) was statistically significantly higher in the patient group with a previous history of endourological intervention (p<0.05) (Table 4). In addition, according to the results of our study, the possibility of distal urethral stenosis increased in patients with cardiovascular disease (p<0.05) (Table 4). Lumen et al. [18] reported that most urethral strictures after major cardiac surgery or neurosurgery occured in the anterior urethra. They stated that the cause of these strictures were increasing ischemia of the corpus spongiosum during the systemic blood circulatory failure and the hypothermia.

Although the main etiological causes of urethral stricture are idiopathic and iatrogenic factors, it is a fact that many other factors may play a role in the development of stricture. It is well known that patients with coronary artery disease (CAD) are more likely to have erectile dysfunction (ED) [19, 20]. In addition, the severity of CAD is related to the severity of ED [19, 20]. There is a limited number of study which investigated the relationship between urethral stricture and local ischemia and vascular pathologies. However, the possibility that local tissue ischemia and vascular pathologies causing erectile dysfunction, may cause also urethral strictures occurred after urethral catheter or endourological interventions, should not be ignored. Also it should not be ignored that urethral strictures may be the first sign of a generalized systemic atherosclerosis that affects the pelvic end arteries, like erectile dysfunction. Considering the common perfusion of the penis and urethra from the internal pudendal artery, the relationship between urethral stricture and urethral ischemia may be correlated with the relationship between erectile dysfunction and defective erectile perfusion. In our study, it was observed that the urethral strictures of patients with CAD were mostly localized in the anterior urethra, which is more difficult to perfusion. These results are also consistent with previous literature. Based on all these results; It may be beneficial to evaluating patients with anterior urethral stricture in terms of cardiovascular disease, also like in patients with erectile dysfunction. For example, a grading system like “cardiac risk stratification based on Princeton Consensus” which used in erectile dysfunction may also be used in urethral strictures [4].

Our study has some limitations. These were natural shortcomings due to the retrospective planning. The number of factors investigated to find out which parameters affect the total number of VIU operations performed, the length and localization of the urethral stricture, were limited. Because of our study was of a retrospective nature, we had to investigate only the parameters that could be accessible. In addition, the erectile function status of the patients was not recorded, and its relationship with other parameters could not be investigated. This is another limitation of our study.

Although our study has a retrospective nature, we think that it gave meaningful results, because of its large number of participants. In addition, because of our study was single-centered, it has a more homogeneous nature in terms of surgical equipment, demographic factors and surgeon factors. In our study, factors that have not been fully investigated before or factors about which there is a limited data investigated, and meaningful results were obtained about these factors. This is another superiority of our study.

In conclusions, the avoidance of endourological interventions or urethral catheter insertions in people with cardiovascular disease may have a potential role in prevention of urethral stricture disease. Condom catheters may be used as an alternative method in such patients. If invasive urinary diversion is absolutely necessary, using percutaneous cystostomy may be more appropriate to reduce the risk of urethral stricture. It may be beneficial to evaluating patients with anterior urethral stricture in terms of cardiovascular disease, also like in patients with erectile dysfunction. Adding a directive about this subject to the guidelines may be a useful practice in terms of early diagnosis and treatment of urethral stricture and cardiovascular diseases. More comprehensive and prospective studies are needed to support our results.

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

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Authors' contributions to the article

M.C.T. constructed the main idea and hypothesis of the study, developed the theory of the study. M.C.T. edited the material and method section. M.C.T. and S.O. made the evaluation of the data in the results section. Discussion part of the article was written by M.C.T. Discussion part of the article reviewed by S.O., made necessary corrections and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Evaluation of urinary tract infections in a two-year follow-up after renal transplantation: a single center experience

Renal transplant sonrası iki yıllık izlemde gelişen üriner sistem enfeksiyonlarının değerlendirilmesi: tek merkez deneyimi

Tuğba Sarı, Belda Dursun, Mevlüt Çeri, İlknur Kaleli, Hüseyin Turgut, Murat Özban

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Abstract

Purpose: After renal transplantation, urinary tract infection (UTI) is observed in 23-75% of cases. In this study, we aimed to investigate the incidence of UTIs after renal transplantation, the causative pathogens and the predisposing factors that increase the risk.

Materials and methods: Patients who underwent renal transplantation in our hospital between 2016-2017 were included in the study. Postoperative immunosuppressive treatments; It consisted of basiliximab, mycophenolate mofetil, tacrolimus and prednisolone combination. In perioperative antibiotic prophylaxis, clindamycin was used in one patient and cefuroxime axetil was used in the others. A double-J stent was used in all patients during urinary catheterization and anastomosis. Patients were given trimethoprim sulfamethoxazole (TMP-SXT) for *Pneumocystis jirovecii* prophylaxis for 6 months postoperatively.

Results: Twenty-five patients who underwent kidney transplantation were included in the study. UTI was detected in 12 patients (48%). One patient had neurogenic bladder, three had nephrolithiasis and one had vesicoureteral reflux. 8 of the patients had at least two UTI attacks. In total 38 UTI attacks; There were 7 (18.4%) nitrite positivity. UTI was detected in 15 (39.5%) patients during the first 3 months after transplantation. While 7 (18.4%) of the urine cultures were gram positive and 27 (71.1%) were gram negative bacteria, 4 (10.5%) were found as contamination. *Escherichia coli* (34.2%) was the most common causative agent, followed by *Klebsiella pneumoniae* (21.1%), *Enterococcus faecium* (18.4%), *Pseudomonas aeruginosa* (5.3%) and other gram negative (%). 10.5 uropathogens were found to be followed. When compared with basal and UTI GFR (glomerular filtration rate) levels, the GFR values detected during UTI were decreased significantly (p=0.00). The most frequently preferred antibiotics in UTI treatment were ertapenem 42.1%, levofloxacin 10.5%, seftriaxon 10.5% and fosfomycin 10.5%.

Conclusion: Improperly treated UTI negatively affects the outcome of transplantation and increases mortality. Therefore, risk factors, antibiotic resistance and empirical treatments should be reviewed and treatment success should be increased.

Key words: Renal transplantation, transplantation, UTI.

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Öz

Amaç: Renal transplantasyon sonrası, %23-75 oranında üriner sistem enfeksiyonu (ÜSE) görülmektedir. Bu çalışmada böbrek nakli sonrası ÜSE sıklığı, neden olan patojenler ve riski artıran predispozan faktörlerin araştırılması amaçlanmıştır.

Gereç ve yöntem: 2016-2017 yılları arasında hastanemizde renal transplant yapılan hastalar çalışmaya dahil edildi. Postoperatif immunsupresif tedavileri; basiliksimab, mikofenolat mofetil, takrolimus ve prednizolon kombinasyonundan oluştu. Perioperatif antibiyotik profilaksisinde bir hastada klindamisin, diğerlerinde sefuroksim aksetil kullanıldı. Tüm hastalara üriner kateterizasyon ve anastomoz esnasında double- J stend kullanıldı. Hastalara postoperatif dönemde 6 ay boyunca *Pneumocystis jirovecii* profilaksisi için trimetoprim sulfametaksazol (TMP-SXT) verildi.

Bulgular: Böbrek transplantasyonu yapılan 25 hasta çalışmaya dahil edildi. On iki hastada (%48) ÜSE saptandı. Bir hastada nörojenik mesane, üçünde nefrolitiyazis ve birinde vezikoüreteral reflü mevcuttu. Hastaların

Tuğba Sarı, Assoc. Prof. Pamukkale University Faculty of Medicine, Deparment of Infectious Diseases and Clinical Microbiology, Denizli, Turkey, e-mail: drtugba82@gmail.com (https://orcid.org/0000-0003-3204-2371) (Corresponding Author)

Belda Dursun, Prof. Pamukkale University Faculty of Medicine, Department of Nephrology, Denizli, Turkey, e-mail: belda.dursun@gmail.com (https://orcid.org/0000-0003-3235-0577)

Mevlüt Çeri, Assoc. Prof. Pamukkale University Faculty of Medicine, Department of Nephrology, Denizli, Turkey, e-mail: mevlutceri@gmail.com (https://orcid.org/0000-0002-2276-5157)

İlknur Kaleli, Prof. Pamukkale University Faculty of Medicine, Deparment of Microbiology, Denizli, Turkey, e-mail: ikaleli@pau.edu.tr (https://orcid.org/0000-0001-7783-8723)

Hüseyin Turgut, Prof. Pamukkale University Faculty of Medicine, Deparment of Infectious Diseases and Clinical Microbiology, Denizli, Turkey, e-mail: hturgut@pau.edu.tr (https://orcid.org/0000-0001-8877-3179)

Murat Özban, Prof. Pamukkale University Faculty of Medicine, Deparment of General Surgery, Denizli, Turkey, e-mail: muratozban@yahoo.com (https://orcid.org/0000-0002-8795-0185)

8'inde en az iki ÜSE atağı mevcuttu. Toplam 38 ÜSE atağında; 7 (%18,4) nitrit pozitifliği saptandı. 15'inde (%39,5) transplantasyon sonrası ilk 3 ay içerisinde ÜSE saptandı. İdrar kültürlerinin 7'sinde (%18,4) gram pozitif, 27'sinde (%71,1) gram negatif bakteri üremesi olurken, 4'ü (%10,5) kontaminasyon olarak bulundu. Üreyen etkenler arasında *Escherichia coli* (%34,2) ilk sırada yer alırken, bunu sırasıyla *Klebsiella pneumoniae* (%21,1), *Enterococcus faeciu*m (%18,4), *Pseudomonas aeruginosa* (%5,3) ve diğer gram negatif (%10,5) üropatojenlerin izlediği bulundu. ÜSE öncesi bazal ve ÜSE sırasındaki GFR (glomerüler filtrasyon hızı) düzeyleri karşılaştırıldığında ÜSE sırasında saptanan GFR değerlerinin öncesine göre anlamlı derecede azaldığı saptandı (p=0.00) ÜSE tedavisinde en sık tercih edilen antibiyotikler ertapenem %42,1, levofloksasin %10,5, seftriakson %10,5 ve fosfomisin %10,5 idi.
Sonuç: Transplant alıcılarında profilaksi ve tedavi amaçlı antibiyotiklerin kullanımına bağlı üropatojenlerin direnç oranları artmaktadır. Uygunsuz tedavi edilen ÜSE, transplantasyonun sonucunu olumsuz etkilemekte ve mortaliteyi arttırmaktadır. Bu yüzden hastaların risk faktörleri, antibiyotik dirençleri, ampirik tedaviler gözden geçirilmeli ve tedavi başarısının arttırılması sağlanmalıdır.

Anahtar kelimeler: Renal transplant, transplant, ÜSE.

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Introduction

Bacterial infections are common after renal transplantation, and the most common cause of these is urinary tract infections (UTI) at a rate of 30-79%. 60% of UTIs cause bacteremia [1]. UTI occurs in 25% of kidney transplant recipients within one year of transplant and accounts for 45% of infectious complications. Asymptomatic bacteriuria (ASB), uncomplicated UTI, and complicated UTI comprise 44%, 32%, and 24% of cases, respectively [2]. Many factors, such as older age, female gender, comorbidities, type and duration of immunosuppression, foreign material in the urinary system, transplant kidneys affected by ischaemia-reperfusion injury, non-functioning native kidneys, and abnormal lower urinary tracts, cause UTI in renal transplant patients [3-5]. In addition, urinary system catheters, kidney or ureter traumas during surgery, structural abnormalities, neurogenic bladder, renal failure, and possible rejection also increase the risk of UTI [3, 4, 6]. In this study, the first two-year follow-up was performed because of the high risk of UTI after renal transplantation. It was aimed to investigate the frequency of UTI, causative pathogens and predisposing factors that increase the risk after renal transplantation.

Methodology

All of the patients included in this study have underwent renal transplantation in our hospital between 2016-2017, and were evaluated retrospectively. This study was conducted in accordance with the Declaration of Helsinki, and it was approved by the ethics committee of Medical Faculty of Pamukkale University. Patients' demographic, clinical and laboratory data were collected from patient records in the transplantation records of nephrology clinic. Postoperative immunosuppressive therapies were administered with interleukin-2 receptor (IL-2R) antagonist followed by triple maintenance immunosuppressive therapy including oral prednisolone, mycophenolate mofetil (MMF). All patients received *Pneumocystis jirovecii* antimicrobial prophylaxis with trimethoprim-sulfamethoxazole.

In perioperative antibiotic prophylaxis, clindamycin was used in one patient and cefuroxime axetil was used in the others. A double-J stent was used in all patients during urinary catheterization and anastomosis. Diagnosis of UTI; In patients with dysuria, urgency, pollakiuria, and suprapubic tenderness, bacteriologically, >10 leukocytes/mm3 in the midstream urine obtained after proper perineal cleansing and in blood agar and EMB agar overnight at 37°C. In the samples prepared by incubation, $\geq 10^5$ cfu/ml bacterial growth was determined. Recurrent attacks were defined as having three or more UTI within a year, or two recurrent attacks within 6 months and relapse attacks was defined developing UTI within a week or two with the same microorganism [7].

The presence of stenosis or functional abnormality in the genitourinary system and the detection of UTI in underlying comorbid and immunosuppressive conditions were classified as complicated UTI. All organ transplant recipients with symptomatic UTI were evaluated as complicated UTI [8]. Antibiotic susceptibility was determined according to the

Clinical and Laboratory Standards Institute 2015 recommendations [8]. Intermediate and resistance were recognized as non-susceptible. MDR was defined as non-susceptible to at least one agent in ≥3 antimicrobial categories [9].

Isolates were identified by conventional methods and their antibiotic susceptibility was investigated by disc diffusion method in accordance with EUCAST criteria [9]. The data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical program, version 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY). The independent samples t-test was used for variables that met the assumption of normal distribution, and mean and standard deviation values were given. The Mann-Whitney U test was used for variables in which the assumption of normal distribution was not met, and median, first and third quartile values (25-75%) were given. The Chi-square test was used to compare categorical variables. The Hosmer and Lemeshow test was used to evaluate the statistical power of the model. A value of $p<0.05$ was considered significant.

Results

25 patients who underwent kidney transplantation, two-year follow-up was completed after transplantation were included in the study. The patients were between 20-65 years old and their mean age was 46.5±13.04 years. The mean follow-up period of the patients was 13.8±5.2/month. Before transplantation, 21 (84%) were in the hemodialysis program, while 3 (12%) were on peritoneal dialysis. One patient had no previous history of dialysis. Mean dialysis time before transplantation was found to be 80±62.7/month (0-192). 16 (64%) transplanted from living donor, 10 (40%) transplanted from deceased donor. Causes of chronic kidney failure; hypertension (9 (36%)), diabetes mellitus (DM) (6 (24%)), chronic interstitial nephritis (4 (16%)), chronic glomerular disease (4 (16%)), obstructive uropathy (2 (%) 8)), found as. Table 1 summarizes demographic characteristics of the characteristics of 12 (48%) patients with UTI and 13 (52%) patients without UTI.

One of the patients with UTI (2.6%) had a neurogenic bladder, three had nephrolithiasis and one had vesicoureteral reflux. A total of 38 UTI attacks were detected in 12 patients with UTI. Of these, 3 (7.9%) were classified as cystitis and 35 (92.1%) as complicated UTI. Eight of 12 patients (66.7%) had at least two episodes of UTI. 28 (73.6%) attacks were evaluated as reinfection and 6 (26.4%) attacks were considered as relapses. A total of 38 UTI attacks; Nitrite positivity was detected in 7 (18.4%) of them. Within the first 3 months after transplantation in 15 (39.5%), 22 (57.9%) within the first 6 months, 30 (79%) within the first year, 8 (21.1%) one year later, an attack of UTI was detected. UTI and BK virus positivity in urine by real time PCR in 4 of the patients included in the study (BK virus positive in both blood and urine in 3 of them, and high viraluria ($>10^7$ copies/ml) in urine in two of them. CMV positivity was detected in the blood of 6 (36%) patients with UTI by real time PCR.

Gram positive bacteria were grown in 7 (18.4%) and gram negative bacteria in 27 (71.1%) urine cultures, while 4 (10.5%) were found to be contaminated. *Escherichia coli* 13 (34.2%) (2 (15.3%) extended-spectrum beta-lactamase (ESBL) positive), *Klebsiella pneumoniae* 8 (21.1%) (6 (75%) ESBL positive), *Enterococcus faecium* 7 (18.4%), *Pseudomonas aeruginosa* 2 (5.3%), other gram negative uropathogens 4 (10.5%) and 4 (10.5%) were found as contamination (Figure 1). Twenty-eight (73.7%) of 30 samples were TMP-SMX resistant, 15 (39.5%) of 25 samples were ceftriaxone resistant, 15 (39.5%) of 27 samples were quinolone resistant, 3 of 19 samples (7.9% were found to be carbapenem resistant (Figure 1). The rate of ESBL was found to be 36%, and 100% in those who had two or more UTI attacks. As the basal creatinine levels increased, the frequency of UTI increased, and the GFR (glomerular filtration rate) levels before and during UTI were compared, and the GFR values detected during UTI decreased significantly compared to before ($p=0.00$) (Table 2).

The most commonly preferred antibiotics in the treatment of UTI are ertapenem 16 (42.1%), teicoplanin 7 (18.4%), levofloxacin 4 (10.5%), ceftriaxone 4 (10.5%) and fosfomycin 4 (10.5%) was. It was also found that a cefixime, a meropenem, and an imipenem treatment were given.

In conclusion, in a prospective study examining 4388 solid organ transplant recipients

Table 1. Demographic and clinical characteristics of renal transplant recipients

	Total (n:25)	UTI detected (n:12)	UTI not detected (n:13)	*p* value
		Mean±SD or N		
Gender				0.07
Female	17	6	11	
Male	8	6	2	
Age	46.5±13	49.8±11.9	43.5±13.7	0.2
Transplantation age	45±13.1	48.1±12.2	42.07±13.7	0.2
Double J stent duration	66.3±18.2	72.6±19.8	63.5±18.4	0.5
Donor characteristic				0.4
Living donor	16	7	9	
Deceased donor	9	5	4	
CRF cause*				0.6
HT*	9	4	5	
DM*	6	4	2	
Chronic interstitial nephritis	4	1	3	
Chronic glomerular disease	4	2	2	
Obstructive Uropathy	2	2	0	
Dialysis type				0,5
Hemodialysis	21	10	11	
Peritoneal dialysis	3	2	1	
No dialysis	1	0	1	
Mean dialysis time before transplantation	80.04±62.7	95.4±55.8	65.8±67.5	0.2
Presence of obstructive uropathy	5	3	2	0.4
Delayed graft function				0.2
Needs dialysis in first week	2	2	0	
No need for dialysis in the first week	23	10	13	

CRF: Chronic renal failure, HT: Hypertension, DM: Diabetes mellitus

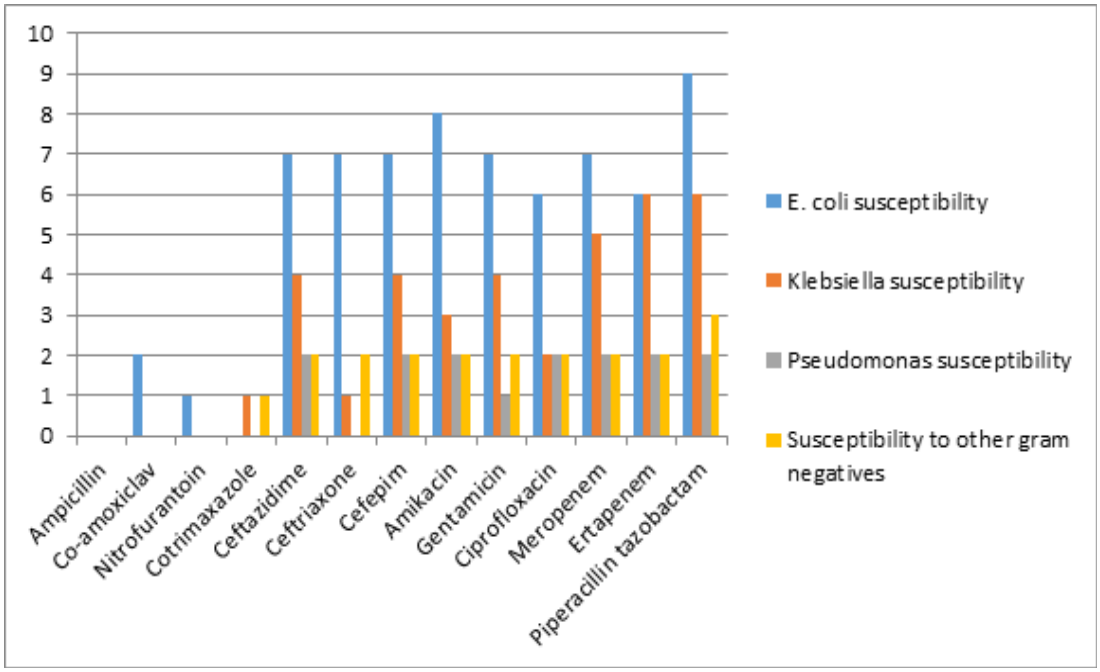

Figure 1. Antibiotic susceptibility of gram negative uropathogens evaluated in the study

Table 2. Comparison of GFR and tacrolimus levels detected before and during UTI

	Before UTI	During UTI	*p* value
GFR mL/min/1.73 m^2	76.07±48.03	67.3±40.2	0.00
Serum tacrolimus level	6.7±2.8	6.1±2.3	0.2

over a two-year period, the incidence of UTI was reported as 0.23/1000 transplant days. Among all solid organ transplantations, the risk of UTI is 4.9% in the pancreas, 2.2% in the heart, 1.6% in the liver and 0.7% in the lung, while the highest rate was reported in kidney transplantation as 7.3% [10]. In another study that included 177 renal transplant patients, the frequency of at least one UTI attack was reported as 41.9% during the two-year follow-up [4]. In our study, the frequency of UTI attacks was 48%.

UTI is most commonly detected in the first 3-6 months in renal transplant recipients due to surgical trauma, urinary catheterization and intensive immunosuppressive therapy [11, 12]. In our study, the frequency of UTI was found to be 39.5% in the first 3 months and 57.9% in the first 6 months. In a cohort of 867 patients, UTI was reported as 21% within the first year after transplantation [13]. In a study conducted in Yemen, this rate was reported to be much higher as 33.3% [14]. In our study, this rate was found to be quite high as 79.9% in the first year.

Abbott et al. [15] reported that UTIs in the first 6 months increased the risk of death and graft, according to the results of 28942 patients they evaluated retrospectively. It has been reported that creatinine levels rise acutely in pyelonephritis after transplantation, but this regresses with treatment [16]. In our study, the GFR values before renal transplantation and at the time of detection of UTI were compared and it was found that the GFR values determined during UTI were significantly lower than before.

Similar to our study, the frequency of UTI increased as basal creatinine levels increased [17].

Similar to our study, the majority of microorganisms causing UTI in renal transplant recipients are gram-negative bacteria (70%), mainly *E.coli* and *Klebsiella pneumoniae*, *Enterococcus faecium* and *Pseudomonas aeruginosa* [2, 17-19]. Multidrug-resistant urinary pathogens are increasing all over the world. Renal dysfunction was found to be more prominent in UTIs developed with multi-drug-resistant microorganisms [18].

Resistance rates of uropathogens due to antibiotics used for prophylaxis and treatment are increasing in transplant recipients. In a review, it was found that 62% of UTIs developed in renal transplant recipients due to TMP-SMX treatment used for prophylaxis developed due to TMP-SMX resistant strains [20]. In the RESITRA cohort, which evaluated UTIs developing in renal transplant recipients, ESBL positive *E.coli* rates were 23% and quinolone resistances; It was found to be 38-45% in *E.coli*, 25-31% in Klebsiella and 21% in *P.aeruginosa*. TMP-SMX resistance in *E.coli* is 77% [10].

In the study of Senger et al. [21], UTIs developing in renal transplant recipients were evaluated; ciprofloxacin resistance was found to be 50% in *E.coli* at the first month after transplantation, 32.4% after 6 months, and 70.6% for TMP-SMX. In a study examining 295 renal transplant recipients in Poland, the rate of ESBL positive Enterobacteriaceae was found to be 52.5% and it was reported to be associated with long-term use of ceftriaxone [22]. In a study from Turkey, ESBL positive *E.coli* and *Klebsiella spp*. rate was found to be 52.8% [23]. In our study, TMP-SXT resistance of all microorganisms causing UTI was found to be 73.7%.

The incidence of recurrent UTI in renal transplant recipients has been reported to be 2.9-27% [24-26]. The most common cause of recurrent UTI in 201 renal transplant recipients in the UK has been reported as urinary stents remaining for more than 30 days [27]. In addition, female gender, prolonged Foley's catheterization, coexisting diabetes mellitus, induction of anti-thymocyte globulin (ATG) therapy, CMV disease, vesicoureteral reflux, anatomical urological malformation, re-transplants have been reported to be associated with recurrent UTI [24, 26]. In two studies conducted in recent years, it has been reported that multi-drug-resistant microorganisms are the cause of recurrent UTI [18, 19]. In our

study, 28 (73.6%) UTI attacks were evaluated as reinfection and 6 (26.4%) attacks were considered as relapses.

For prophylaxis for recurrent UTI, treatment is recommended between 6 weeks and 3 months in some studies [28, 29]. In a study including 136 renal transplant patients, 15 of 34 patients with recurrent UTI were given nitrofurantoin prophylaxis between 10 weeks and 3 months before or recently in transplantation, but its effect in preventing UTI was found to be insufficient [25]. Prolonged use of antibiotics also causes antibiotic resistance. Some authors recommend that secondary prophylaxis be given to those with a history of DM, UTI, or those receiving high-dose immunosuppressive therapy [30]. Microorganisms expressing extended-spectrum beta-lactamase have been reported with a rate of 13% in the first attack of UTI and at a rate of 45% during the third attack [31]. In our study, the rate of ESBL was found to be 36%, and 100% in those who had two or more UTI attacks.

Inappropriately treated UTI adversely affects the outcome of transplantation and increases mortality. Therefore, empirical treatments should be reviewed and treatment success should be increased by taking into account the risk factors, clinical characteristics, severity of infection, previously used antibiotics and past infections, and rates of resistance in the hospital. Any obstruction and/or reflux anomalies that facilitate the risk of UTI should be corrected, urinary catheterization and urinary stent times should be shortened as much as possible.

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Contribution of the authors

T.S. developed the theory and performed the computations, verified the analytical methods B.D. and M.C. supervised the findings of this work. T.S. wrote the manuscript. All authors discussed the results and contributed to the final manuscript.

Research Article

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Effects of glabridin on cell proliferation and long non-coding RNA expression in HEC-1B cells

HEC-1B hücrelerinde glabridinin hücre proliferasyonu ve uzun kodlamayan RNA ekspresyonu üzerindeki etkileri

Muhammed Fatih Doğan, Mücahit Seçme, Yasemin Şahin, Osman Çiftçi

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Abstract

Purpose: Endometrial cancer is one of the most common gynecological cancers in the world. Glabridin is a main isoflavone in Glycyrrhiza glabra (licorice) root. It has several therapeutic effects such as anti-proliferative and anti-inflammatory. Long non-coding RNAs (LncRNAs) play a role in a variety of cellular processes, and their abnormal expression may contribute to tumor development and progression. In this study, the effects of glabridin on LncRNAs gene expression and viability of HEC-1B human endometrial cancer cell lines have been investigated.

Materials and methods: Glabridin was applied to HEC-1B cells in concentrations of 1 μM, 10 μM, 20 μM, 40 μM, 60 μM, and 80 μM. Glabridin's effect on HEC-1B cell proliferation was also evaluated using MTS assay. Expression profiles of LncRNAs such as H19, RNU43, LNC-MYC-3:1 and ABCC5-AS1:1 were determined by real-time PCR.

Results: Glabridin reduced the viability of HEC-1B cells in a time- and dose-dependent manner. The half maximal inhibitory concentration (IC50) dose in HEC-1B cells was detected to be 21.32 μM and 13.5 μM at the 24th and 48 hours, respectively. Glabridin has been observed to cause a significant decrease in the expression of H19 and RNU43 while increasing in the expression of LNC-MYC-3:1 and ABCC5-AS1:1.

Conclusion: Glabridin could induce HEC-1B cell death by regulating LncRNAs expression. As a result, glabridin is a potential candidate for a more effective therapeutic agent against human endometrial cancer.

Key words: Glabridin, endometrial cancer, long non-coding RNA, HEC-1B.

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Öz

Amaç: Endometrium kanseri dünyada en sık görülen jinekolojik kanserlerden biridir. Glabridin, Glycyrrhiza glabra (meyan kökü) kökündeki ana izoflavonoidlerden biridir. Glabridin anti-proliferatif ve anti-inflamatuar gibi çeşitli farmakolojik etkilere sahiptir. Uzun kodlamayan RNA'lar (LncRNAs) çeşitli hücresel mekanizmalarda rol oynar ve bunların değişen ekspresyonu, tümör gelişimine ve ilerlemesine katkıda bulunabilir. Bu çalışmada, glabridinin LncRNAs gen ekspresyonlarına etkileri ve HEC-1B insan endometriyal kanser hücre hattının canlılığı üzerindeki etkileri araştırılmıştır.

Gereç ve yöntem: Glabridin HEC-1B hücrelerine 1 uM, 10 uM, 20 uM, 40 uM, 60 uM ve 80 uM konsantrasyonlarda uygulandı. Glabridin'in HEC-1B hücre canlılığı üzerindeki etkisi MTS testi kullanılarak değerlendirildi. Çalışmamızda araştırdığımız LncRNAs olan H19, RNU43, LNC-MYC-3:1 ve ABCC5-AS1:1 ekspresyon profilleri Real time-PCR ile yöntemi ile belirlendi.

Bulgular: Glabridin, zamana ve doza bağlı bir şekilde HEC-1B hücrelerinin canlılığını azalttı. Glabridinin HEC-1B hücrelerinde maksimum yarı inhibisyon konsantrasyon (IC50) dozu 24. ve 48. saatlerde sırasıyla 21,32 μM ve 13,5 μM olarak tespit edildi. Glabridin'in LNC-MYC-3:1 ve ABCC5-AS1:1 ekspresyonunu arttırırken H19 ve RNU43 ekspresyonunda önemli bir azalmaya neden olduğu tespit edilmiştir.

Sonuç: Glabridin muhtemelen LncRNAs ekspresyonlarını düzenleyerek HEC-1B kanser hücrelerinin ölümünü sağlamıştır. Sonuç olarak, glabridin insan endometriyal kanserine karşı ileride kullanılabilecek etkili bir terapötik ajan olarak önemli bir potansiyel taşımaktadır.

Anahtar kelimeler: Glabridin, endometriyal kanser, uzun kodlamayan RNA, HEC-1B.

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Muhammed Fatih Doğan, Asst. Prof. Pamukkale University Faculty of Medicine, Department of Medical Pharmacology, Denizli, Turkey, e-mail: mfatihdogan89@gmail.com (https://orcid.org/0000-0003-4628-2771) (Corresponding Author)

Mücahit Seçme, Asst. Prof. Ordu University Faculty of Medicine, Department of Medical Biology, Ordu, Turkey, e-mail: mehtersecme@gmail.com (https://orcid.org/0000-0002-2084-760X)

Yasemin Şahin, PhD. Pamukkale University Faculty of Medicine, Department of Medical Pharmacology, Denizli, Turkey, e-mail: yasemins@pau.edu.tr (https://orcid.org/0000-0003-4226-674X)

Osman Çiftçi, Prof. Pamukkale University Faculty of Medicine, Department of Medical Pharmacology, Denizli, Turkey, e-mail: osmciftci@gmail.com (https://orcid.org/0000-0001-5755-3560)

Introduction

Endometrial cancer (EC) is the fourth most common cancer in women worldwide after breast, lung, and colorectal cancers, and its incidence is rapidly increasing [1]. North America and Europe have ten times the incidence of less developed countries [2]. Cancer invasion and metastasis are multi-step processes that cause the majority of cancer deaths [3]. Understanding the molecular mechanisms that drive tumor cell proliferation and metastasis, as well as developing a treatment strategy, is thus critical for EC. Tumor cell proliferation, invasion, metastasis, and apoptosis are all associated with the dysregulation of multiple signaling pathways [4].

Long non-coding RNAs (LncRNAs) are longer than 200 nucleotides in length and regulate cell growth by activating or inhibiting specific signaling pathways [4]. Previous study has revealed that LncRNAs have the potential to be biomarkers and therapeutic targets in cancer diagnosis and treatment [5]. Ren et al. [6] reported that H19 expressed by carcinoma-associated fibroblasts of the colorectal tumor stroma contributes to tumor development and chemoresistance. Nevertheless, the roles of LncRNAs in controlling cell proliferation in many cancer types, including EC, are not fully understood.

Licorice root (*Glycyrrhiza glabra*) has been used widely in traditional medicine of different countries [7], and glabridin is the main flavonoid constituent of licorice root [8]. Glabridin has many pharmacological properties such as anti-proliferative [9], anti-inflammatory [10], anti-asthmatic [11]. It has been shown that glabridin can inhibit human hepatoma cells by inhibiting the JNK1/2 signaling pathway [12]. Glabridin can inhibit human breast adenocarcinoma cells by inhibiting the focal adhesion kinase signaling pathway [13]. Furthermore, Huang et al. [14] reported that glabridin induces human promyelocytic leukemia cells apoptosis through p38 MAPK and JNK1/2 pathways and could serve as a potential additional chemotherapeutic agent for treating acute myeloid leukemia.

In this study, we investigated the effects of glabridin on long non-coding RNA gene expression and viability of the cultured HEC-1B human endometrial cancer cell.

Materials and methods

Chemicals

Glabridin, ≥98% (HPLC), powder was purchased from Sigma Chemical Co. (St. Louis, MO, USA, CAS no: 59870-68-7). Glabridin was dissolved in dimethylsulfoxide (DMSO).

Cell culture

HEC-1B cancer cell line (ATCC/ HTB-113) was used in this study. HEC-1B cells were grown in DMEM medium supplemented with 2 mM L-glutamine, penicilin (20 units/ml), streptomycin (20 µg/ml), and 10% (vol/vol) heat-inactivated fetal bovine serum at 37°C in a saturated humidity atmosphere containing 5% CO_2. HEC-1B cells were seeded in 96 well plates at 5000 cells per well. After 24 hours, cancer cells were applied with glabridin at different concentrations as 1 µM, 10 µM, 20 µM, 40 µM, 60 µM and 80 µM.

Determination of cell viability: MTS assay

Cell viability was determined by the MTS method (CellTiter 96® AQueous MTS Reagent Powder and phenazine methosulfate) according to the manufacturer's instructions. The absorbance values from the negative controls were calculated and the results were accepted as 100% cell viability. IC_{50} concentrations were calculated in the GraphPad Prism (GraphPad Software, Version 7) program using the cell viability results.

RNA isolation and Real Time-PCR

Glabridin were applied at IC50 concentrations to HEC-1B cells seeded in 6-well plates. At the end of the 48h incubation time, total RNA isolation, cDNA synthesis and RT-PCR analysis were performed for gene expression analysis, respectively. Only cell medium was added to the control group used to compare the results. Total RNA isolation from cells was performed using One Step RNA Reagent (BioBasic) according to the manufacturer's protocol. According to the protocol, One Step RNA Reagent was added at 1 ml per well and the cells were removed with a scraper. It was centrifuged by adding 200 µl of chloroform and 500 µl of isopropyl alcohol, respectively. The cell pellet obtained was washed with 1 ml of ethanol and then dissolved with 30 µl of RNase-DNase free water. The concentration and purity of the isolated total RNAs were

measured with a Nanodrop spectrophotometer. As a result of the measurements, the expected purity value of 260/280 for RNA was accepted as approximately 2.0.

cDNA synthesis was performed according to the manufacturer's protocol Total-Reveal Comprehensive cDNA Synthesis kit (abm, Cat No: G904, Canada). The expression analysis of H19, RNU43, LNC-MYC-3:1, and ABCC5-AS1:1 was performed by Real Time RT-PCR (SteoPne Plus RT-PCR, Applied Biosystem) according to the ABT 2x-X qPCR SYBEr-Green Master Mix (Cat No. Q03-02-05, Turkey) protocol. The RT-PCR conditions for the genes were: pre-denaturation at 95°C for 3 min, followed by 40 cycles of denaturation at 95°C for 15 s and 60°C for 60 s. GAPDH was used as housekeeping gene for normalization of the PCR data. The primer sequences of long non-coding RNAs and GAPDH used in the quantification of RT-PCR were given in Table1.

Statistical analysis

The values represent the means ± standard deviation, and the experiments were repeated three times (n=3). In the analysis of RT-PCR data, quantitation was performed using the 2-ΔΔCT method. For RT-PCR analysis RT² Profiler™ PCR Array Data Analysis program on the Internet-based Gene Globe platform was used.

Results

Cytotoxic assay and cell viability by MTS

Glabridin decreased HEC-1B cell viability in a time- and dose-dependent manner. The IC50 doses of glabridin in our study were calculated to be 21.32 μM at the 24th hour and 13.50 μM at the 48th hour (Figure 1, 2).

Gene expression levels by Real time-PCR

RT-PCR analysis revealed that, in comparison to the control group, dose group cells displayed reduced levels of H19, RNU43 and enhanced levels of LNC-MYC-3:1, and ABCC5-AS1:1 expression. The expressions of statistically significant and non-significant genes are shown in Table 2 (p<0.05).

Table 1. Primer sequences of the genes were used in this study

Gene	Primer sequences	
GAPDH	F	GTCTCCTCTGACTTCAACAGCG
	R	ACCACCCTGTTGCTGTAGCCAA
LNC-MYC-3:1	F	CGACTACTCATGGCTGGTTT
	R	AAGAAGCAGAACGTCCAAGT
ABCC5-AS1:1	F	CGACTCACAGGGTACTCAAAG
	R	CCAGCTTGTGAGAGTAGAGTTG
RNU43	F	ACTTATTGACGGGCGGACA
	R	AATCAGAACGTGACAATCAGCAC
H19	F	CGTGACAAGCAGGACATGA
	R	TCCGTGGAGGAAGTAAAGAAAC

Table 2. Effects of glabridin on fold change of the LncRNAs according to control group

Gene Name	Fold change	*p* value
LNC-MYC-3:1	5.21	0.32
ABCC5-AS1:1	2.14	0.18
H19	0.29	0.29
RNU43	0.22	0.003

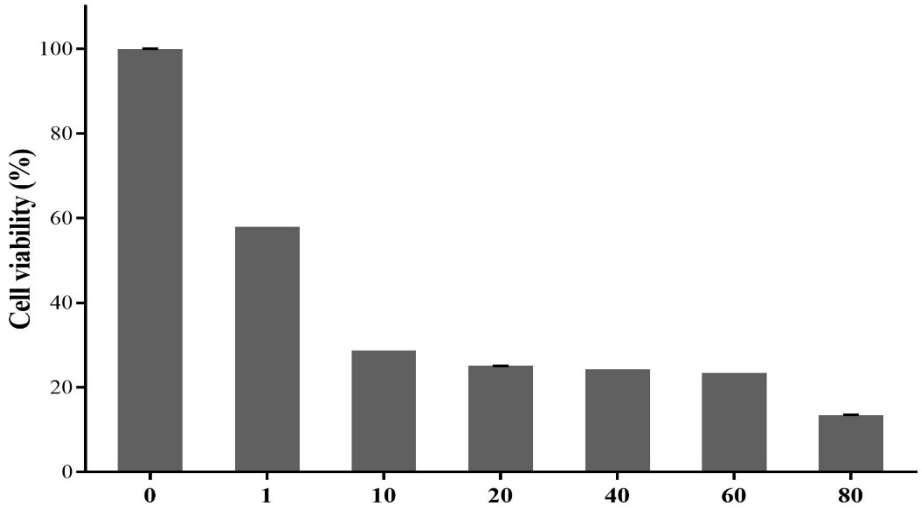

Figure 1. Cytotoxic effect of glabridin in HEC1-B cells. HEC1-B cells cultured in presence of glabridin for 24 by MTS assay
Data represent mean of 3 determinations per condition repeated 3 times. Results are shown as mean ± SD. IC50 dose of glabridin in HEC-1B cells was detected 21.32 μM at 24th hour

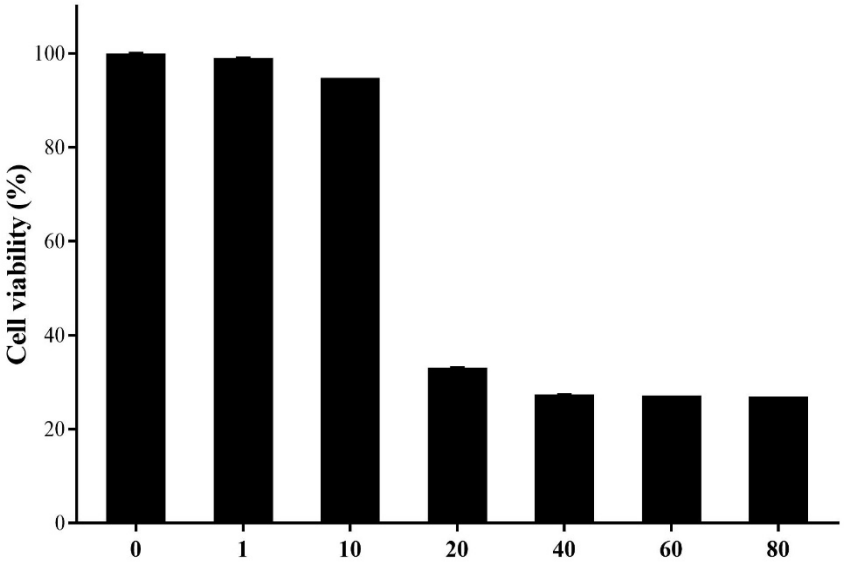

Figure 2. Cytotoxic effect of glabridin in HEC1-B cells. HEC1-B cells cultured in presence of glabridin for 48 by MTS assay
Data represent mean of 3 determinations per condition repeated 3 times. Results are shown as mean ± SD. IC50 dose of glabridin in HEC-1B cells was detected 13.5 μM at 48th hour

Discussion

EC is the fourth most common malignancy in women and the most common gynecologic cancer in developed countries [15]. LncRNA is a relatively new discovery in the RNA world that plays an important role in EC development and progression [16]. LncRNAs may be important components of the molecular mechanisms that shape the genome's three-dimensional structure [17]. Lnc-RNAs are emerging as critical regulators of cellular and disease processes. They may also play a role by competing for gene loci of miRNAs to indirectly regulate mRNA expression [18]. It has been reported that LncRNAs has a significant impact on the proliferation, migration, and invasion of cancer cells [19]. Increasing evidence suggests that LncRNAs can serve as potential therapeutic targets in cancer [20]. In addition, the special functional significance of LncRNAs suggests that they could be used as promising biomarkers in clinical cancer therapy [16]. Glabridin has been shown in previous studies to inhibit cancer cell proliferation via various mechanisms, including the miR-148a/SMAd2 signaling pathway in breast cancer cells [21] and the braf/MEK signaling pathway in hepatocellular carcinoma cells [22]. Here, we examined the effects of glabridin on viability and LncRNAs gene expression of the cultured HEC-1B cells.

LncRNAs could be tumor suppressor and oncogene genes that bind directly to RNA, DNA, or protein to perform biological functions such as cell proliferation, differentiation, apoptosis, and migration [23]. In our study, changes in gene expressions of H19, RNU43, LNC-MYC-3:1 and ABCC5-AS1:1 were analyzed. Zhao et al. [24] suggested that H19 contributed to the aggressiveness of EC by modulating the epithelial-mesenchymal transition process. Furthermore, H19 has been shown to promote the migration, invasion, and metastasis of colorectal cancer cells in vitro and *in vivo* [25]. RNU43 has also been identified as an intronic small nucleolar RNA within cancer-related genes [26]. Our findings showed that glabridin reduced mRNA expression of H19 and RNU43 compared to control cells, implying that glabridin may play a role in inhibiting HEC-1B cell proliferation by decreasing expression of these genes. The overexpression of ABCC5 in hepatocellular and breast carcinoma is associated with multidrug resistance, which can induce tumor resistance [27, 28]. Zhang et al. [29] discovered that ABCC5 expression was increased in colorectal cancer cells and reported that overexpression of antisense LncRNAs played an important role in ABCC5 regulation. Similarly, in our study, glabridin increased the expression of ABCC5-AS1:1, an antisense LncRNA, in HEC-1B. MYC family genes are frequently activated in human cancer, and their activation results in increased expression of their protein products [30]. In the present study, ABCC5-AS1:1 and LNC-MYC-3:1 mRNA expression was not significantly increased in the glabridin-treated cell.

As a result, glabridin exerted its influence by upregulating or downregulating the expression of LncRNAs. It has been reported that glabridin at concentrations higher than 10 μM was toxic to Ishikawa cells and decreased cell proliferation [31]. The IC50 of glabridin was found to be 21.32 μM at 24 hours and 13.50 μM at 48 hours in this study. Collectively, we discovered that glabridin changes the expression of LncRNAs in endometrial cancer cells. Glabridin inhibited EC cell proliferation, possibly via LncRNAs effects.

In conclusion, LncRNAs have been identified as critical regulators in the tumor formation and cancer development processes. Thus, LncRNAs may be an important therapeutic target for cancer treatment. In the present study, glabridin is thought to act as an anti-cancer agent in HEC-1B cells by regulating the expression of LncRNAs. Further *in vitro* and *in vivo* research is needed to demonstrate glabridin's anticancer effect via this mechanism.

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

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Ethics committee approval: The study is a cell culture study that does not require ethics committee approval.

Authors' contributions to the article

M.F.D., M.S. and Y.S. studied experimental processes and collected data. M.F.D. interpreted the data and prepared the draft text. M.S. and Y.S. prepared tables and graphs. M.S. and O.C. performed the statistical analysis. M.F.D. and O.C. critically reviewed the final version of the article. All authors approved the final version of the article.

Research Article

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Evaluation of continuous renal replacement therapy results applied in the intensive care unit

Yoğun bakım ünitesinde uygulanan sürekli renal replasman tedavisi sonuçlarının değerlendirilmesi

İlknur Hatice Akbudak, Çağla Erdoğan, İsmail Hakkı Akbudak

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Abstract

Purpose: Acute kidney injury diagnosed patients are in need of renal replacement therapy (RRT). Continuous RRT is believed to be safer because the rates of fluid and solute removal are slower than with intermittent hemodialysis. In many centers, CRRT is preferred in special conditions such as increased cranial pressure, sepsis, burns, heart and liver failure. In our study, we present one year data of CRRT usage in our ICU.

Materials and methods: This study included the patients who admitted to the Internal Medicine Intensive Care Unit of our university between January 2019 and June 2020. Among these patients, those over 18 years of age and those who had acute renal failure during their hospitalization and received continuous renal replacement therapy were included in the study.

Results: Mean SOFA scores at admission were 2.7 which is an indication for severe disease. Lengths of ICU stay were long and approximately 77 percent of these patients died in ICU. When the comorbid conditions of the patients were examined, it was seen that oncological diseases were the most common. It was followed by hypertension, diabetes mellitus and heart diseases. Considering the KDIGO scores of the patients diagnosed with AKI, it was seen that 60 percent of them were grade 5. Treatment could be applied for an average of 25 hours.

Conclusion: Indications, timing and benefits of CRRT are the questions that need to be research and yet remained unsolved. With evolving of technology, CRRT will be our most useful helper in ICUs.

Key words: CRRT, acute kidney injury, renal replacement therapy.

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Öz

Amaç: Akut böbrek hasarı teşhisi konan hastaların renal replasman tedavisine (RRT) ihtiyacı vardır. Sürekli RRT'nin daha güvenli olduğuna inanılmaktadır çünkü sıvı ve çözünen uzaklaştırma oranları aralıklı hemodiyalizden daha yavaştır. Birçok merkezde kraniyal basınç artışı, sepsis, yanıklar, kalp ve karaciğer yetmezliği gibi özel durumlarda CRRT tercih edilmektedir. Çalışmamızda yoğun bakım ünitemizde CRRT kullanımının bir yıllık verilerini sunuyoruz.

Gereç ve yöntem: Bu çalışmaya Ocak 2019-Haziran 2020 tarihleri arasında üniversitemiz Dahiliye Yoğun Bakım Ünitesi'ne başvuran hastalar dahil edilmiştir. Bu hastalardan 18 yaş üstü ve yatışı sırasında akut böbrek yetmezliği gelişen ve sürekli renal replasman tedavisi alanlar çalışmaya dahil edildi.

Bulgular: Başvuru anında ortalama SOFA skoru 2.7 idi ve bu ciddi hastalık göstergesiydi. Yoğun bakımda kalış süreleri uzundu ve bu hastaların yaklaşık yüzde 77'si yoğun bakımda öldü. Hastaların komorbid durumları incelendiğinde en sık onkolojik hastalıkların olduğu görüldü. Bunu hipertansiyon, diabetes mellitus ve kalp hastalıkları izledi. ABH tanısı alan hastaların KDIGO puanlarına bakıldığında yüzde 60'ının derece 5 olduğu görüldü. Ortalama 25 saat tedavi uygulanabildi.

Sonuç: CRRT'nin endikasyonları, zamanlaması ve faydaları, araştırılması gereken ve henüz çözülmemiş sorulardır. Gelişen teknoloji ile birlikte CRRT, yoğun bakım ünitelerinde en faydalı yardımcımız olacaktır.

Anahtar kelimeler: CRRT, akut böbrek hasarı, renal replasman hasarı.

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İlknur Hatice Akbudak, Asst. Prof. Pamukkale Univertsy, School of Medicine, Department of Anesthesiology and Reanimation, Denizli, Turkey, e-mail: ilhakbudak@gmail.com (https://orcid.org/0000-0001-9937-9169)

Çağla Erdoğan, M.D. Pamukkale Univertsy, School of Medicine, Department of Anesthesiology and Reanimation, Denizli, Turkey, e-mail: caglaerdogan89@gmail.com (https://orcid.org/0000-0001-8772-6565) (Corresponding Author)

İsmail Hakkı Akbudak, Assoc. Prof. Pamukkale Univertsy, School of Medicine, Department of Internal Medicine, Denizli, Turkey, e-mail: ishakbudak@gmail.com (https://orcid.org/0000-0002-3716-9243)

Introduction

Acute kidney injury (AKI) is seen in 5–45 % of patients who admitted to intensive care units (ICU), and renal replacement therapy (RRT) is one of the treatments that have been used. %4-10 of AKI diagnose patients are in need of RRT [1]. AKI has been treated with hemodialysis and peritoneal dialysis but in critically ill patients, cardiovascular instability is a major contraindication for these modalities. Continuous RRT is a safer and well tolerated option in ICU [2].

Usages of RRT, timing and choice of modalities in ICU have been investigated and there are several trials published about these questions. Some trials suggested that CRRT and intermittent RRT have similar outcomes tolerance [3, 4]. Based on clinical practice, hypotension is the most common reason for CRRT. CRRT is believed to be safer because the rates of fluid and solute removal are slower than with intermittent hemodialysis [5]. In many centers, CRRT is preferred in special conditions such as increased cranial pressure, sepsis, burns, heart and liver failure [6].

In this study, we are presenting the data of CRRT which had been used in our ICU. We will try to explain about our indications, timing and discuss the result of these treatments.

Material and methods

This retrospective study was performed at the Pamukkale University Hospital. The permission for this study had taken from Ethics Committee of the Pamukkale University, Medical School.

This study included the patients who admitted to the Internal Medicine Intensive Care Unit of our university between January 2019 and June 2020. Among these patients, those over 18 years of age and those who had acute renal failure during their hospitalization and received continuous renal replacement therapy were included in the study. Patient's data was obtained from electronic data stored in software in the hospital computers.

Data collection

Demographic data, clinical symptoms reason for the necessity of follow-up in the intensive care unit, laboratory findings and comorbidities were recorded. Acute Physiology and Chronic Health Assessment II (APACHE II), Sequential Organ Failure Assessment (SOFA), and The Simplified Acute Physiology Score II (SAPS II) score calculated and noted. Acute kidney injury had evaluated according to 'Kidney Disease Improving Global Outcomes' According to (KDIGO) guidelines [7]. CRRT onset time, duration time, modalities and the preferred anticoagulation method had recorded. The patients discharge status (dead, alive), and length of stay in the ICU were also recorded and acute clinical situations were examined.

Statistical analysis

All statistics were considered descriptive only. Descriptive statistics were used and median, mean and standard deviations were calculated. Continuous variables were defined by the mean ± standard deviation and categorical variables were defined by number and percent. To test whether numerical measurements satisfy the assumption of normal distribution Kolmogorov Smirnov test had been used.

Results

Patients who received CRRT treatment on the specified dates were added to the study. 60 patients were identified and their demographic characteristics were analyzed. It was observed that the majority of the patients were male and over 60 years of age (Table 1).

Mean SOFA scores at admission were 2.7 which is an indication for severe disease. Lengths of ICU stay were long and approximately 77 percent of these patients died in ICU (Table 1).

When the comorbid conditions of the patients were examined, it was seen that oncological diseases were the most common. It was followed by hypertension, diabetes mellitus and heart diseases. Hematological diseases were seen in ten patients. Most of the patients were in septic conditions. Procalcitonin, CRP and ferritin levels were noted. They were higher than other patients in our ICU. The levels of these parameters can be seen at Table 1.

Considering the KDIGO scores of the patients diagnosed with AKI, it was seen that 60 percent of them were grade 5. Grade 4 and 5 patients underwent CRRT. The time to start CRRT after diagnosis was variable, but it could be started

within an average of 3 hours. CRRT duration was variable due to hemodynamic instability or device-related difficulties. Treatment could be applied for an average of 25 hours. Considering the scores of the 14 surviving patients at discharge, a great improvement was seen (Table 2).

Table 1. Demographics and clinical characteristics of patients

Age (Mean ± S.D)	68.97±12.16
Sex (M/F)	42 (70%) /18 (30%)
SOFA score (Mean ± S.D)	2.71±1.32
Length of ICU stay (day) (Mean ± S.D)	15.87±11.57
Exitus	46 (76.6%)
Comorbidities	
Oncological Diseases	47 (78.3%)
Hypertension	41 (68.3%)
Diabetes Mellitus	38 (63.3%)
Coronary Artery Disease	29 (48.3%)
Cardiac Failure	12 (20%)
Hematological Disease	10 (16.6%)
Laboratory Findings at Admission	
Procalcitonin (Mean ± S.D)	2.9±10.51
C-reactive Protein (CRP) (Mean ± S.D)	123.83±86
Ferritin (Mean ± S.D)	1023.33±1335.09

S.D: Standard Deviation

Table 2. Treatment properties of patients

Scores at Beginning of CRRT	
KDIGO Grade 4	24 (40%)
KDIGO Grade 5	36 (60%)
CRRT	
Time of onset (minutes)	3.5±1.8
Duration time (hours)	25.8±12.7
Modalities	Continuous venovenous hemodialysis (CVVHD) – all patients
Preferred Anticoagulation	Heparin – all patients
Scores at Discharge (number of patients)	
KDIGO Grade 2	7 (11.6%)
KDIGO Grade 3	6 (10%)
KDIGO Grade 4	1 (1.6%)

S.D: Standard Deviation

Discussion

The use of CRRT in critically- ill patients has been increasing in recent years. Many ICUs have this option of treatment for AKI. In this study, we investigated the data of CRRT used in patients in our ICU. We chose this method against routine hemodialysis because of many reasons. The most common reason was hemodynamic instability due to sepsis. Being an internal diseases intensive care unit causes that our patients mostly admitted from oncology and hematology wards. This explains the high percent of these comorbidities in our patients.

Our initiation time was earlier than most of the studies about CRRT. The STARRT-AKI, is a large study that had 3019 patients and included many different patients from ICUs. Patients were selected to the accelerated RRT protocol group or standard RRT group randomly. There was no statistical difference in mortality between these group and between subgroups (sepsis, KDIGO grading, type of admission) [8].

Mortality rate was high in our patients. Most of the patients were immunosuppressed due to malignancies and chemotherapies. They were admitted to ICU because of sepsis and septic shock. This situation may explain high rates of mortalities.

In a prospective cohort study that investigates outcomes of cancer and non-cancer patients with acute kidney injury and need of renal replacement therapy admitted to general intensive care units found that higher mortality rate in patients can be attributed to severity of organ dysfunctions as shown by higher SOFA scores. They studied 773 patients who needs RRT and their mortality rate was %70 overall. 78 percent of these deaths were cancer patients [9].

Fourteen patients had survived AKI and could discharged. There was significant improvement in their KDIGO grading. KDIGO grade 2, 3 and 4 were noted. Mostly, the injuries were mild and patients needed follow-ups for renal functions. In a study which investigated Korean critically-ill patients in ICU, the data showed that %25 patients of solid diseases and %33.3 patients of hematologic diseases were RRT independent. This showed that we can maybe raise their survival rates but some of these patients have permanent renal injury [10]. In the cohort study, >85% of surviving patients were not dependent on RRT at hospital discharge [9]. In the study of Soares et al. [11] renal function recovered in 82% of patients at 6 months of follow-up.

CRRT has some technical limitation as seen in our cases. Such problems like filter clotting, intravascular device problems cause short treatment time. CRRT needs educated stuff including doctors and nurses. When technical problems are encountered, it is necessary to find and solve the problem. Education is essential in this regard.

In a review about CRRT complications, possible complications and interventions discussed. Mechanical complications such as vascular access related complications and extracorpeal circuit complications were major limitations for the therapy. Complications related to catheters include development of arrhythmias, hemothorax, pneumothorax, pericardial tamponade, and sepsis due to catheter infection. Premature filter clotting encountered in some patients contributes to substantial down time compromising dialysis [12].

Our study has multiple limitations. Patients are from internal medicine wards and they have multiple comorbidities that have high mortalities. This fact may raise our mortality rates. Patient variability is low due to the same fact.

As result; indications, timing and benefits of CRRT are the questions that need to be researched and yet remained unsolved. With evolving of technology, CRRT will be our most useful helper in ICUs.

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

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Authors' contributions to the article

I.H.A., C.E., I.H.A. have constructed the main idea and hypothesis of the study.

I.H.A., C.E. developed the theory and arranged the material and method section.

I.H.A., C.E., I.H.A. have done the evaluation of the data in the Results section.

Discussion section of the article is written by I.H.A., C.E.

I.H.A., C.E., I.H.A. reviewed, corrected and approved.

In addition, all authors discussed the entire study and approved the final version.

Research Article

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Demographics, clinical, laboratory findings and treatment results of pediatric patients with IgA Vasculitis: single-center experiences

IgA Vaskülitli çocuk hastaların demografik, klinik, laboratuvar bulguları ve tedavi sonuçları: tek merkez deneyimi

Ceyhun Acari, Meral Torun Bayram, Gizem Yıldız, Salih Kavukcu, Alper Soylu

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Abstract

Purpose: Immunoglobulin A (IgA) vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is a vasculitis characterized by the accumulation of IgA in the vessel walls. In this study, we purposed to evaluate the demographics, clinical and laboratory findings, and treatments and responses of patients diagnosed with IgAV/HSP in our center.

Materials and methods: The records of 201 IgAV/HSP patients who were followed up in the pediatric nephrology-rheumatology clinic were evaluated retrospectively.

Results: It was seen with the equal frequency between girls and boys. While all patients had purpura, other findings were gastrointestinal, joint, renal, subcutaneous edema, and testicular involvement, in order of frequency. The rate of patients who developed intussusception was 2.5%, and none required surgical treatment. Biopsy was performed in patients with persistent proteinuria or hematuria. Histopathological diagnoses were mesangial proliferation, crescent, and minimal change, respectively. While the rate of renal involvement was high in cases with rash and relapse (p=0.046), there was no difference in gastrointestinal and joint involvement. In the histopathological findings of the boys, the crescent was higher than in the girls (p=0.017).

Conclusion: IgAV/HSP generally has a good prognosis, but some patients suffer from renal involvement. In our study, renal histopathology in cases with renal involvement showed milder findings in girls than in boys, but there was no difference in other findings. Renal involvement was higher in relapsed patients.

Key words: IgA vasculitis, renal involvement, Henoch-Schonlein purpura, renal histopathology.

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Öz

Amaç: Henoch-Schönlein purpurası (HSP) olarak adlandırılan İmmünoglobin A (IgA) vasküliti (IgAV), damar duvarlarında IgA baskın immün birikimi ile karakterize küçük damar vaskülitidir. Bu çalışmada merkezimizde IgAV/HSP tanısı almış hastaların demografik özelliklerini, klinik ve laboratuvar bulgularını tedavilerini ve tedavi yanıtlarını değerlendirmeyi amaçladık.

Gereç ve yöntem: Çocuk romatoloji ve nefroloji kliniğinde takipli 201 IgAV/HSP hastasının kayıtları retrospektif olarak değerlendirildi.

Bulgular: Kız ve erkekler arasında hastalık eşit sıklıkta görüldü. Hastaların tamamında purpura varken diğer bulgular sıklık sırasına göre gastrointestinal, eklem, renal, subkutan ödem, testiküler tutulum idi. İnvajinasyon gelişen hastaların oranı %2,5'tu ve hiçbirinde cerrahi tedavi gerekmedi. Persistan proteinüri veya hematürisi olan hastalara biyopsi uygulandı. Histopatolojik tanıları sırayla mezengial proliferasyon, kresent ve minimal değişiklik idi. Döküntü ile relaps gelişen olgularda renal tutulum oranı yüksek iken (p=0,046) gastrointestinal ve eklem tutulum oranlarında fark yoktu. Renal tutulum olan erkeklerin böbrek histopatolojik bulgularında kresent kızlara göre daha yüksek oranda görüldü (p=0,017).

Sonuç: IgAV/HSP, genel olarak, iyi prognoza sahiptir, ancak renal tutulumdan muzdarip hastalar vardır. Çalışmamızda renal tutulum gerçekleşen olgularda böbrek histopatolojisi kızlarda erkeklere göre daha hafif bulgular gösterirken diğer bulgularda fark yoktu. Relaps gelişen olgularda renal tutulum daha fazla idi.

Anahtar kelimeler: IgA vasküliti, renal tutulum, Henoch-Schonlein purpurası, renal histopatoloji.

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Ceyhun Acari, MD. Dokuz Eylul University, Faculty of Medicine, Pediatric Rheumatology, Izmir, Turkey, e-mail: ceyhun_acari@hotmail.com (https://orcid.org/0000-0002-7175-0015) (Corresponding Author)

Meral Torun Bayram, Assoc. Prof. Dokuz Eylul University, Faculty of Medicine, Pediatric Nephrology, Izmir, Turkey, e-mail: meralt.bayram@yahoo.com (https://orcid.org/0000-0003-3760-7028)

Gizem Yıldız, MD. Dokuz Eylul University, Faculty of Medicine, Pediatric Nephrology, Izmir, Turkey, e-mail: gizemhhuyuk@hotmail.com (https://orcid.org/0000-0001-9513-6661)

Salih Kavukcu, Prof. Dokuz Eylul University, Faculty of Medicine, Pediatric Nephrology, Izmir, Turkey, e-mail: s.kavukcu@deu.edu.tr (https://orcid.org/0000-0002-9959-881X)

Alper Soylu, Prof. Dokuz Eylul University, Faculty of Medicine, Pediatric Nephrology, Izmir, Turkey, e-mail: alper.soylu@deu.edu.tr (https://orcid.org/0000-0002-5901-7398)

Introduction

Immunoglobin A (IgA) vasculitis (IgAV), previously named Henoch-Schönlein purpura (HSP), is a small vessel vasculitis characterized by IgA-dominant immune accumulation in the vessel walls [1]. While it may occur as systemic or limited vasculitis in a single organ, skin, kidney, gastrointestinal system, and joints are frequently involved [1]. Immunoglobulin A (IgA) vasculitis/Henoch-Schönlein purpura (IgA/HSP) has an annual incidence of 20 per 100,000 [2]. It is commonly seen between 3-15 years of age. Although it is more common in males, the male-female ratio varies between 1.2:1-1.8:1. IgAV/HSP is seen especially in autumn, spring, and winter. This is explained by the relationship between IgAV/HSP and infections [3]. An upper respiratory tract infection occurs in about half of IgAV/HSP cases, but the disease is also associated with possible triggers such as vaccines and insect bites [4].

Characteristic symptoms are palpable purpura, arthritis/arthralgia, abdominal pain, hematuria, or proteinuria. Gastrointestinal (GI) involvement is seen in 10-40% and renal findings in 10-55% of patients. Renal involvement during the chronic period and gastrointestinal involvement in the acute period are major causes of morbidity and mortality [5]. IgAV/HSP is self-limited in most cases; however, renal involvement may be associated with severe glomerulonephritis, leading to end-stage renal disease. Delay in treatment can lead to fibrosis and progression to chronic kidney disease in patients with severe nephritis [6].

The diagnosis of IgAV/HSP is based on clinical and histopathological evidences. The American College of Rheumatology (ACR) defined diagnostic criteria for HSP patients, in 1990 [7]. Subsequently, the Ankara 2008 criteria were approved by the European League Against Rheumatism (EULAR), European Society of Pediatric Rheumatology (PRES), and Pediatric Rheumatology International Trials Organization (PRINTO) [8]. In accordance with Ankara 2008 criteria, palpable purpura became an obligatory feature, arthritis/arthralgia and kidney involvement were included and the age criterion was removed. Ankara 2008 criteria had a similar specificity (87.7% vs. 87%) but higher sensitivity (100% vs. 87.1%) in children compared to the ACR criteria [8].

In this study, we aimed to evaluate the demographic characteristics, clinical and laboratory findings, and treatments and responses of patients diagnosed with IgAV/HSP.

Materials and methods

The records of 201 IgAV/HSP patients in the pediatric rheumatology and nephrology outpatient clinic were evaluated retrospectively. Local ethics committee approval was obtained for the study. (2022/26-18)

The diagnosis of IgAV/HSP patients was confirmed according to the 2008-EULAR-PRINTO-PRES classification criteria [8]. The patient records, demographic characteristics, clinical laboratory findings at the time of diagnosis, treatments, treatment results, and disease course were evaluated retrospectively. Clinical findings such as abdominal pain and/or gastrointestinal bleeding (melena, hematochezia, or fecal occult blood) were considered as gastrointestinal involvement, hematuria, proteinuria, and/or increased serum creatinine renal involvement. Laboratory parameters included hemogram, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum immunoglobulin A (IgA), serum creatinine, estimated glomerular filtration rate (eGFR), fecal occult blood, and 24-hour urine protein excretion. *MEFV* gene analysis was performed in patients who had severe abdominal pain, significant acute phase response, or recurrent clinical findings.

Statistical analysis

The statistical analyzes were performed with SPSS 20.0 software. Quantitative variables were presented as mean ± standard deviation or median (minimum-maximum) values, while categorical variables were presented as number of cases and percentage. The groups were evaluated for normal distribution using the Kolmogorov-Smirnov test. Mann Whitney U and Chi-square tests were used to compare groups for mean values and to compare ratios between groups. $p<0.05$ was considered statistically significant.

Results

Of the patients diagnosed with IgAV/HSP vasculitis, 102 (50.7%) were female, 99 (49.3%) were male, and the age at diagnosis was

7.5±3.0, and the follow-up period was 27.2±26 months. While all patients had purpura, they had gastrointestinal, joint, renal involvement, scalp edema, and orchitis, in order of frequency. Preceding respiratory tract infection history was present in 87 (43.3%) patients. One or more relapses were observed during follow-up in 53 (26.4%) patients. Relapses were manifested as skin findings in 42 (20.9%) patients, renal findings in 6 (3%), and gastrointestinal findings in 5 (2.5%) patients. The demographic and clinical findings are shown in Table 1. *MEFV* gene analysis was studied in 47 patients with high acute phase response, recurrent rash, fever, and abdominal pain. At least one or more *MEFV* variants were detected in 25 patients. The most frequently seen mutation was *M694V*. The *MEFV* gene distributions of the patients are given in Table 2. Renal biopsy was performed in 39 patients with persistent proteinuria or hematuria. The pathological findings of the patients were mesangial proliferation 21 (53.8%), crescentic glomerulonephritis 12 (30.7%), and minimal change 6 (15.3%), respectively. The renal biopsy results are given in Table 3. Treatments are shown in Table 1. Spontaneous remission was observed in 79 patients, while treatment was started in 112 patients. 102 (39.3%) of these patients had complete remission, and 10 (5.0%) had partial remission. The outcomes of the patients are shown in Table 4.

The distribution of clinical and histopathological findings between male and female patients is shown in Table 5. While there was a higher rate of renal involvement in relapsed cases, this relationship was not observed in GIS and joint involvement. The relationship between relapse development and system involvement in IgAV/HSP cases is given in Table 6.

Table 1. Demographic, clinical, and laboratory data of patients Immunglubolin a Vasculitis/Henoch-Schonlein Purpura (IgAV/HSP)

Demographics	
• Number	201
• Female / Male	102/99
• Onset age (year)	7.5±3.0
• Follow-up period (month)	27.2±26.2
Clinical findings [N (%)]	
• Purpura	201 (100)
• Arthritis/arthralgia	112 (55.7)
• Gastrointestinal involvement	117 (58.2)
• Renal involvement	70 (34.8)
• Invagination	5 (2.5)
• Scalp edema	34 (16.9)
• Preceding infection	87 (43.3)
• Testicular involvement	13 (6.5)
• Relapse	53 (26.4)
• Skin	42 (20.9)
• Renal	6 (3.0)
• Gastrointestinal	5 (2.5)
Laboratory results	
• Hemoglobin (g/dL)	12.3±1.3
• Leukocytes(/mm3)	11.638±5.133
• Platelets (/mm3)	367.489±141.510
• ESR (mm/h)	28.2±21.3 (2-121)
• CRP (mg/L)	18.7±31.9 (0-233)
• IgA (mg/dL)	192.0±101.2
• Proteinuria [N (%)]	64 (31.8)
• Hematuria [N (%)]	59 (29.4)
Treatment [N (%)]	
• NSAID	20 (10)
• Corticosteroids	104 (51.7)
• Colchicine	16 (8)
• Azathioprine	18 (9)
• Mycophenolate mofetil	3 (1.5)
• Cyclophosphamide	1 (0.5)
• ACE-I	26 (12.9)
• Omega-3	19 (9.5)

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, NSAID: Nonsteroid anti-inflammatory drugs
ACE-I: Angiotensin-converting enzyme inhibitors

Table 2. Distribution of *MEFV* gene mutations in 47 Henoch Schonlein purpura patients

	N	%
No mutation	22	47
Homozygous mutation		
• M694V / M694V	3	6
• R202Q / R202Q	2	5
Compound heterozygous mutation		
• M694V / R202Q	3	6
• M694V / M680I	1	2
• E148Q / P369S	1	2
Heterozygous mutation		
• M694V / -	5	11
• E148Q / -	4	9
• R202Q / -	3	6
• V726A / -	1	2
• A744S / -	1	2
• K695R / -	1	2

Table 3. Pathological diagnosis distributions of patients who underwent renal biopsy (N:39)

	N (%)
Minimal glomerular change	6 (15.3)
Crescent	12 (30.7)
Mesangial proliferation	21 (53.8)

Table 4. The outcome of patients at two-year follow-up

Outcome	[N (%)]
Spontaneous remission	79 (39.3)
Partial remission	10 (5.0)
Complete remission	102 (50.7)

Table 5. Distribution of clinical findings and renal pathological diagnoses by gender

Clinical findings [N (%)]	Kız	Erkek	*p*
• Arthritis/arthralgia	60 (58.8)	52 (52.5)	0.225
• Gastrointestinal involvement	38 (37.2)	40 (40.4)	0.377
• Renal involvement	37 (36.2	33 (33.3)	0.386
• Invagination	2 (2)	3 (3)	0.486
• Scalp edema	15 (14.7)	19 (19.1)	0.255
• Preceding infections	49 (48.0)	38 (38.3)	0.108
• Relapse			
• Skin	18	24	
• Renal	4	2	0.550
• Gastrointestinal	2	3	
Pathological diagnoses [N (%)]	17	22	
Minimal glomerular change	5 (29.4)	1 (4.5)	
Crescent	6 (35.3)	6 (27.2)	0.017*
Mesangial proliferation	6 (35.3)	15 (68.1)	

p<0.05 significant

Table 6. Relationship between other system involvements and recurrent purpura

	Recurrence (+)	Recurrence (-)	*p*
Renal involvement	24 (34.2)	46 (65.7)	0.046*
Gastrointestinal involvement	20 (25.6)	58 (74.3)	0.494
Joint involvement	28 (26.6)	77 (73.3)	0.524

**p*<0.05 significan

Discussion

IgAV/HSP is characterized by palpable purpura, joint, GI, renal findings, and subcutaneous edema. In our study, we reported the experiences of pediatric IgAV/HSP in the tertiary pediatric nephrology-rheumatology center in the west of Turkey. IgAV/HSP is most common between 3-15 years of age and peaks between 5-7 years of age [9-11]. In studies from Turkey, the mean age of IgAV/HSP has been reported to be between 7 and 9 years [3, 6, 12-14]. In our study, the age of onset was 7.5±3.0 years, and males and females were equally affected. In the literature, besides the studies reporting gender equality, there are also studies showing male, or female dominance [3, 6, 12-14].

The etiopathogenesis of IgAV/HSP has yet to be fully elucidated. It is thought to be triggered by respiratory infections or other infectious diseases [15]. The frequent occurrence of IgAV/HSP in autumn and spring supports the idea that infections trigger the disease. Medications, vaccines, and nutrients can also be triggers [9]. In our study, 87 patients (43.3%) had a history of infection as a predisposing factor. The preceding infection history rate varies between 21.4-68.8% [6, 12, 13]. Sixty-nine patients (34%) were hospitalized at the time of admission. Almost all of the patients hospitalized were patients presented gastrointestinal findings. In two studies from Taiwan and Turkey, hospitalization rates were reported as 40.5% and 38.9%, respectively [11, 12]. The Korean study reported a lower rate of hospitalization [16]. These differences in hospitalization rates may be due to differences in disease severity and indications for hospitalization. In particular, the fact that GIS involvement is an acute condition that can result in rapid deterioration, the anxiety of the family, and the level of sensation of the disease may be the reason for this difference. The most common indication for hospitalization was GI involvement, and corticosteroid therapy was given to these patients as 30 mg/kg or 1-2 mg/kg/day methylprednisolone.

All patients had purpura, and 34 (16.9%) had subcutaneous edema (scalp edema). In other studies, this rate has been reported between 25.3-51.3% [11, 12]. Arthritis-arthralgia is the secondly common finding in IgAV/HSP [8]. Arthritis-arthralgia has been reported in 50-70% of patients with IgAV/HSP [12-14, 17]. Also, there are studies reporting higher rates of joint involvement (91.9%) [18]. In our study, the incidence of arthritis-arthralgia was 55.7%. NSAIDs were sufficient in the treatment of these patients. GI involvement was 55.8% in our cohort. The patients in this group were those with abdominal pain accompanied by occult blood in the stool or intestinal wall edema or free fluid findings on abdominal ultrasonography. There was no case of massive rectal bleeding. The rate of GI involvement in IgAV/HSP cases has been reported to be between 32-72% [3, 6, 12-14, 19]. Intussusception is the most important surgical complication in IgAV/HSP and develops in 0.7-13.6% [20]. Five (2.5%) patients had intussusception. These patients improved with corticosteroid therapy without the need for surgery or pneumatic reduction. In other studies, this rate was between 2.3-5.6% [12, 14].

It is generally recommended that patients with IgAV/HSP should be followed for at least six months to detect renal involvement [9]. Renal involvement in HSP has been reported as 20-50% in the literature [8, 21-25]. In our study, renal involvement was determined as 34.8% in the first 6-month period. Of these patients, 22 (31.4%) had nephrotic, 42 (60%) non-nephrotic proteinuria, 57 (81.4%) microscopic, and 26 (37.1%) macroscopic hematuria. Rarely, especially in patients with isolated hematuria and proteinuria, renal involvement may occur in a later period. None of our patients had renal failure or end-stage renal disease. Renal biopsy was performed in 39 patients with persistent or nephrotic proteinuria. All biopsy patients had IgAV/HSP nephritis ranging from minimal glomerular changes to diffuse crescent formation. The histopathological diagnoses of these patients were mesangial proliferation in 22 (56.4%), crescent in 12 (30.7%), and minimal change in 6 (15.3%), respectively. Karadag et al. [12] reported that six crescents, four mesangial proliferation, and three minimal glomerular changes were detected in 13 patients who underwent biopsy. They administered high-dose methylprednisolone and cyclophosphamide treatments to patients who developed IgAV/HSP nephritis. None of their patients developed end-stage renal disease or renal disease failure [12].

Testicular involvement is manifested by pain and swelling and may require evaluation by an experienced pediatric surgeon to rule out testicular torsion – this distinction is important because the former is conservative in treating, and the latter is an acute surgical emergency [19]. Testicular involvement developed in 13 patients (6.5%). In other studies, the rate of testicular involvement has been reported between 1.9-6% [6, 12, 13].

Mutation in at least one allele was detected in 25 (53.2%) patients whose *MEFV* mutation analysis was studied. The most frequently seen mutation was *M694V*. An increased *MEFV* mutation rate has been shown in the literature among patients with IgAV/HSP [26-28]. However, there is no consensus on the effect of *MEFV* gene mutations on the clinical severity of IgAV/HSP [12].

Our study did not detect any difference in the incidence of clinical findings between male and female genders. However, in renal biopsy results, while minimal glomerular changes were higher in females, mesangial proliferation was higher in males (p=0.017).

Some studies reveal the relationship between recurrence and the presence of nephritis [17, 24, 25]. The recurrence was present in 53 (26.4%) of our patients. The recurrences were seen in skin, renal, and GI. In our study, there was a significant relationship between recurrences and the development of nephritis (p=0.046). We did not observe any relationship between recurrences and gastrointestinal and joint involvement. The frequency of relapses reported in previous studies ranges from 3% to 65%, and relapses are mostly seen as skin findings [12, 17, 21, 23, 29]. Studies with higher relapse rates defined relapse as a new exacerbation of skin lesions or other clinical manifestations following the resolution of the disease for at least two weeks or one month [21, 23]. In studies with low incidence, symptoms occurring before three months were accepted as a prolonged course of IgAV/HSP, and exacerbations occurring in a more extended period were considered as recurrence [12, 17]. In our study, we considered relapse as a new exacerbation of clinical symptoms following at least two weeks or one-month resolution of the disease.

In conclusion, this study aimed to share our knowledge and experience to help better define demographic findings, risk factors, management and follow-up of the disease, and associated complications. In our patients, the most common finding and the most frequent recurrence were seen in the skin. The renal involvement rate was higher in cases with recurrence. Gastrointestinal and renal findings significantly accompanied skin findings at the onset of the disease and were the most important causes of morbidity and hospitalization. GIS and renal flare are less responsible for relapses. In cases with renal involvement, renal histopathology shows milder findings in girls than in boys. IgAV/HSP generally has a good prognosis, but some patients suffer from renal involvement. Ultimately, multicenter studies are needed to prevent and improve the long-term renal involvement results of IgAV and to develop an optimal approach to treatment and follow-up.

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Ethics committe approval: Permission for the study was obtained from the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University (09/11/2022 , 2022/36-18).

Authors' contributions to the article

C.A., A.S., S.K. and M.T.B. constructed the main idea and hypothesis of the study. C.A., M.T.B. and A.S. developed the theory and arranged/edited the material and method section. C.A. and M.T.B. evaluated the data in the results section. C.A. and M.T.B. wrote, reviewed, corrected and approved the discussion section. In addition, all authors discussed the entire study and approved the final version.

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Evaluation of the level of knowledge about cancer prevention and early screening methods in healthcare workers

Sağlık çalışanlarında kanserden korunma ve erken tarama yöntemleri ile ilgili bilgi düzeylerinin değerlendirilmesi

Halil Sağınç, Burcu Yapar Taşköylü

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Abstract

Purpose: The purpose of this article is to investigate the effect of planned training of healthcare workers to increase awareness of cancer prevention and early screening programmes.

Material and methods: In our cancer early diagnosis training, a questionnaire with 15 questions was applied to 60 healthcare workers on the awareness of cancer prevention and early screening programmes. Three male and fifty-seven female healthcare workers who participated in the training were included in the study. Wilcoxon signed-rank test and Mann-Whitney U test have been used to investigate the effect of the training on healthcare workers.

Results: Following the 15-question questionnaire administered to 60 healthcare workers, the Wilcoxon signed-rank test showed that the median correct response in the pre-education test was 12, while the median correct response in the post-education test was 13, which was statistically significant (p=0.00). The median correct answer was 12 in the pre-education test in women and 8 in the pre-education test in men (p=0.02). The number of correct answers was significantly higher between men and women in the pre-education test in favour of women. The post-education test median response was 13 in women and 11 in men (p=0.13). No statistical significance was found between pre-education test and post-education test according to age, educational status, nurses and other healthcare workers.

Conclusion: It was found that the level of knowledge increased statistically significantly with information about cancer early diagnosis methods and prevention methods in healthcare workers working in the hospital. It was seen that the level of knowledge increased more in male healthcare workers with cancer information training. Utilisation of new tests such as fecal immunochemical testing (FITs) in colorectal cancer, screening with low dose thorax CT (LDCT) in lung cancer and autofluorescence imaging bronchoscopy (AFI), narrow band imaging bronchoscopy (NBI) increases the diagnosis of cancer at early stages.

Key words: Cancer education, nurses, healthcare workers, cancer prevention and early screening.

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Öz

Amaç: Kanserden korunma ve erken tarama programlarının farkındalığını arttırmak için sağlık çalışanlarına planlı eğitiminin etkisini araştırmaktır.

Gereç ve yöntem: Kanser erken tanı eğitimimizde kanserden korunma ve erken tarama programlarının bilinirliği üzerine 60 sağlık çalışanına 15 soru ile anket uygulandı. Eğitime katılan 3 erkek, 57 kadın sağlık çalışanı çalışmaya alındı. Wilcoxon işaretli sıralar testi ve Mann-Whitney U testi kullanarak eğitimin sağlık çalışanları üzerindeki etkisi araştırıldı.

Bulgular: 60 hemşire ve sağlık çalışanına uygulanan 15 soruluk anket yanıtlandığında Wilcoxon işaretli sıralar testi ön test doğru yanıt median 12 iken son test median doğru yanıt median 13 istatistiksel olarak anlamlı bulundu (p=0,00). Kadınlarda ön testte median doğru 12, erkeklerde ön testte median 8' dir (p=0,02). Erkekler ile kadınlar arasında ön testte belirgin kadınlar lehine doğru sayısı fazlaydı. Kadınlarda son testmedian yanıt 13, erkeklerde son testte median yanıt 11'dir (p=0,13). Yaş, eğitim durumu, hemşire ve diğer sağlık çalışanlarına göre anket ön test ve son testler arasında istatistiksel anlamlılık bulunmadı.

Sonuç: Hastenede çalışan sağlık çalışanlarında kanser erken tanı yöntemleri, korunma yöntemleri ile ilgili bilgilendirme ile bilgi düzeylerinin istatistiksel anlamlı olarak arttığı görülmüştür. Erkek sağlık çalışanlarında kanser bilgilendirme eğitimi ile bilgi düzeylerinin daha fazla arttığı görüldü. Kolorektal kanserinde fekal immünokimyasal test (FITs), akciğer kanserinde düşük doz toraks BT (LDCT) ile tarama ve otofloresan görüntüleme bronkoskopisi (AFI), dar bant görüntüleme bronkoskopisi (NBI) gibi yeni tetkiklerin kullanılması erken evrede kanser tanısının konulmasını arttırır.

Halil Sağınç, Asst. Prof. Pamukkale University Faculty of Medicine Radiation Oncology, Denizli, Turkey, e-mail: halilsaginc@hotmail.com (https://orcid.org/0000-0002-3269-0267) (Corresponding Author)

Burcu Yapar Taşköylü, Asst. Prof. Pamukkale University Faculty of Medicine Radiation Oncology, Denizli, Turkey, e-mail: drburcuyapar@gmail.com (https://orcid.org/0000-0003-4755-2753)

Anahtar kelimeler: Kanser eğitim, hemşire, sağlık çalışanları, kanserden korunma ve erken tarama

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Introduction

Cancer is the second leading cause of death after cardiovascular diseases. The mortality rate from cancer is lower in societies where cancer is detected at an early stage. The incidence of cancer is gradually increasing and this increase has led to the need to initiate cancer screening programmes. In addition to early diagnosis and screening of cancer, it is very important to raise awareness about the causes, risk factors and symptoms of cancer in the society and to create behavioural change. Early diagnosis and screening studies for cancer prevention should be planned by those working to improve public health [1]. Implementation of cancer early diagnosis and screening programs are recommended by the World Health Organization [2]. The national community-based cancer screenings of the Ministry of Health of the Republic of Turkey are conducted by Cancer Early Detection, Screening and Education Centres (KETEM), Family Health Centres (FHC) and Community Health Centres (TSM). It is recommended to perform mammography every two years in women aged 40-69 years for breast cancer, HPV and pap smear test every five years in women aged 30-65 years for cervical cancer, and Fecal Occult Blood Test every two years and colonoscopy every 10 years in all men and women aged 50-70 years for colorectal cancers [3]. In the guidelines of the European Society of Medical Oncology (ESMO), it is recommended by the European Breast Cancer Commission for women over the age of 40, while women over the age of 50 are necessarily asked to have mammograms in every one year or two years. Particularly those with a family history of breast cancer with or without a BRCA mutation are recommended to have annual mammograms and breast MRI scans [4]. In many countries of the world, nurses are involved in health education of healthy/patient individuals to increase early diagnosis of cancer [5]. When individuals at risk are given the necessary warnings and information by healthcare personnel, they go to the health institution and switch from a passive role to an active role in disease screening. As part of the prevention programme, nurses can also prevent complications by educating and regularly monitoring patients [6]. Nurses also have an important role and responsibility in the process of protecting women from breast cancer and acquiring the habit of self-examination [5]. Self-manual examination, which is an economical and easy method that every woman can easily perform, is a technique developed especially for the investigation/examination of cancer. In order to get to know the breast tissue better and to determine possible changes, it is necessary to perform manual self-examination at regular and periodic intervals, to be willing to have a breast examination, to know the examination technique well and to feel responsible for its practice [7].

Cervical cancer is the best example of cancers that can be prevented by protection. After the researches, it is assumed that providing education contributes to the elimination of women's lack of knowledge [1]. In protecting against cervical cancer, it is important to know the factors that are thought to cause cancer from the point of view of measures to be taken [6]. Human papillomavirus DNA test recommended by ASCO is repeated every 5 years between the ages of 25 and 65, and is repeated every 10 years if it is negative 2 times in 5 year periods between the ages of 30-65. HPV DNA testing is performed in HIV-positive women [8]. The American Society of Clinical Oncology (ASCO) primarily performs faecal occult blood test and faecal immunochemical test in asymptomatic individuals aged 50-75 years. Flexible sigmoidoscopy and colonoscopy are recommended according to the tests. Digital rectal examination, double-contrast barium enema radiography, flexible sigmoidoscopy, and colonoscopy are recommended for symptomatic individuals [9].

The US Preventive Services Task Force (USPSTF) prefers clinicians and individuals to decide together on PSA-based screening for prostate cancer in men aged 55-69 years, while PSA-based screening is recommended for men aged 70 years and older [10]. Subclinical prostate cancer is common in men over the

age of 50. PSA-based screening should not be performed in men who do not have symptoms. In the European Society of Medical Oncology (ESMO) guidelines, PSA testing is used in men over 70 years of age in patients with symptoms [11].

Lung cancer is the most common cancer-causing cancer in the world, and early diagnosis is important for long-term survival. Increased survival is achieved by low-dose thorax CT screening in high-risk individuals [12]. Lung cancer is the most common cancer-causing disease in the world, and early diagnosis is important for long-term survival. Low-dose thorax CT screening improves survival in high-risk individuals [12]. NBI (narrow-band imaging) video bronchoscopy is a new endoscopic technique for detecting submucosal and mucosal microvascular lesions. In many studies, NBI (narrow-band imaging) is superior to white light video bronchoscopy. Autofluorescence video bronchoscopy and narrow-band imaging video bronchoscopy provide easier detection of premalignant lesions in the airway [13].

Material and methods

Study design

A pre-education test and post-education test questionnaire were administered to 60 nurses and healthcare workers working in the hospital on 11 April 2022 during cancer early diagnosis and prevention information training. In the questionnaire, questions about cancer incidence, risk factors causing cancer as the cause of death of the most common cancers, cancer symptoms, cancer diagnosis, cancer treatment options, regular exercise, proper nutrition were asked in our cancer early diagnosis training. In addition, early cancer detection tests such as fecal occult blood test for colon cancer, mammography for breast cancer, HPV and pap smear tests for cervical cancer are administered by the Ministry of Health of the Repuplic of Turkey, KETEM, and were asked in our questionnaire. In the pre-education and post-education survey, early cancer diagnosis methods, prevention methods were evaluated whether cancer information in nurses and other healthcare workers was statistically significant. 15 questions were asked in the pre-education test and post-eduction test in the survey about early diagnosis.

Statistical analysis

Survey questions applied to 60 people were statistically evaluated by using the answers in SPSS 20 programme. The answers given to the questions before and after the questionnaire about early diagnosis and cancer prevention were evaluated using the Wilcoxon signed-rank test. Their responses according to age, gender, educational status, nurse, and other healthcare workers were evaluated using the Mann-Whitney U test. A p-value of <0.05 was considered significant in statistical evaluation.

The study protocol was approved by the Medical Ethics Committee at Pamukkale University. The study was conducted in accordance with the principles set out in the Helsinki Declaration. Written consent was obtained from the study participants. The researcher informed the participants about the study and obtained their verbal and written informed consent.

Results

The median age of the healthcare workers involved in the study was 40.5 SD 6,879, minimum age 24, and maximum age 53. Of those who participated in the education, 57 women and 3 men were healthcare workers. 52 nurses and 8 other healthcare workers were enrolled in the early diagnosis study. Cancer early diagnosis and cancer prevention survey questions were shown in Table 1.

The data were evaluated for normal distribution with Kolmogorov Smirnov test and with graphics. When 15 questions were answered using the nonparametric Wilcoxon signed-rank test, the median correct answer was 12 in the pre-education test and 13 in the post-education test. (p=0.00).

Age, gender, education, nurses, and other healthcare workers' demographic characteristics were shown in Table 2.

According to the Mann-Whitney U test applied to age, gender, educational status, nurses and other healthcare workers, the median of the answers given to the questionnaire questions was 12 between the ages of 18-40 in the pre-education test and 11 over the age of 40 in the pre-education test (p=0.60). While the median of the responses to the post-training

Table 1. Cancer early diagnosis screening informational education questionnaire questions (Q) for nurses and healthcare workers

Q-1	What is the disease that most often leads to death after cardiovascular diseases?
Q-2	What is the most common cancer in women in Turkey?
Q- 3	What is the most common cancer in men in Turkey?
Q-4	What is the most common cancer that causes death in Turkey?
Q-5	Which treatment is not one of the curative treatments of cancer?
Q-6	Which is not of the risk factors that cause breast cancer?
Q-7	Which quadrant of the breast is most common for cancer?
Q-8	What is the most common symptom of breast cancer?
Q-9	What first should do the women to early detection and diagnose of breast cancer?
Q-10	Which is not one of the risk factors leading to lung cancer?
Q-11	Which of the methods of diagnosis of lung cancer is not used?
Q-12	Which is not used by the Republic of Ministry of Health's cancer early detection centers (KETEM) for routine cancer screening?
Q-13	Which is not one of the risk factors that lead to stomach cancer?
Q-14	Which methods are not effective in protecting against cancer?
Q-15	Which cancer can be prevented by vaccination in women?

Table 2. Demographic characteristics of nurses and healthcare workers (n=60)

	Demographic characteristics	**N Percent**
Age	18-40 years 40 years>	28 (46.7%) 32 (53.3%)
Gender	Male Female	3 (5%) 57 (95%)
Academic degree of Nurses and Healthcare Workers	High school Bachelor / Master	27 (45%) 33 (55%)
Profession	Nurse Other Healthcare Worker	52 (86.7%) 8 (13.3%)

test was 13 between the ages of 18-40, the median of the responses to the post-education test was 13 over the age of 40 (p=0.20). No statistical significance was found between pre-test or post-test on age. According to gender, in the pre-education test the median was 12 in women, while it was 8 in men (p=0.02). In the post-education test the median is 13 in women, while it is 11 in men (p=0.13). There is no difference between men and women in the post-test median, whereas there is a difference in the pre-test median with incorrect answers to the questions about early diagnosis and prevention. The correct number of responses in nurses' pre-test the median was 11.50, while the pre-education test results in other healthcare workers the median was 13 (p=0.69), while the post-test results the median was 13 in nurses, and the post-test in other healthcare workers the median was 14 (p=0.17). There were no statistically significant differences between the correct numbers among nurses and other healthcare workers. According to educational status, the pre-test median of high school graduates was 11.50, while the pre-test median of bachelor/master graduates was 12 (p=1.00). The median number of correct answers in the post-test of high school graduates was 13, while the median number of correct answers in the post-test of bachelor / master graduates was 13 (p=0.84). There was no statistical significance in the number of correct answers of the survey test according to educational status. The pre-test and post-test results of the Wilcoxon signed-rank test applied to 60 healthcare workers and the Mann-Whitney U test results between age, gender, educational status, nurses and other healthcare workers are shown in Table 3.

Table 3. Results of education for nurses and healthcare workers

	Educational tests		Correct answer	*p*
Wilcoxon signed-rank test		pre-test	Median 12.00 min:6-max:15	*p*=0.00
		post-test	Median 13.00 min:9-max:15	
Mann-Whitney U Test	18-40 years	pre-test	Median 12.00 min:6-max:14	*p*=0.60
	40 years>	pre-test	Median 11.00 min:7-max:15	
	18-40 years	post-test	Median 13.00 min:9-max:14	*p*=0.20
	40 years>	post-test	Median 13.00 min:10-max:15	
	Female	pre-test	Median 12.00 min:7-max:15	*p*=0.02
	Male	pre-test	Median 8.00 min:6-max:11	
	Female	post-test	Median 13.00 min:9-max:15	*p*=0.13
	Male	post-test	Median 11.00 min:10-max:13	
	Nurse	pre-test	Median 11.50 min:7-max:15	*p*=0.69
	Healthcare Worker	pre-test	Median 13.00 min:6-max:14	
	Nurse	post-test	Median 13.00 min:9-max:15	*p*=0.17
	Healthcare Worker	post-test	Median 14.00 min:10-max:14	
	High school	pre-test	Median 11.50 min:7-max:15	*p*=1.00
	Bachelor/Master	pre-test	Median 12.00 min:6-max:14	
	High school	post-test	Median 13.00 min:9-max:15	*p*=0.84
	Bachelor/Master	post-test	Median 13.00 min:10-max:15	

While 50 people (83.3%) gave the correct answer in the pre-test about self-examination for breast cancer detection, 54 people (90%) gave the correct answer in the post-test. While the rate of those who knew the early cancer screening tests performed at KETEM was 75% in 45 people in the pre-test, an increase in knowledge was observed in 48 people (80%) in the post-test. While 48 people (80%) knew the symptoms of breast cancer correctly in the pre-test, it was 56 people (93.3%) in the post-test. For a vaccine that protects against cervical cancer, 59 people gave 98.3% correct answers in the pre-test and 60 people gave 100% correct answers in the post-test.

Discussion

In this study, it was observed that the knowledge of healthcare professionals about cancer prevention and early diagnosis methods increased with the education. In our study, self-examination response in the most common method of early diagnosis of breast cancer in women, 50 people (83.3%) answered correctly in the pre-education test, while 54 people (90%) answered correctly in the post-education test.

While 48 people (80%) knew the symptoms of breast cancer correctly in the pre-education test, it was 56 people (93.3%) in the post-education test. While the early diagnosis rate of those who knew mammography for breast cancer, pap smear test for cervical cancer, and fecal occult blood test for colon cancer was 75% in 45 people in the pre-education test, an increase in knowledge was observed in 48 people (80%) in the post-education test. Awareness about self-manual examination and mammography increased among healthcare workers after the training. According to a study supporting our study, 236 (41.7%) nurses who accepted to participate from 565 nurses working in a university hospital were administered self-actualisation, health responsibility, exercise, nutrition, interpersonal support, stress management, healthy lifestyle behaviours assessment scale score. In this study, it was found that the total score of the healthy lifestyle behaviours scale was higher in nurses who had adequate breast cancer knowledge, performed regular self-examination for breast cancer and received training on breast cancer [14]. In a study in which 200 female healthcare personnel working in hospitals participated, demographic data, breast self-manual examination, mammography, breast ultrasonography, smear test, hepatitis vaccination, human papillomavirus (HPV) vaccination were questioned with a seventeen-question survey. 21% of the participants stated that they had never performed breast self-manual examination, 56% had never had mammography and/or breast USG, and 56.5% had never had a smear test. 72% (n=144) of the

participants knew about the HPV vaccine, and 6.5% had the HPV vaccine. It was determined that they did not get enough of the HPV vaccine, which prevents early diagnosis and cancer. In addition to institutional studies evaluating the knowledge and attitudes of women's healthcare workers on this issue, it has been reported that in-house training programmes should be established if necessary [15]. Similarly, our study showed that the knowledge level of healthcare workers increased after the training. We believe that training programmes will increase the implementation of early diagnosis methods. In another study that is similar to ours, the knowledge level of midwives, nurses, and healthcare workers for early diagnosis and cancer prevention is increased with regular education, and health education is one of the most important roles for the community, especially the group at risk [6]. In one study, women have not enough information about the symptoms of cancer, early diagnosis, and screening of cancer.

The results of this study are similar to our study, and in our National Cancer Screening Programme, screening against cancer has been increased with breast, cervical and colon cancer risk factors, symptoms, prevention, early diagnosis and awareness trainings [1]. In a study with a sample of 254 women, it was found that 44.1% of the women living in the neighbourhood where the study was conducted had never had mammography, and when the reasons were questioned, 99.2% of the women who did not have mammography were due to lack of information and education. Lack of knowledge about educational levels and early screening tests prevent early diagnosis of breast cancer. They stated that education would increase the implementation of cancer screening tests [16]. In a study of another 280 women, they reported that if education for breast cancer is increased, self-manual examination, which is an effective diagnostic method, believing in the examination, detection of breast cancer will increase if it is applied at the right time and frequency [5]. In a study conducted with 153 female cases, breast cancer and cervical cancer symptoms, cancer early diagnosis and prevention methods information data were collected and women were trained after the education phone calls and home visits were made to the women for six months to keep track of the changes. At the end of the study, it was found that 84% of women began to practice self-manual examination of the breast. As a result, it was reported that women's knowledge about breast and cervical cancer changed positively with planned follow-up and education [17]. In a study conducted on 161 women with no health education working in support services in hospitals, it was found that 81.4% of the women knew the early diagnosis and screening methods of breast cancer. 49.1% of the women said that they knew breast self-manual examination, but only 6.2% said that they did it once a month. Clinical breast examination was performed by 32.9% of women, breast ultrasound by 22.4% and mammography by 22.3%. The majority of the women stated that they did not have any of these methods performed. As seen in our study, the level of breast cancer knowledge of women increased statistically significantly after planned education compared to the pre-education period [18]. In a study of 800 women, 80.5 % had heard from some sources that they should perform breast self-manual examination. Of the women who had heard about breast self-manual examination, 12.6% stated that they regularly performed breast self-manual examination once a month. While 30.4% of the women stated that they had been clinically examined at least once by health personnel, 36.8% of women over the age of forty had had mammography at least once. It was also determined that women who received breast health education were 3.81 times more likely to perform breast self-manual examination and 3.41 times more likely to have had clinical breast examination than women who did not receive breast health education. In order to disseminate early diagnosis behaviours, it is important to first determine the factors that are effective in women's performing these behaviours, then to organise training programmes and to support this training with reminders [19].

In our study, questions were asked about breast cancer self-manual examination, mammography, HPV testing for cervical cancer, fecal occult blood tests used for stomach and colon cancers used for an early diagnosis made by KETEM in our country. Nurses and healthcare workers were informed about the most common cancers, symptoms of cancer, ways to protect against cancer, exercise, diets. Early diagnosis is important to reduce mortality

and morbidity from cancer. We believe that new tests should be used for the early diagnosis of cancer. New tests determined by the Ministry of Health can be added to the KETEM cancer screening program to improve survival by diagnosing more types of cancer. New studies are used in breast cancer, lung cancer, and colon cancer. The use of the fecal occult blood test for colorectal cancer screening is supported by randomized trials demonstrating effectiveness in cancer prevention and widely recommended by guidelines for this purpose. The fecal immunochemical test (FIT), as a direct measure of human hemoglobin in stool, has several advantages relative to the conventional fecal occult blood test and is increasingly used relative to that test [20]. Autofluorescence imaging bronchoscopy (AFI) in lung cancer is used in Endobronchial lesions and narrow-band imaging bronchoscopy (NBI) is used to evaluate the diagnosis of premalignant airway lesions in the mucosal and submucosal vascular system [12, 13, 21]. Low-dose thorax CT (LDCT) screening for early diagnosis of lung cancer for heavy smoking, an increase in diagnosis has been observed [22]. For early-stage non-small cell lung cancer with peripheral blood samples, a concept analysis in 182 patients was evaluated in microRNA when miR-126-3p in disease-free survival and overall survival were statistically significant. They reported that miR-126-3p may be a prognostic marker in early-stage non-small cell lung cancer [23]. Early diagnosis of low contrast lesions of breast cancer can be detected using semi -monochromatic techniques. It can provide high-quality images in combination with fixed digital breast tomosynthesis (s-DBT) over a short scan time using an X-ray source array that makes the semi-monochromatic technique difficult to use alone possible [24]. When evaluated for early detection with the Panseer test, a non-invasive blood test based on tumour DNA methylation circulation, stomach, oesophageal, colorectal, lung and liver cancers were detected four years early in 191 of 605 asymptomatic patients. 223 cases of cancer were diagnosed when a blood sample test was taken. Five different common cancers were detected four years earlier by the panseer test with a specificity of over 95% [25]. Many cancers can be detected early and survival can be improved by adding the panseer test to the Ministry of Health's screening programme.

In conclusion, knowledge about early diagnosis methods and prevention methods in cancer increased statistically significantly in nurses and other healthcare workers working in the hospital. There has been seen a significant increase in the knowledge level of male healthcare workers after receiving cancer awareness education. The use of new diagnostic methods such as fecal immunochemical testing in colorectal cancer, screening with low-dose thorax CT in lung cancer and autofluorescence imaging bronchoscopy, narrow-band imaging bronchoscopy increases the diagnosis of early-stage cancer.

Conflict of interest: The authors declare that they have no conflict of interest.

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Authors' contributions to the article

H.S. have constructed the main idea and hypothesis of the study. H.S. and B.Y.T. developed the theory and arranged/edited the material and method section. H.S. has done the evaluation of the data in the results section. The discussion section of the article was written by H.S., and reviewed, corrected and approved by B.Y.T. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Investigation of post-traumatic growth with traumatic and psychological effects in children and adolescents diagnosed with cancer

Kanser tanılı çocuk ve ergenlerde travma sonrası büyüme ile travmatik ve ruhsal etkilenmenin incelenmesi

Merve Aktaş Terzioğlu, Tuğçe Söyleyici Mert, Selin Yakarışık, Hande Şenol

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Abstract

Purpose: The aim of this study was to evaluate and compare traumatic and mental effects and PTG by comparing a patient group in hematological-oncological cancer remission with a healthy control group.

Materials and methods: Children and adolescents aged 8-18 years, who were in remission with a diagnosis of childhood cancer, and presented at the Paediatric Hematology Department of Pamukkale Unıversity between 1 September 2021 and 30 April 2022 were included as the study group and a control group was formed of healthy children and adolescents with no history of cancer diagnosis. The Post-Traumatic Growth Inventory (PTGI), the Child Revised Impact of Events Scale (CRIES-13) and the Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV) were applied to all the children in both groups. A sociodemographic information form prepared by the researchers, and the Revised Child Anxiety and Depression Scale- Parent Version (RCADS-PV) were applied to parents.

Results: Evaluation was made of 27 patients aged 8-18 years with a diagnosis of childhood cancer who were in remission, and a control group of 25 healthy children. No statistically significant difference was determined between the groups in respect of parental ages, family structure, parental educational levels, and mean monthly family income (p>0.05). In the comparisons of the raw scores of the RCADS-PV between the two groups, RCADS-PV Panic Disorder, Obsessive Compulsive Disorder, and Depression subscale scores were found to be statistically significantly higher in the control group than in the remission group (p=0.048; p=0.045; p=0.047). When the CRIES-13 scores of the two groups were compared, no statistically significant difference was found (p=0.659).When the PTGI scales and subscales of the two groups were compared; while no statistically significant difference was found in the total PTGI score (p=0.066), the change in life philosophy subscale and the change in relationships with others subscale was found to be statistically significantly higher in the remission group than in the control group (p=0.038; p=0.05).Considering the relationship between CRIES-13 and PTGI scale scores, no statistically significant relationship was found in the remission group.

Conclusion: Cancer survivors grow from this negative experience, become stronger and survive with positive gains; they can adjust their expectations from themselves, the world and their future. Considering the current prevalence of cancer and increasing survival rates with treatments, new multicenter studies with larger samples are needed on this subject.

Key words: Post-traumatic growth, trauma, cancer, child, adolescent.

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Öz

Amaç: Hematoloji-onkoloji kanser remisyonunda olan hasta grubu ve sağlıklı kontrol grubunun karşılaştırarak travmatik ve ruhsal etkilenmelerini ve post travmatik büyümelerini değerlendirmek ve karşılaştırmak amaçlanmıştır.

Gereç ve yöntem: 01 Eylül 2021-30 Nisan 2022 tarihleri arasında Pamukkale Üniversitesi Çocuk Hematolojisi Anabilim Dalı'na başvuran ve çalışmaya katılmayı kabul eden çocukluk çağı kanser tanısı remisyonda olan 8-18 yaş arası çocuk ve ergenler ile daha önce çocukluk çağı kanser tanısı almamış sağlıklı kontrol grubu çocuk ve ergenler ile çalışma tamamlanmıştır. Çocuk ve ergenlere Travma Sonrası Büyüme Envanteri (PTGI), Revize Edilmiş Çocuk Olayın Etkisi Ölçeği -13 (CRIES-13), Çocuklarda Anksiyete ve Depresyon Ölçeği-Yenilenmiş-Çocuk Formu (ÇADÖ-Y-ÇF) ölçekleri uygulanmıştır. Ebeveynlere de Sosyodemografik form ve Çocuklarda Anksiyete ve Depresyon Ölçeği-Yenilenmiş-Ebeveyn Formu (ÇADÖ-Y-EF) uygulanmıştır.

Bulgular: Çalışmaya 8-18 yaş arası, 27 çocukluk çağı kanser tanısı remisyonda olan hasta ve 25 sağlıklı kontrol katılmıştır. İki grup arasında anne baba yaşı, aile yapısı, anne ve babanın öğrenim durumu ve ortalama aylık

Merve Aktaş Terzioğlu, Asst. Prof. Department of Child and Adolescent Mental Health and Diseases, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: merveaktasterzioglu@gmail.com (https://orcid.org/0000-0002-7668-8222) (Corresponding Author)

Tuğçe Söyleyici Mert, M.D. Department of Child and Adolescent Mental Health and Diseases, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: tsoyleyici@pau.edu.tr (https://orcid.org/0000-0003-1462-6728)

Selin Yakarışık, Asst. Prof. Department of Pediatric Hematology-Oncology, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: selinyakarisik@gmail.com (https://orcid.org/0000-0002-7797-3084)

Hande Şenol, Asst. Prof. Department of Biostatistics, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: handesenol@gmail.com (https://orcid.org/0000-0001-6395-7924)

gelir dağılımında istatistiksel olarak anlamlı düzeyde bir farklılık saptanmamıştır (p>0,05). ÇADÖ-Y-EF Panik Bozukluk, Obsesif Kompulsif Bozukluk, Depresyon alt ölçek skorları kontrol grubunda remisyon grubuna göre istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır (p=0,048; p=0,045; p=0,047). İki grubun CRIES-13 puanları karşılaştırıldığında istatistiksel olarak anlamlı farklılık bulunmamıştır (p=0,659). İki grubun PTGI ölçek ve alt ölçekleri karşılaştırıldığında; total PTGI puanında istatistiksel olarak anlamlı farklılık saptanmazken (p=0,066), PTGI ölçeğinin Yaşam Felsefesinde Değişim ve Başkalarıyla İlişkilerde Değişim alt ölçek ortalaması hasta grubunda kontrol grubuna göre istatistiksel olarak anlamlı düzeyde yüksek saptanmıştır (p=0,038; p=0,05). CRIES-13 ve PTGI ölçek puanları arasındaki ilişkiye bakıldığında, remisyon grubunda istatistiksel olarak anlamlı ilişki bulunmamıştır.
Sonuç: Kanseri yenenler bu olumsuz deneyimden büyüyerek, güçlenerek ve olumlu kazanımlarla sağ çıkarak; kendilerinden, dünyadan ve geleceklerinden beklentilerini ayarlayabilmektedir. Günümüzdeki kanser prevalansı ve tedavilerle artan sağkalım oranları göz önüne alındığında bu konuda yapılacak çok merkezli ve daha büyük örneklemli yeni çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Travma sonrası büyüme, travma, kanser, çocuk, ergen.

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Introduction

With developments and new treatments for cancers in childhood, they are mostly no longer fatal and survival rates have increased. Together with the increase in survival, there has been an increase in the number of children and adolescents coping with chronic disease and the psychological difficulties brought about by cancer. In the long-term follow-up of children and young people diagnosed with cancer, some emotional and cognitive symptoms may be seen [1, 2].

Cancer treatment, especially the treatments for childhood cancers can be extremely difficult psychologically [3]. There are several stressful situations such as the psychosocial stressor factors experienced in the treatment process by children diagnosed with cancer and their families, changes in physical appearance, a worsening of the prognosis, and uncertainty about the future [4]. Developments in cancer treatment have increased survival rates, so the focus of researchers has shifted to adaptation and coping mechanisms [5]. Previous studies have shown that as a result of trauma experienced, the resilience of these young people has increased and they can adapt better to the process [6].

Does cancer count as a trauma? This remains a matter of debate. The diagnosis of a life-threatening disease corresponds to the DSM-IV definition of a traumatic event. However, this definition changed in DSM-V, in which it was stated that when the cancer diagnosis was not related to a sudden and catastrophic event, it is not accepted as a traumatic event requiring post-traumatic stress disorder (PTSD) testing. Research has shown that there are both negative and positive outcomes of cancer. Many individuals who have undergone cancer treatments have been reported to have expressed positive feelings about being diagnosed with cancer [5]. Post-traumatic growth (PTG) can be defined as the cognitive process gone through to find meaning in a traumatic event by re-interpreting the traumatic event encountered in a positive way [5, 7].

It has been reported that being able to take a stronger approach to changes in the individual's outlook of a difficult experience such as cancer by making positive psychosocial changes in life priorities and interpersonal relationships can lead to positive results [5, 7]. Post-traumatic growth results in an increase in self-confidence, decreased vulnerability to the event experienced, and gives new meaning to the positive aspects of life. Development of the process in this way can be a protective psychological factor against the trauma experienced [7]. From a review of literature, it can be seen that 58-83% of trauma survivors retrospectively reported PTG following problems [8].

Although studies related to PTG have aimed to reduce the psychosocial stressors and improve quality of life of cancer survivors, it is not possible to completely eliminate all the problems experienced [9]. The process of the negative event experienced by the individual can cause PTSD, depression, and anxiety symptoms [10]. Following a negative event,

results may emerge parallel to the findings of both PTG and PTSD [11]. These results show that both negative and positive effects of a traumatic event may be seen at the same time, and sometimes negative outcomes may pass to a stage of positive outcomes. Previous studies have shown that children diagnosed with cancer can demonstrate different behaviours from healthy children to events after having experienced this trauma [12, 13].

There is an increasing number of paediatric hematology and oncology patients referred for consultation in paediatric psychiatry practice. This has made paediatric psychiatrists feel that they need more information about this patient group. Recognising that patients diagnosed with cancer and in remission have stronger coping skills and strategies was of guidance for this research on the subject of PTG.

From the starting point of this information and our clinical experience, the hypothesis of this study was that PTG would be seen in a patient group diagnosed with cancer and in remission, and there would be fewer mental effects due to the coping skills and mechanisms developed with trauma.

The aim of this study was to evaluate and compare traumatic and mental effects and PTG by comparing a patient group in hematological-oncological cancer remission with a healthy control group.

Material and method

Children and adolescents aged 8-18 years, who were in remission with a diagnosis of childhood cancer, and presented at the Paediatric Hematology Department of Pamukkale University between 1 September 2021 and 30 April 2022 were included as the study group and a control group was formed of healthy children and adolescents with no history of cancer diagnosis. Power analysis was applied to determine the sample size.

The effect size was seen to be obtained at a strong level (d=0.96) in the reference study [14]. Considering that a lower level of effect size (d=0.9) could be obtained, it was calculated from the results of the power analysis that it was necessary to include 42 subjects (21 in each group) to be able to obtain 80% power in a 95% confidence interval.

The study included a group of 27 children and adolescents previously diagnosed with childhood cancer and currently in remission, and a control group of 25 healthy children and adolescents with no history of cancer diagnosis. Although a detailed psychiatric examination was not performed, it was questioned whether the individuals in the healthy group had a diagnosis of any mental disorder and whether they were treated for mental disorders. Those who did not have any mental or physical complaints, diagnosis or treatment were included in the group.

The Post-Traumatic Growth Inventory (PTGI), the Child Revised Impact of Events Scale (CRIES-13) and the Revised Child Anxiety and Depression Scale-Child Version (RCADS-CV) were applied to all the children in both groups. A sociodemographic information form prepared by the researchers, and the Revised Child Anxiety and Depression Scale-Parent Version (RCADS-PV) were applied to parents. Both parents and participants were informed verbally and in writing, verbal consent was obtained from the participants and written consent was obtained from their parents. A “voluntary consent form” was signed for both the remission and healthy control groups. Exclusion criteria was determined as the decision not to participate or continue the study.

Data collection tools

Post-Traumatic Growth Inventory (PTGI):

The PTGI was developed to measure psychological growth after traumatic experiences. This scale consists of 21 items with 6-point Likert-type responses [7]. High points indicate positive psychological changes because of negative life events. In the original form of the scale there were 5 subscales. The internal consistency of the 21 items was determined as α=0.90.

In a study which classified the potential changes which could occur after traumatic experiences or crises, a trend form of the measurement tool was used. The Turkish adaptation of the scale was done by Kagan et al. [15]. The Turkish form of the scale comprises 3 subscales of change in self-perception, change in life philosophy, and change in relationships with others. Different studies in literature have shown that the scale is suitable for use with children and adolescents [16-22].

The Revised Child Anxiety and Depression Scales- Child and Parent Version (RCADS)

The RCADS was developed to measure symptoms of anxiety disorders and depression in children and adolescents [23]. The scale contains 47 items and has a 4-point Likert type scoring. It can be applied to children between the ages of 8-18. It consists of major depressive disorder, social phobia, panic disorder, separation anxiety disorder, generalized anxiety and obsessive-compulsive disorder subscales. There is a parent version of the scale, which consists of 47 items with 4-point Likert-type responses regarding the child's symptoms. Validity and reliability studies of the Turkish version of the scale were conducted by Gormez et al. [24].

Child Revised Impact of Events Scale-13 (CRIES-13):

This scale, for which the Turkish validity and reliability study was conducted by Çeri, consists of 13 questions. Suitable for 8-18 age range. The scale is adapted from the Impacts of Events Scale (IES). The highest 65 points can be obtained in the scoring of the Likert type scale. A score of 30 and above indicates the risk for PTSD [25-27].

Sociodemographic data form:

This form was created by the researchers to record age, education status, medical history and diagnosis of the child, and the age, education level, income level, medical history and diagnosis of the parents.

Statistical analysis

Data obtained in the study were analysed statistically using SPSS vn. 25.0 software (IBM, Armonk, NY, USA). Continuous variables were stated as mean ± standard deviation values and categorical variables as number (n) and percentage (%). In the comparisons of two independent groups of data, the significance of the difference between two means test was used when parametric assumptions were met, and the Mann Whitney U-test if not. Correlations between variables were examined with the Spearman correlation test. Statistical significance in all the tests was evaluated in a 95% confidence interval at a value of $p<0.05$.

Results

Evaluation was made of 27 children aged 8-18 years with a diagnosis of childhood cancer who were in remission, and a control group of 25 healthy children aged 8-18 years. The mean age of the children was 13.48±3.64 years (range, 8-18 years) in the remission group and 14.48±2.1 years (range, 10-18 years) in the control group. The mean duration of remission was 36.78±28.29 months (range, 2-99 months). There was no statistically significant difference between the groups in terms of parental age, family structure, parental education level and average family income ($p>0.05$). The family structure, educational levels, and family income levels are shown in Table 1. All scale scores were evaluated according to the age at which they were diagnosed and the duration of remission. No statistically significant difference was found.

In the remission group, remission was obtained in the follow-up of a diagnosis of Pre-B-cell ALL in 40.7% of the patients, Hodgkin's lymphoma in 18.5%, AML in 14.8%, Burkitt lymphoma in 7.4%, T-ALL in 7.4%, Non-Hodgkin's lymphoma in 7.4%, and Mixed Hodgkin's lymphoma in 3.7%. Due to the limitation in the sample group, statistically significant results could not be obtained when the diagnoses and scale scores of the individuals were evaluated.

In the comparisons of the raw scores of the RCADS parent scale (RCADS-PV) between the two groups, the mean raw score of the panic disorder subscale was determined to be 2.52±3.15 in the patient group and 3.56±2.83 in the control group, with a statistically significant difference determined between the groups ($p=0.048$). The mean raw score of the OCD subscale was 3.07±3.17 in the patient group and 4.84±3.36 in the control group, and the difference was determined to be statistically significant ($p=0.045$). The mean raw score of the depression subscale was 4.81±4.74 in the patient group and 7.12±4.97 in the control group, and the difference was determined to be statistically significant ($p=0.047$). When the RCADS child scale (RCARDS-CV) points were compared between the two groups, no statistically significant difference was determined (Table 2). The raw scores of the child and parent RCADS of both groups are shown in Table 2.

Table 1. The family structure, educational levels, and family income levels

	Remission		Control		*p*
	n	%	n	%	
Family Structure					
Core family	19	70.4	19	76	0.733
Extended Family	6	22.2	3	12	
Divorced	1	3.7	2	8	
Deceased	1	3.7	1	4	
Mother's education status					
Primary education	15	55.6	14	56	0.589
High school	8	29.2	5	20	
University	4	14.8	6	24	
Father's education status					
Primary education	13	48.1	13	52	0.753
High school	10	37	7	28	
University	4	14.8	5	20	
Family income					
< Single Minimum Wage	11	40.7	12	48	0.810
Single Minimum Wage – Double Minimum Wage	10	37	9	36	
> Double Minimum Wage	6	22.2	4	16	

Chi-square test

Table 2. The raw scores of RCADS-PV

RCADS	Remission Mean±SD	Control Mean±SD	*p*
PV AD	19.81±14.98	25.2±14.59	0.133 (z=-1.503)
PV SAD	3.15±3.22	2.76±2.92	0.802 (z=-0.251)
PV GAD	4.33±3.79	5.76±3.72	0.099 (z=-1.65)
PV PD	2.52±3.15	3.56±2.83	0.048* (z=-1.977)
PV SP	6.74±5.59	8.28±5.22	0.27 (z=-1.103)
PV OCD	3.07±3.17	4.84±3.36	0.045* (z=-2.009)
PV DD	4.81±4.74	7.12±4.97	0.047* (z=-1.985)
CV AD	21.3±17.59	25.12±16.88	0.284 (z=-1.072)
CV SAD	2.52±2.68	2.24±2.42	0.816 (z=-0.233)
CV GAD	5.15±5.13	6.2±3.81	0.105 (z=-1.623)
CV PD	2.85±3.66	4.2±3.71	0.083 (z=-1.734)
CV SP	7.81±6.93	8±5.95	0.804 (z=-0.248)
CV OCD	2.93±3.28	4.48±3.45	0.069 (z=-1.821)
CV DD	5.19±4.53	7.24±5.94	0.177 (z=-1.351)

* $p<0.05$ statistically significant, z: Mann Whitney U test, SD: standard deviation
RCADS: Revised Child Anxiety and Depression Scales
RCADS-PV: Revised Child Anxiety and Depression Scales-Parent Version
RCADS-CV: Revised Child Anxiety and Depression Scales-Child Version
AD: Anxiety Disorder, SAD: Separation Anxiety Disorder, GAD: Generalized Anxiety Disorder
PD: Panic Disorder, SP: Social Phobia, OCD: Obsessive Compulsive Disorder
DD: Depressive Disorder

In the study, the CRIES-13 score of 30 and above was found to be 22.2% in the remission group and 16% in the control group. When the CRIES points of both groups were compared, no statistically significant difference was determined (p=0.659). In the comparisons of the PTGI and subscales of both groups, no statistically significant difference was determined in respect of the total scale points (p=0.066). In the change in life philosophy subscale, the mean points were 15.59±7.31 in the remission group and 11.36±7.00 in the control group, with the difference determined at a statistically significant level (p=0.038). The subscale points of the change in relationships with others were 10.59±6.32 in the remission group and 7.24±5.68 in the control group, and the difference between the two groups was determined to be statistically significant (p=0.05). The CRIES and PTGI scale points of the groups are shown in Table 3.

Table 3. The CRIES-13 and PTGI scale and subscale points

	Remission Mean±SD	Control Mean±SD	*p*
CRIES- 13	17.19±15.46	17.8±13.15	0.659 (z=-0.441)
PTGI	54.78±23.03	43.24±20.99	0.066 (t=1.883)
Change in self-perception	28.59±12.08	24.64±11.41	0.232 (t=1.211)
Change in life philosophy	15.59±7.31	11.36±7	**0.038* (t=2.129)**
Change in relationships with others	10.59±6.32	7.24±5.68	**0.05* (t=2.006)**

CRIES-13: Child Revised Impact of Events Scale; PTGI: Post-Traumatic Growth Inventory
* p<0.05 statistically significant, t: In independent groups t test; z: Mann Whitney U test
SD: standard deviation

Correlation analysis of the clinical scale points (RCADS-PV, RCADS-CV, CRIES-13, PTGI) was performed separately in the remission and control groups.

The correlations between the raw scores of all the subscales of the RCADS-PV/ RCADS-CV and the CRIES-13 scale points were examined in both remission and control group. The correlations between the remission group scales are shown in Table 4. The correlations between the scales in the control group are shown in Table 5.

The correlation between the raw score of the generalised anxiety subscale of the RCADS-PV and the PTGI subscale of change in life philosophy was examined. In the remission group, a moderate level positive correlation was observed (p=0.036, r=0.405). The correlations between the remission group scales are shown in Table 4.

When the relationships were examined between the CRIES-13 and PTGI scale points in the remission group, no statistically significant relationship was determined. When the relationships were examined between the CRIES-13 and PTGI scale points in the control group, a moderate level positive correlation was determined between the PTGI total score (p=0.022, r=0.455), and the subscale points of change in self perception (p=0.010, r=0.507) and change in life philosophy (p=0.032, r=0.429). The relationships between the CRIES-13 and PTGI scale points are shown in Table 6.

Discussion

The aim of this study was to evaluate the levels of traumatic and mental effects and post-traumatic growth by comparing a group of patients in cancer remission and a control group. The study results showed that the anxiety, depression, and OCD raw scores of the RCADS-PS were statistically significantly higher in the control group than in the remission group who had been diagnosed with cancer and were in remission. In addition, the PTGI subscale points of the change in life philosophy and change in relationships with others were found to be statistically significantly higher in the remission group than in the control group. In the comparisons of the CRIES points, no statistically significant difference was determined between the two groups.

One of the hypotheses of this study was that the children and adolescents who had been diagnosed with cancer would develop coping skills and coping mechanisms and the mental effects would be lower in this group.

Table 4. Remission group scale correlations

RCADS		CRİES-13	PTGI	Change in self-perception	Change in life philosophy	Change in relationships with others
RCADS-PV AD	**r**	**0.853****	0.045	-0.016	0.130	0.161
	p	<0.001	0.823	0.938	0.517	0.422
RCADS-PV SAD	**r**	**0.670****	-0.160	-0.186	-0.203	0.125
	p	<0.001	0.426	0.352	0.309	0.533
RCADS-PV GAD	**r**	**0.654****	0.273	0.206	**0.405***	0.207
	p	<0.001	0.168	0.303	0.036	0.301
RCADS-PV PD	**r**	**0.729****	-0.116	-0.138	0.046	-0.142
	p	<0.001	0.564	0.493	0.820	0.479
RCADS-PV SP	**r**	**0.607****	0.251	0.180	0.329	0.273
	p	0.001	0.206	0.369	0.094	0.168
RCADS-PV OCD	**r**	**0.765****	-0.003	-0.047	0.088	0.104
	p	<0.001	0.987	0.814	0.664	0.606
RCADS-PV DD	**r**	**0.795****	-0.103	-0.197	0.041	-0.029
	p	<0.001	0.610	0.326	0.839	0.887
RCADS-CV AD	**r**	**0.733****	0.065	<0.001	0.128	0.143
	p	<0.001	0.746	0.999	0.524	0.477
RCADS-CV SAD	**r**	**0.564****	-0.105	-0.181	-0.137	0.201
	p	0.002	0.604	0.365	0.496	0.316
RCADS-CV GAD	**r**	**0.633****	0.195	0.121	0.314	0.146
	p	<0.001	0.331	0.548	0.111	0.468
RCADS-CV PD	**r**	**0.804****	0.010	0.009	0.098	-0.030
	p	<0.001	0.962	0.963	0.625	0.884
RCADS-CV SP	**r**	**0.585****	0.118	0.077	0.125	0.185
	p	0.001	0.558	0.701	0.535	0.356
RCADS-CV OCD	**r**	**0.484****	0.014	-0.068	0.122	0.140
	p	0.10	0.946	0.737	0.545	0.485
RCADS-CV DD	**r**	**0.686****	-0.085	-0.121	0.024	-0.117
	p	<0.001	0.675	0.548	0.905	0.560

RCADS: Revised Child Anxiety and Depression Scales
RCADS-PV: Revised Child Anxiety and Depression Scales-Parent Version
RCADS-CV: Revised Child Anxiety and Depression Scales-Child Version
AD: Anxiety Disorder, SAD: Separation Anxiety Disorder, GAD: Generalized Anxiety Disorder
PD: Panic Disorder, SP: Social Phobia, OCD: Obsessive Compulsive Disorder
DD: Depressive Disorder; CRIES-13: Child Revised Impact of Events Scale
PTGI: Post-Traumatic Growth Inventory, * $p<0.05$ statistically significant
r: Spearman correlation coefficient

Table 5. Control group scale correlations

RCADS		CRİES-13	PTGI	Change in self-perception	Change in life philosophy	Change in relationships with others
RCADS-PV AD	**r**	**0.549****	0.363	**0.410***	**0.443***	-0.003
	p	0.004	0.075	0.042	0.027	0.990
RCADS-PV SAD	**r**	0.341	-0.018	0.023	0.047	-0.104
	p	0.095	0.931	0.911	0.823	0.620
RCADS-PV GAD	**r**	**0.421***	**0.475***	**0.521****	**0.541****	0.092
	p	0.036	0.017	0.008	0.005	0.660
RCADS-PV PD	**r**	0.354	0.146	0.239	0.219	-0.135
	p	0.082	0.486	0.250	0.293	0.519
RCADS-PV SP	**r**	**0.481***	0.305	0.370	0.372	-0.097
	p	0.015	0.138	0.069	0.067	0.646
RCADS-PV OCD	**r**	**0.402***	**0.486***	**0.441***	**0.613****	0.105
	p	0.046	0.014	0.027	0.001	0.618
RCADS-PV DD	**r**	**0.408***	0.057	0.224	0.207	-0.255
	p	0.043	0.787	0.282	0.321	0.220
RCADS-CV AD	**r**	**0.646****	0.274	0.369	0.308	-0.003
	p	<0.001	0.186	0.069	0.135	0.987
RCADS-CV SAD	**r**	**0.490***	-0.052	0.014	0.015	-0.027
	p	0.013	0.805	0.947	0.943	0.898
RCADS-CV GAD	**r**	**0.607****	0.268	0.334	0.325	0.049
	p	0.001	0.196	0.103	0.112	0.818
RCADS-CV PD	**r**	**0.600****	0.173	0.281	0.212	-0.004
	p	0.002	0.410	0.173	0.309	0.987
RCADS-CV SP	**r**	**0.498***	0.348	**0.437***	0.322	0.028
	p	0.011	0.088	0.029	0.117	0.894
RCADS-CV OCD	**r**	**0.541****	0.227	0.287	0.380	-0.021
	p	0.005	0.275	0.164	0.061	0.921
RCADS-CV DD	**r**	**0.528****	0.022	0.154	0.086	-0.151
	p	0.007	0.918	0.462	0.681	0.470

RCADS: Revised Child Anxiety and Depression Scales
RCADS-PV: Revised Child Anxiety and Depression Scales-Parent Version
RCADS-CV: Revised Child Anxiety and Depression Scales-Child Version
AD: Anxiety Disorder, SAD: Separation Anxiety Disorder, GAD: Generalized Anxiety Disorder
PD: Panic Disorder, SP: Social Phobia, OCD: Obsessive Compulsive Disorder
DD: Depressive Disorder, CRIES-13: Child Revised Impact of Events Scale
PTGI: Post-Traumatic Growth Inventory, * $p<0.05$ statistically significant
r: Spearman correlation coefficient

Table 6. Correlation between CRIES-13 AND PTGI scale scores in remission and control groups

CRIES-13		PTGI	Change in self-perception	Change in life philosophy	Change in relationships with others
	r	-0.017	-0.067	0.089	0.066
Remission	*p*	0.934	0.740	0.660	0.745
Control	r	**0.455***	**0.507****	**0.429***	0.275
	p	0.022	0.010	0.032	0.183

CRIES-13: Child Revised Impact of Events Scale; PTGI: Post-Traumatic Growth Inventory
* $p<0.05$ statistically significant; r: Spearman correlation coefficient

The study results were consistent with this hypothesis. Previous studies in literature have also shown results that children and adolescent cancer patients in remission have fewer mental complaints and exhibit higher self concepts [5, 28-30]. It has been reported that adolescents who have been saved from cancer show lower psychological distress and use avoidance coping strategies less. In the results of another study, it was reported that surviving children and adolescent cancer patients have a lower probability of being anxious and depressive [31].

Another hypothesis was that PTG would be observed in the remission group who had been diagnosed with cancer and were in remission. The study results confirmed the hypothesis. Growing up from a difficult cancer experience, children's interpretations of themselves and their environment change and their focus on the positive aspects of life increases [5, 9]. In studies on childhood cancers; many survivors report more positive changes in their behavior towards others, and these positive changes have been suggested to result from experiences with childhood cancer and its treatment [9, 32]. It has been reported that post-traumatic growth can also be seen in young children, it is not age-related, and post-traumatic growth may occur independently of age and cognitive maturity level [5]. Although consistent with the developmental functions and difficulties of children and adolescents, these findings show the importance of understanding how this experience is processed by children and adolescents in remission [9].

When the CRIES-13 scores of the two groups were compared, there was no statistically significant difference, but CRIES-13 scores of 30 and above were found in more participants in the remission group than in the control group. This may have been due to the limited number of the sample or to differences in individual coping mechanisms, and could be a sign of post-traumatic growth. PTSB has worked with young adult cancer survivors in the literature [33-39]. the frequency of PTSD has been reported to vary between 6.2% and 21.6% [36, 37]. In a study in Japan, although no difference was seen between a remission group and a control group in respect of IES-R points ≥25, the median total IES-R points were found to be higher in the remission group [14]. Similarly, although no statistical difference was observed between the groups in our study, CRIES-13 scores were found to be 30 and above in numerically more participants in the remission group.

In this study, when the relationship was examined between the raw scores of all the RCADS parent and child subscales and the CRIES -13 scale points, strong and moderate level positive correlations were determined with mental disorders in both the remission and control groups. This showed that trauma increased the predisposition to mental diseases. The lifetime risk of a predisposition to mental disease is higher as a result of an individual having experienced cancer or another challenging life event and having processed this as trauma. Events that are seen as ordinary or that are not seen as a disaster by most people may cause a post-traumatic psychopathology as the event has special meaning for the individual [40, 41].

When the relationships between the CRIES-13 and PTGI points were examined in this study, a moderate level positive correlation was determined between the PGTI total score and the subscale points of change in self-perception and change in life philosophy in the control group. In the literature, growth indicators, such as positive changes in relationships with oneself and others, have been shown to be independent of PTSD and treatment of children [9]. Post-traumatic reactions can be multifaceted. In pediatric cancers, posttraumatic growth is thought to be a measure of coping mechanisms rather than an outcome [9, 42].

Limitations/Strengths

The number of participants is the most important limitation of the study. There could also have been bias in the sample as it was formed of those who volunteered to participate in the research. Therefore, the results cannot be generalised to all children and adolescents, and there is a need for further multicentre studies with larger samples. Nevertheless, that the findings contribute to an area which has not been sufficiently studied can be considered a strength of this study.

As a result; the resulting data contribute to an understudied field and provide a better understanding of children and adolescents who

are cancer survivors. Cancer survivors grow from this negative experience, become stronger and survive with positive gains. Considering the current prevalence of cancer and increasing survival rates with treatments, new multicenter studies with larger samples are needed on this subject.

Conflicts of interest: No conflict of interest was declared by the authors.

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Authors' contributions to the article

M.A.T. constructed the main idea and hypothesis of the study. M.A.T., T.S.M., S.Y. and H.Ş. developed the theory and organized the material and method section. Data collection was done by M.A.T., T.S.M. and S.Y. and data analysis was done by H.Ş., M.A.T., T.S.M. and H.Ş. evaluated the data in the results section. The discussion section of the article was written

by M.A.T., T.S.M., S.Y. and H.Ş reviewed the article and made the necessary corrections and approved it. In addition, all authors discussed the entire study and approved the final version.

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Frequency of rheumatic diseases in patients with familial Mediterranean fever

Ailesel Akdeniz ateşi hastalarında romatizmal hastalıkların sıklığı

Gülçin Otar Yener, Selçuk Yüksel, Zahide Ekici Tekin, Hülya Türkmen

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Abstract

Purpose: Mutations in the Mediterranean FeVer (MEFV) gene, which causes familial Mediterranean fever (FMF), may also cause the emergence of other specific rheumatic diseases. This study aims to determine the frequency of other rheumatologic diseases in paediatric FMF patients, evaluate whether there are clinical and genetic differences between those with and without concomitant rheumatologic diseases, and compare the data with previous studies.

Materials and methods: The files of FMF patients who were followed up at the paediatric rheumatology department were reviewed retrospectively. Demographic data, MEFV mutations, treatment, disease severity scores, and concomitant rheumatic diseases were recorded from the files.

Results: There were 303 FMF patients (154 female/149 male). The mean age at diagnosis was 7.04±3.9 years. The mean disease duration was 5.33±3.13 years. In the cohort, 41 FMF patients (13.5%) were diagnosed with another rheumatic disease. There were 22 cases of juvenile idiopathic arthritis (53.6%), seven cases of vasculitis (17%), six cases of periodic fever aphthous stomatitis and adenitis syndrome (14.6%), three cases of Behçet's disease (7.3%), two cases of acute rheumatic fever (4.8%), and one case of systemic lupus erythematosus (2.4%). Thirty-two of these of these 41 FMF patients (78%) had the *M694V* mutation (homozygous in 11, heterozygous in 21). Disease activity scores Pras and ISSF scores were higher in FMF patients with rheumatic diseases (p=0.002 and p<0.001, respectively).

Conclusion: Other rheumatologic diseases should be evaluated in FMF patients. Regarding other accompanying rheumatic diseases, the *M694V* mutation and disease severity scores are notable factors.

Key words: Familial Mediterranean fever, rheumatic disease, MEFV mutation.

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Öz

Amaç: Ailesel Akdeniz ateşine (FMF) neden olan Mediterranean FeVer (MEFV) genindeki mutasyonlar başka spesifik romatizmal hastalıkların da ortaya çıkmasına neden olabilir. Bu çalışmanın amacı pediatrik FMF hastalarında diğer romatizmal hastalıkların sıklığını belirlemek, eşlik eden romatizmal hastalığı olan ve olmayanlar arasında klinik ve genetik farklılık olup olmadığını değerlendirmek ve verileri önceki çalışmalarla karşılaştırmaktır.

Gereç ve yöntem: Çocuk romatoloji bölümünde takip edilen FMF hastalarının dosyaları retrospektif olarak incelendi. Dosyalardan demografik veriler, MEFV mutasyonları, tedavi, hastalık şiddet skorları ve eşlik eden romatizmal hastalıkları kaydedildi.

Bulgular: 303 FMF hastası (154 kadın/149 erkek) vardı. Ortalama tanı yaşı 7,04±3,9 idi. Ortalama hastalık süresi 5,33±3,13 yıldı. Kohortta 41 FMF hastasına (%13,5) başka bir romatizma hastalığı teşhisi kondu. 22 juvenil idiyopatik artrit (%53,6), yedi vaskülit (%17), altı periyodik ateş aftöz stomatit ve adenit sendromu (%14,6), üç Behçet hastalığı (%7,3), iki akut romatizmal ateş (%4,8) ve bir sistemik lupus eritematozus (%2,4) olgusu vardı. Bu 41 FMF hastasının 32'sinde (%78) *M694V* mutasyonu vardı (11'i homozigot, 21'i heterozigot). Hastalık şiddet skorları Pras ve ISSF skorları romatizmal hastalığı olan FMF hastalarında daha yüksekti (sırasıyla p=0.002 ve p<0.001).

Sonuç: FMF hastalarında diğer romatolojik hastalıklar da değerlendirilmelidir. Eşlik eden diğer romatizmal hastalıklarda ise *M694V* mutasyonu ve hastalık şiddet skorları önemli faktörlerdir.

Anahtar kelimeler: Ailesel Akdeniz ateşi, romatizmal hastalık, MEFV mutasyonu.

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Gülçin Otar Yener, M.D. Gaziantep Medicalpoint Hospital, Department of Paediatric Rheumatology, Gaziantep, Turkey, e-mail: gulcinotar@gmail.com (https://orcid.org/0000-0003-2575-6309) (Corresponding Author)

Selçuk Yüksel, Prof. Pamukkale University School of Medicine, Department of Paediatric Rheumatology and Paediatric Nephrology, Denizli, Turkey, e-mail: selcukyuksel@yahoo.com (https://orcid.org/0000-0001-9415-1640)

Zahide Ekici Tekin, M.D. Ankara Bilkent City Hospital, Children's Hospital, Department of Paediatric Rheumatology, Ankara, Turkey, e-mail: zahideekici20@gmail.com (https://orcid.org/0000-0002-5446-667X)

Hülya Türkmen, M.D. Celal Bayar University School of Medicine, Paediatrics Department, Manisa, Turkey, e-mail: dr.hulya_87@hotmail.com (https://orcid.org/0000-0002-1142-5464)

Introduction

Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disease. It is characterised by recurrent episodes of fever and polyserositis. Turkish, Jewish, Armenian, and Arab populations are the most affected by FMF [1]. Clinical findings are used to diagnose and the diagnosis is supported by the ethnicity, family history, and genetic testing. FMF is an autosomal recessive disease caused by mutations in the *MEFV* gene. The *MEFV* gene encodes pyrin (also known as marenostrin), and mutations in the *MEFV* gene can result in an inability to control inflammation [2]. Gain-of-function mutations in the *MEFV* gene lead to increased levels of the most potent pro-inflammatory cytokine, interleukin (IL)-1 beta [3]. Furthermore, cytokine levels, such as TNF-α, IL-6, and sIL-2r, were higher during an acute FMF attack than during the silent period and in healthy controls [4]. In addition, studies have shown that colchicine, the primary treatment for FMF patients, decreases serum inflammatory cytokine levels, such as IL-6, IL-8, and TNF- α in FMF patients [5]. These cytokine interactions may increase the frequency and severity of other rheumatologic diseases in FMF, particularly juvenile idiopathic arthritis, vasculitis, and other autoimmune diseases.

Few studies have focused on the relationship between FMF and concomitant diseases in children [6-11]. Recent studies have found that the frequency of associated diseases ranged from 12.8% to 18.9% among FMF patients, but in these studies, some of the concomitant diseases were non-rheumatic, such as asthma, migraine, etc. [6-11]. The primary objective of this study was to determine the prevalence of other rheumatic diseases in paediatric FMF patients. The secondary goal was to determine whether clinical and genetic differences between those with and without concomitant rheumatic diseases.

Materials and methods

The medical files of paediatric patients with FMF diagnosed and followed up at the paediatric rheumatology unit in a university hospital in the last ten years (2010-2020) were retrospectively reviewed. To be included in the study, the patient had to have completed at least one year of follow-up and regularly come to the control visits (generally every 3-6 months). Data, including demographic information (age, gender, and disease duration), clinical features, *MEFV* gene mutations, medications, and co-occurring rheumatic diseases, were recorded from the files.

The diagnosis of FMF was made according to Turkish paediatric FMF criteria [12]. The criteria included at least three attacks with 6-72 hours duration of fever, abdominal pain, chest pain, arthritis, and family history. At least two criteria are required for the diagnosis of FMF. Patients with FMF and concomitant rheumatic diseases were included in the study and divided into two main groups. The diagnosis of concomitant rheumatic diseases, such as juvenile idiopathic arthritis (JIA), vasculitis, periodic fever aphthous stomatitis and adenitis (PFAPA) syndrome, Behçet's disease, acute rheumatic fever, and systemic lupus erythematosus were evaluated by the previously defined criteria for those diseases [13-18]. Sanger sequencing was used to analyse *MEFV* gene variants in exons 2, 3, 5, and 10. The severity of the disease was determined by the Pras score, which was adjusted based on the colchicine dose and the international severity score system for familial Mediterranean fever (ISSF) score [19-21].

Despite getting the maximum permissible dose for 6 months, one episode per month was defined as resistance to colchicine treatment.

The study was approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study and this research was in compliance with the declaration of Helsinki.

Statistical analysis

Statistical analysis was performed using SPSS software, version 21.0. Variables were investigated using analytic methods (Kolmogorov-Smirnov) to determine whether they were normally distributed. The descriptive analysis data were expressed as mean-standard deviation (SD) or median, minimum-maximum, where appropriate. Fisher's exact and Pearson's chi-square tests were used for differences between categorical parameters. Continuous data were analysed by Student's t-test or Mann-Whitney U test, as appropriate. A p-value <0.05 was considered statistically significant.

Results

The study included a total of 303 patients (154 female/149 male). The mean age at diagnosis was 7.04±3.9 years. The mean disease duration was 5.33±3.13 years. FMF history in relatives was 52.1% (158 patients). Clinical features at diagnosis were abdominal pain in 201 patients (66.3%), chest pain in 12 patients (3.9%), arthritis in 25 patients (8.2%), and orchitis in 1 patient (0.3%). Forty-one (13.5%) of the 303 FMF patients were diagnosed with FMF and an accompanying rheumatic disease (20 females, 21 males).

There were 22 cases of JIA (53.6%), seven cases of vasculitis (17%), six cases of periodic fever aphthous stomatitis and adenitis (PFAPA) syndrome (14.6%), three cases of Behçet's disease (7.3%), two cases of acute rheumatic fever (4.8%), and one case of systemic lupus erythematosus (2.4%). There were 11 enthesitis-related arthritis patients, eight oligoarticular arthritis patients, and three rheumatoid factor negative polyarticular arthritis patients among the 22 JIA patients. There were seven patients with vasculitis, six with IgA vasculitis, and one with polyarteritis nodosa (PAN). There was no difference between the FMF groups with and without rheumatic disease in terms of age, gender, family history, disease duration, or colchicine dosage (Table 1).

Figure 1 shows the *MEFV* mutation analyses of the cohort. Table 2 shows the

Table 1. Demographic features of familial Mediterranean fever patients

	All patients (n=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (n=41)	*p*
Mean age (years)	12.24±4.93	12.32±4.91	11.74±5.09	0.48
Female/male n/n	154/149	134/128	20/21	0.77
Family history n (%)	158 (52.1%)	136 (51.9%)	22 (53.7%)	0.83
Mean age at diagnosis of FMF (years)	7.04±3.9	7.04±3.81	7.02±4.46	0.96
Disease duration (years) (mean)	5.33±3.13	5.42±3.11	4.76±3.28	0.21
Colchicine dosage (mg/day) (median)	1 (0.5-1.5)	1 (0.5-1.5)	1 (0.5-1.5)	0.21

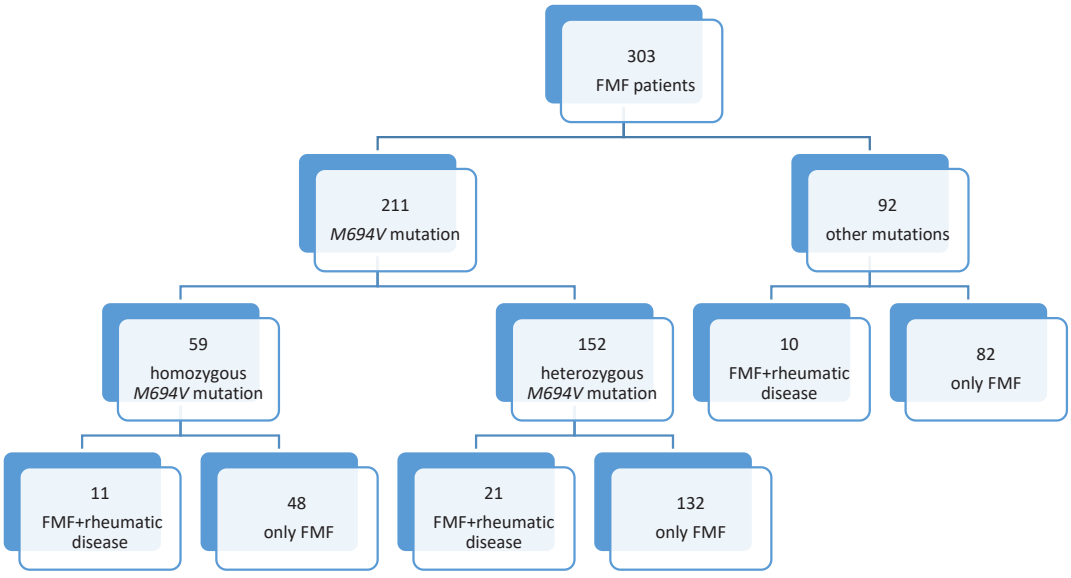

Figure 1. *MEFV* mutation of patients

Table 2. Mutations of familial Mediterranean fever patients

	All patients (n=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (n=41)	*p*
M694V positivity n (%)	211 (69.6%)	180 (68.7%)	32 (78%)	0.37
M694V homozygosity n (%)	59 (19.4%)	48 (18.3%)	11 (26.8%)	0.2
M680I positivity n (%)	50 (16.5%)	45 (17.1%)	5 (12.1%)	0.42
V726A positivity n (%)	34 (11.2%)	31 (11.8%)	3 (7.3%)	0.59
E148Q positivity n (%)	39 (12.9%)	34 (12.9%)	5 (12.1%)	0.88

MEFV mutations of all cohorts. Table 3 depicts the *MEFV* mutation analyses of patients with coexisting rheumatic diseases. The *M694V* mutation in the *MEFV* gene was found in 32 of 41 FMF patients with rheumatic disease, which was significantly greater than the prevalence in FMF patients without rheumatic disease (78% *vs.* 68.7%). Similarly, the percentage of *M694V* homozygous mutations was higher in the group with an associated rheumatic disease (26.8% *vs.* 18.3%).

Colchicine was administered to all patients. Due to concomitant disorders, methotrexate, etanercept, tocilizumab, and sulfasalazine were additionally given to six, five, two, and two

Table 3. Mutations of familial Mediterranean fever patients with rheumatic diseases

Mutations	Disease	n=41
Homozygous		**12**
M694V/M694V	Enthesitis-related arthritis	4
	Polyarticular JIA RF negative	2
	IgA vasculitis	2
	Oligoarticular JIA	2
	Polyarteritis nodosa	1
M680I/M680I	Behçet's disease	1
Heterozygous		**24**
M694V/-	PFAPA	5
	Enthesitis related arthritis	4
	Oligoarticular JIA	3
	IgA vasculitis	2
	Behçet's disease	1
V726A/-	IgA vasculitis	1
	Acute rheumatic fever	1
E148Q/-	Enthesitis-related arthritis	2
	Polyarticular JIA	1
	Oligoarticular JIA	1
	PFAPA	1
K695R/-	Acute rheumatic fever	1
	Behçet's disease	1
Compound heterozygous		**5**
M694V/M680I	Enthesitis related arthritis	1
	Oligoarticular JIA	1
	Systemic lupus erythematosus	1
	IgA vasculitis	1
M694V/V726A	Oligoarticular JIA	1

PFAPA: Periodic fever aphthous stomatitis and adenitis syndrome
JIA: Juvenile idiopathic arthritis
IgA: Immunoglobulin A

patients, respectively, in addition to colchicine. Two colchicine-resistant FMF patients with *M694V* homozygous mutations received anti-IL1B treatment.

There was a statistically significant difference in terms of Pras scores between the FMF groups with and without rheumatic disease (median 6 *vs*. 5, *p*=0.002). The ISSF scores of the groups were also significantly different (median 2 *vs*. 3, *p*<0.001) (Table 4).

Table 4. Severity scores of familial Mediterranean fever patients with and without a rheumatic disease

	All patients (N=303)	Without rheumatic diseases (n=262)	With rheumatic diseases (N=41)	*p*
Pras severity score median (min-max)	5 (4-9)	5 (4-9)	6 (4-9)	0.002*
Pras severity score category, mild, n (%)	194 (64%)	175 (66.8%)	19 (46.3%)	0.01*
Pras severity score category, moderate, n (%)	101 (33.3%)	82 (%31.3%)	19 (46.3%)	0.057
Pras severity score category, severe, n (%)	8 (2.6%)	5 (1.9%)	3 (7.3%)	0.079
ISSF severity score median (min-max)	2 (0-7)	2 (0-5)	3 (0-7)	<0.001*
ISSF severity score category, mild, n (%)	215 (71%)	199 (76%)	16 (39%)	<0.001*
ISSF severity score category, moderate, n (%)	86 (28.4%)	63 (%24)	23 (56.1%)	<0.001*
ISSF severity score category, severe, n (%)	1 (%0.3)	0 (%0)	1(%2.4)	0.01*

ISSF: International severity score system for familial Mediterranean fever
*p<0.05 significant

Discussion

Concurrent diseases in FMF have been explored, and recent studies have indicated that 12.8%-18.9% of FMF patients have an associated disease; however, some of the concomitant diseases in these investigations include asthma, migraines, and other conditions [6-11]. The prevalence of other rheumatic diseases in children with FMF was 13.5% in our study, which is similar to the literature from Turkey (Table 5). The presence of the *M694V* mutation and disease severity scores can all be regarded as relevant risk factors for rheumatic disorders associated with FMF.

The FMF severity score (Pras) was initially established for adults and subsequently adapted for children [19, 20]. This was carried out by adjusting the dosage of colchicine for children. Recently, ISSF scoring criteria have been created and verified for both children and adults [21]. Disease-related sequelae, acute phase measurements, attack traits, and exertional leg pain are all included in this score. As a result, it is the most sensitive and specific. In this study, the ISSF scores were considerably higher in FMF patients with concomitant diseases. We noticed that the severity of the disease was linked to a higher prevalence of comorbidities in our FMF patient population. As a result, clinicians should be aware of the elevated risk of comorbidities in patients with more severe FMF and manage these comorbidities as soon as possible.

Patients with FMF frequently complain of musculoskeletal symptoms [22]. FMF arthritis is characterized by acute attacks of pain and swelling that usually affect large joints in the lower extremities and heal without treatment within 2-3 days. Exertional leg pain is one of the ISSF score's characteristics, and it can be separated from JIA. In our study, 22 patients with FMF (7.2%) had JIA. In other studies, JIA was observed in 1.5-6.1% of FMF patients [7, 8]. Rozenbaum et al. [23] reported three patients with FMF and JIA, all of whom had the *M694V* mutation and had an exceptionally poor prognosis, implying that more aggressive treatment, such as the early use of biologic agents, is required when JIA and FMF coexist.

Table 5. Comparison of the study and the other paediatric studies

	Our cohort	Ozcakar et al. [7]	Kisla Ekinci et al. [8]	Yildiz et al. [9]	Balcı-Peynircioglu et al. [10]	Ayaz et al. [11]
Patient (n)	303	600	494	686	2000	1687
FMF and concomitant disease n (%)	41 (13.5%)	77 (12.8%)	85(17.2%)	130 (18.9%)	94 (4.7%)	118 (7%)
JIA n (%)	22 (7.2%)	21 (3.5%)	27 (5.5%)	42 (6.1%)	31 (1.5%)	63 (3.7%)
IgA vasculitis n (%)	6 (1.9%)	19 (3.1%)	12 (2.4%)	20 (2.9%)	25 (1.2%)	35 (2%)
Polyarteritis nodosa n (%)	1 (0.3%)	9 (1.5%)	NA	3 (0.4%)	1 (0.3%)	1 (0.05%)
PFAPA n (%)	6 (1.9%)	NA	6 (1.2%)	7 (1%)	NA	NA
Acute rheumatic fever n (%)	2 (0.6%)	3 (0.5%)	NA	6 (0.8%)	16 (0.8%)	NA
Behçet's disease n (%)	3 (1%)	1 (0.1%)	NA	1 (0.1)	3 (0.1%)	1 (0.05%)
Systemic lupus erythematosus (nephritis) n (%)	1 (0.3%)	1 (0.1%)	NA	3 (0.4%)	1 (0.05%)	2 (0.1%)

FMF: Familial Mediterranean fever, JIA: Juvenile idiopathic arthritis
PFAPA: Periodic fever aphthous stomatitis and adenitis syndrome
IgA: Immunoglobulin A, NA: Not Available

Etanercept was administered to five patients with JIA and FMF in our cohort. Tocilizumab was used in two individuals with rheumatoid factor-negative polyarticular JIA.

Only a few studies on FMF and paediatric sacroiliitis are currently available [24-26]. In paediatric FMF patients with sacroiliitis, the prevalence of the *M694V* mutation was higher than in adult research [27]. In our analysis, the most common mutations in patients with sacroiliitis were *M694V* mutations (8 of 11 sacroiliitis). In one of the paediatric studies, patients with FMF related sacroiliitis had significantly higher levels of inflammation than those with juvenile spondyloarthropathy [24]. In addition, individuals with juvenile spondyloarthropathy had higher spinal and enthesitis involvement, as well as HLA-B27-positivity, than patients with FMF related sacroiliitis [24]. In the diagnosis of enthesitis-related arthritis, Gulhan et al. [27] found that being HLA B27 negative increases the prevalence of *MEFV* mutation, which could be one of the genetic factors. Since 11 patients with sacroiliitis also had enthesitis in our study, all diagnoses were enthesitis-related arthritis according to ILAR criteria, with only one patient having HLA-B27 positive.

The most prevalent type of vasculitis in children is IgA vasculitis (Henoch-Schönlein purpura). According to several recent studies, vasculitis, particularly IgA vasculitis, is more common among FMF patients than in the general population, with the *M694V* mutation being the most common [28, 29]. Ozdogan et al. [30] reported that IgA vasculitis was present in 7% of FMF patients, and nine patients were diagnosed with FMF after the emergence of IgA vasculitis. According to the Turkish FMF study group, 2.7% of patients with IgA vasculitis [6]. In other studies, IgA vasculitis rates were 1.2-2.9% [7-9]. The prevalence of FMF and IgA vasculitis was 1.9% in this study, and all patients were diagnosed with FMF after IgA vasculitis disease. We investigate FMF clinical findings and *MEFV* mutations in patients with vasculitis on a routine basis in our clinic.

The most common autoinflammatory disorders in childhood are FMF and PFAPA. *MEFV* mutations may be found in

PFAPA patients [31, 32]. According to the literature, PFAPA patients with FMF are more resistant to adenotonsillectomy than patients without FMF [33]. Furthermore, prophylactic colchicine treatment reduces attack frequency and extends episode intervals in PFAPA patients with *MEFV* mutations [34, 35]. Previous studies' rates were 1-1.2% [8, 9]. Six patients (1.9%) with FMF had PFAPA in our study. All of them used colchicine, and five carried the *M694V* mutation.

MEFV mutation carriers may have increased inflammation and suffer from other rheumatic diseases [36]. In a Turkish multicentric FMF study, the homozygous *M694V* mutation was 28%, and the *M694V* allele frequency was 51.4% [6]. In our study, the frequency of the homozygous *M694V* mutation was 19.4%, and the frequency of the *M694V* allele was 69.6%. According to recent investigations, the *M694V* mutation may represent a sensitivity component for concurrent disorders [6]. *MEFV* mutations, according to Ozen et al. [37], may predispose patients to inflammation. In childhood FMF patients, the *M694V* mutation may be a risk factor for rheumatic disorders. *M64V* was the most common mutation in our study. However, there was no difference between the two groups because *M694V* is a prevalent and important mutation in our region.

The first limitation of this study was that it was a retrospective study. The second limitation was the small number of patients because the study was conducted in a single centre.

In conclusion, our study and other studies have shown that other rheumatic diseases are common in FMF patients so, routine rheumatic disease evaluation may be beneficial in FMF patients. Having higher disease severity scores and the presence of the *M694V* mutation are key risk factors for having FMF-related rheumatic disorder.

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

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Authors' contributions to the article

G.O.Y., S.Y., Z.E.T. and H.T. constructed the main idea and hypothesis of the study. G.O.Y., S.Y., Z.E.T. and H.T. developed the theory and arranged/edited the material and method section. G.O.Y. and S.Y. evaluated the data in the results section. G.O.Y. and S.Y., reviewed, corrected, and approved the discussion section of the article. In addition, all authors discussed the entire study and approved the final version.

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snoRNAs are deregulated in patients with Parkinson's Disease

Parkinson tanısı almış hastalarda snoRNA'ların deregülasyonu

Pervin Elvan Tokgün, Ayşe Gaye Tomatır, Fatma Gizem Sarıekiz, Levent Sinan Bir

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Abstract

Purpose: Small nucleolar RNAs are ranging from 65 to 300 nucleotides in length that mediate post-transcriptional RNA modifications. They don't have a 5′-Cap and a poly-A tail and are categorized as C/D box snoRNAs, H/ACA box snoRNAs, and small Cajal body-specific RNAs. snoRNAs have essential roles in important biological processes such as transcription, RNA splicing, cell cycle, and etc. In this study, we tried to reveal differential expressions of snoRNAs in PBMCs of patients with Parkinson's Disease by microarray analysis.

Materials and methods: Patients (n=3) who are considered to have a unilateral onset history and a good response to dopaminergic treatment in the first years were included in the study. 10 ml peripheral blood sample was taken for peripheral blood mononuclear cell isolation. Total RNA was extracted using GeneAll® Hybrid-R™ kit and microarray analysis was performed by using Affymetrix GeneChip Human ST 2.0 platform. Raw data were extracted using Affymetrix Command Console Software 1.1. KEGG pathway and GO terms analyses were performed and protein-protein interaction of host genes were determined by using STRING database.

Results: Data from patients revealed that there were 28 snoRNAs were downregulated and 3 snoRNAs were upregulated.

Conclusion: Here in this study, we evaluated the differential expressions of snoRNAs in patients with a definitive diagnosis of PD by microarray analysis and observed deregulated expressions of some snoRNAs. Differential expression of snoRNA may cause changes in the transcriptional activity of host genes and thus can serve as biomarkers for diseases.

Key words: Parkinson, snoRNA, microarray.

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Öz

Amaç: Küçük nükleolar RNA'lar 65 ila 300 nükleotit uzunluğundadır ve transkripsiyon sonrası RNA modifikasyonlarına aracılık ederler. 5'-uçları ve poli-A kuyrukları yoktur. C/D box snoRNA'lar, H/ACA box snoRNA'lar ve küçük kajal gövdesine özgü RNA'lar olarak sınıflandırılırlar. snoRNA'lar, transkripsiyon, RNA eklenmesi, hücre döngüsü vb. gibi önemli biyolojik süreçlerde önemli rollere sahiptir. Bu çalışmada, Parkinson tanısı alan hastaların PBMC'lerinde snoRNA'ların ifade değişimlerini mikroarray analizi ile ortaya koymaya çalıştık.

Gereç ve yöntem: Unilateral başlangıç öyküsü olan ve ilk yıllarda dopaminerjik tedaviye iyi yanıt verdiği düşünülen hastalar (n=3) çalışmaya alındı. Periferik kan mononükleer hücre izolasyonu için 10 ml periferik kan örneği alındı. Total RNA, GeneAll® Hybrid-R™ kiti kullanılarak izole edildi ve Affymetrix GeneChip Human ST 2.0 platformu kullanılarak mikrodizin analizi yapıldı. Ham datalar, Affymetrix Command Console Software 1.1 kullanılarak çıkarıldı. KEGG yolak ve Gen ontoloji analizleri yapıldı ve lokus genlerin protein-protein değişimi STRING veri tabanı kullanılarak gerçekleştirildi.

Bulgular: Elde edilen veriler, 28 snoRNA'nın upregüle olduğunu ve 3 snoRNA'nın downregüle olduğunu ortaya çıkardı

Sonuç: Bu çalışmada, mikrodizin analizi ile kesin Parkinson tanısı alan hastalarda snoRNA'ların ifade değişimlerini değerlendirdik ve bazı snoRNA'ların deregüle ekspresyonlarını gözlemledik. snoRNA'lardaki ifade değişimi, lokus genlerin transkripsiyonel aktivitesinde değişikliklere neden olabilir ve bu nedenle hastalıklar için biyobelirteçler olarak değerlendirilebilirler.

Anahtar kelimeler: Parkinson, snoRNA, mikrodizin.

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Pervin Elvan Tokgün, PhD. Department of Medical Genetics, Faculty of Medicine, Pamukkale University, Denizli, Turkey, e-mail: parslan@pau.edu.tr (https://orcid.org/0000-0001 9025-4140)

Ayşe Gaye Tomatır, Prof. Department of Medical Biology, Faculty of Medicine, Pamukkale University, Denizli, Turkey, e-mail: tomatir@pau.edu.tr (https://orcid.org/0000-0001-9251-9632) (Corresponding Author)

Fatma Gizem Sarıekiz, MSc. Department of Medical Biology, Faculty of Medicine, Pamukkale University, Denizli, Turkey, e-mail: fgizem.sariekiz@gmail.com (https://orcid.org/0000-0003-2934-802X)

Levent Sinan Bir, Prof. Department of Neurology, Faculty of Medicine, Pamukkale University, Denizli, Turkey, e-mail: sbir@pau.edu.tr (https://orcid.org/0000-0003-3226-3756)

Introduction

As noncoding RNA, small nucleolar RNAs (snoRNAs) are ranging from 65 to 300 nucleotides in length that mediate post-transcriptional RNA modifications. SnoRNAs do not have a 5′Cap and a poly-A tail, and are classified as C/D box snoRNAs (SNORDs), small Cajal body-specific RNAs (scaRNAs) and H/ACA box snoRNAs (SNORAs). Both types of snoRNAs bind to specific protein partners to form complexes called snoRNPs (small nucleolar ribonucleoprotein complexes). snoRNAs are mainly encoded by intronic regions of both protein-coding and non-coding genes [1-3]. Common tasks of snoRNAs include 2'-O-methylation and pseudouridylation of rRNAs. C/D box snoRNAs guide the dioxymethylation of nucleotides, while H/ACA box snoRNAs are responsible for pseudouridylation [4]. snoRNAs play essential roles in biological processes such as transcription, RNA splicing, cell cycle regulation, chromosome segregation, and genomic imprinting [5-7]. Studies have shown that snoRNAs can also regulate cell physiology by performing miRNA-like functions within cells [8].

Parkinson's disease (PD) is a disorder with abnormalities of movement and is clinically diagnosed by bradykinesia, postural instability, tremor, and rigidity of the arms and legs [9]. Clinical diagnosis of PD can show heterogeneity, thus some other conditions such as parkinsonism secondary to vascular disease, essential tremor and progressive supranuclear palsy can mimic PD [10]. Ribosomal RNA (rRNA) is transcribed in the nucleolus and dysregulation of the nucleolus can cause cellular stress which is associated with neurodegenerative diseases including PD [11]. Recent studies have reported several snoRNAs in different organisms.

In this study, we aimed to identify deregulated expressions of snoRNAs in PBMCs of patients with Parkinson's Disease by microarray analysis.

Materials and methods

Patient selection criteria

Ethical approval and patient consent were taken for the study. Patients (n=3) diagnosed with "Parkinson's Disease" were included in our study, considering that they had a unilateral onset history and had a good response to dopaminergic treatment in the first years. The control group consisted of individuals (n=2) over the age of 50, who were determined by excluding secondary parkinsonism cases due to other causes and parkinsonism related to other degenerative diseases.

Sample collection and PMBC preparation

A 10 ml peripheral blood sample was taken using K2EDTA anticoagulant tubes and an "Informed Voluntary Consent Form" was taken from the patients meeting the inclusion criteria. Peripheral blood mononuclear cells (PBMC) are prepared by using Ficoll-Histopaque density gradient centrifugation within 3 hours and directly prepared for RNA isolation.

RNA Isolation

The total RNA was isolated from PBMCs of samples with GeneAll® Hybrid-R™ kit according to manufacturer's instructions. The quantity and integrity of RNA samples were measured by NanoDrop ND-1000 (Thermo Scientific) and Agilent 2100 bioanalyzer using the RNA 6000 Nano Chip. Samples with a purity of 1.8 to 2.0 were accepted for microarray analysis.

RNA labeling, microarray hybridization, and scanning

Microarray analysis was performed by using Affymetrix GeneChip Human ST 2.0 platform. 1µg of total RNA was used as input and then converted into double-stranded cDNA. The cDNA was then fragmented and end-labeled by a TdT (terminal deoxynucleotidyl transferase) reaction. Fragmented and end-labeled cDNAs were hybridized for 16 hours at 45 °C and 60 rpm with the GeneChip Human Gene 2.0 ST oligonucleotide arrays including 53,617 probes. Chips were then stained and washed in the GeneChip Fluidics Station 450 (Affymetrix) and scanned with an Affymetrix Model GCS3000 scanner.

Raw data preparation

Raw data were extracted using Affymetrix Command Console Software 1.1. The raw CEL file which contain intensity data was used for further analysis. Data normalization was performed with Affymetrix Power Tools, R 3.3.3. Hierarchical cluster analysis was performed using complete linkage and Euclidean distance as a measure of similarity.

Microarray data analysis

Data showing expression differences between patients and controls were filtered. Fold changes limits were accepted as "1,5". Values <1,5 indicate downregulation while >1,5 indicate upregulation.

Statistical analysis

GraphPad Prism software (version 7.0; GraphPad) was used for statistical data analysis. Comparisons among groups were performed using Student's t-test or one-way analysis of variance (ANOVA) followed by Tukey's test. $p<0.05$ value was accepted as statistically significant.

Gene ontology and KEGG pathway analysis

KEGG pathway and GO terms analyses were performed to analyze the biological process, molecular functions, and biochemical pathways of snoRNAs determined by microarray analysis.

STRING database analysis

Protein-Protein interaction network analysis was performed using the STRING database (https://string-db.org/).

Results

In order to identify differentially expressed snoRNAs, PBMCs of patients were used for microarray analysis. All microarray data were filtered from among 5,638 Refseq non-coding transcripts. Data from patients revealed that there were 28 snoRNAs were downregulated of which 5 of them were members of the H/ACA box and 15 of them were C/D boxes. Three snoRNAs were upregulated and 1 of them was a member of the H/ACA box whereas 2 of them were C/D boxes. HeatMap analysis of host genes were shown in Figure 1. snoRNA orthological gene database (http://snoopy.med.miyazaki-u.ac.jp) was used for the identification of their localizations (protein-coding genes, introns, ORFs and etc) and target RNAs of snoRNAs. The corresponding data were shown in Table 1.

We used ShinyGo v0.741 Gene Ontology Enrichment Analysis algorithm (http://bioinformatics.sdstate.edu/go74/). Gene ontology analysis was used for revealing biological, molecular, and functional processes in host genes of differentially expressed snoRNAs. In analysis, patients and control groups were compared and all processes were determined by taking the $p<0.05$ value into consideration (Figure 2A-C). GO categories of the corresponding host genes of snoRNAs are given in Table 2. KEGG pathway analysis was performed to determine the relationship in host genes of differentially expressed snoRNAs. According to KEGG analysis, we observed that the major pathway with high significance is related to the ribosome (Figure 3). Protein-protein interactions (PPI) were performed by STRING database. Protein interactions of host genes were shown in Figure 4.

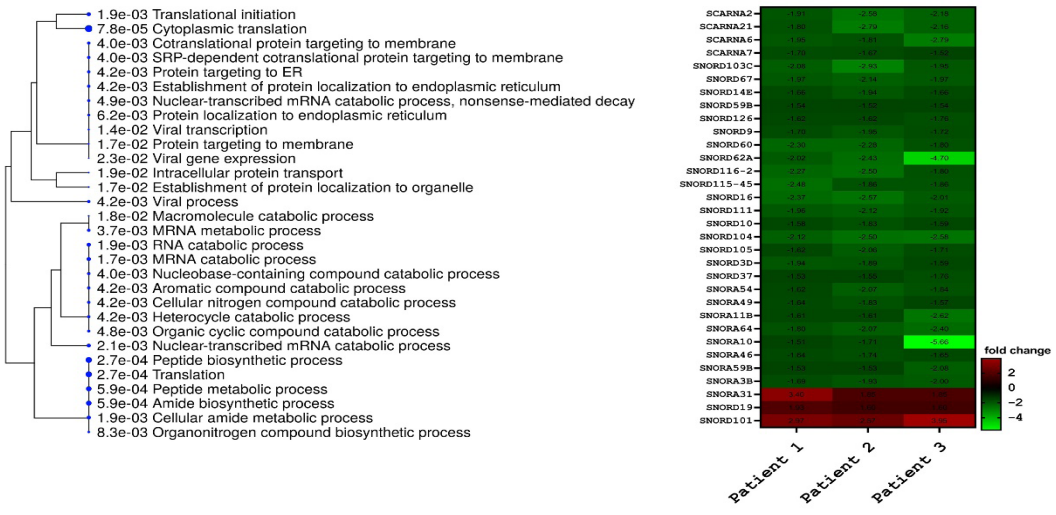

Figure 1. HeatMap analysis of the host genes of snoRNAs with deregulated expressions

Table 1. snoRNAs detected in the PBMCs of the patients

snoRNAs	BOX	Target RNA	Organization	Locus	Expression
SCARNA2	C/D	U2 snRNA	Monocistron	mono:SCARNA2 (mgU2-25/61)	Downregulated
SCARNA21	Unknown	Unknown	Unknown	Unknown	Downregulated
SCARNA6	C/D	U5 snRNA	Intronic	ATG16	Downregulated
SCARNA7	C/D	U1 snRNA	Intronic	KPNA4	Downregulated
SNORD103C	C/D	18S rRNA	Intronic	PUM1	Downregulated
SNORD67	C/D	U6 snRNA	Intronic	CKAP5	Downregulated
SNORD14E	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORD126	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORD9	C/D	U6 snRNA	Intronic	CHD8	Downregulated
SNORD60	C/D	28S rRNA	Intronic	AA974833	Downregulated
SNORD62A	C/D	18S rRNA	Intronic	PRRC2B	Downregulated
SNORD116-2	C/D	Unknown	Unknown	hmm16326423	Downregulated
SNORD115-45	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORD16	C/D	18S rRNA	Intronic	RPL4	Downregulated
SNORD111	C/D	28S rRNA	Intronic	SF3B3	Downregulated
SNORD10	Unknown	U6 snRNA, 28S rRNA	Intronic	EIF4A1	Downregulated
SNORD104	C/D	28S rRNA	Polycistron	Poly:10:AC025362.12	Downregulated
SNORD105	C/D	18S rRNA	Intronic	P2RY11	Downregulated
SNORD3D	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORD37	C/D	28S rRNA	Intronic	EEF2	Downregulated
SNORA54	H/ACA	28S rRNA	Intronic	NAP21L4	Downregulated
SNORA49	H/ACA	Unknown	Intronic	EP400	Downregulated
SNORA11B	H/ACA	Unknown	Intronic	C14orf159	Downregulated
SNORA64	H/ACA	28S rRNA	Intronic	MYRIP, RPS2	Downregulated
SNORA10	H/ACA	18S rRNA, 28S rRNA	Intronic	RPS2	Downregulated
SNORA46	H/ACA	18S rRNA	Intronic	AHSA1, CNOT1	Downregulated
SNORA59B	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORA3B	Unknown	Unknown	Unknown	Unknown	Downregulated
SNORA31	H/ACA	18S rRNA, 28S rRNA	Intronic	TPT1	Upregulated
SNORD19	C/D	18S rRNA	Intronic	GNL13	Upregulated
SNORD101	C/D	Unknown	Intronic	RPS12	Upregulated

Figure 2. Gene ontology analysis A) Molecular Function B) Biological Process C) Cellular component

Table 2. High Level "GO Terms" Category of the Host Genes of snoRNAs

GO Category	Host Genes
Cellular localization	RPS12 RPS2 EEF2 MYRIP RPL4 CKAP5 KPNA4
Catabolic process	RPS12 CNOT1 PUM1 RPS2 RPL4 SF3B3
Macromolecule localization	RPS12 RPS2 MYRIP RPL4 CKAP5 KPNA4
Response to stress	CNOT1 TPT1 PUM1 EEF2 P2RY11
Response to external stimulus	CHD8 TPT1 PUM1 EEF2 P2RY11
Regulation of signaling	CHD8 CNOT1 TPT1 PUM1 MYRIP
Regulation of response to stimulus	CHD8 CNOT1 TPT1 PUM1 P2RY11
Cellular component biogenesis	CNOT1 RPS2 RPL4 CKAP5
Regulation of biological quality	CNOT1 TPT1 PUM1 MYRIP
Immune system process	PUM1 EEF2 P2RY11
Immune response	PUM1 EEF2 P2RY11
Response to endogenous stimulus	CNOT1 EEF2 P2RY11
Biological process involved in interspecies interaction between organisms	TPT1 PUM1 KPNA4
Regulation of molecular function	AHSA1 RPS2 P2RY11
Behavior	CHD8 PUM1
Regulation of immune system process	PUM1 P2RY11
System process	CHD8 EEF2
Response to biotic stimulus	TPT1 PUM1
Cell cycle process	CNOT1 CKAP5
Regulation of cellular component biogenesis	CNOT1 CKAP5
Regulation of developmental process	CNOT1 TPT1
Response to other organism	TPT1 PUM1
Maintenance of cell number	CNOT1 TPT1

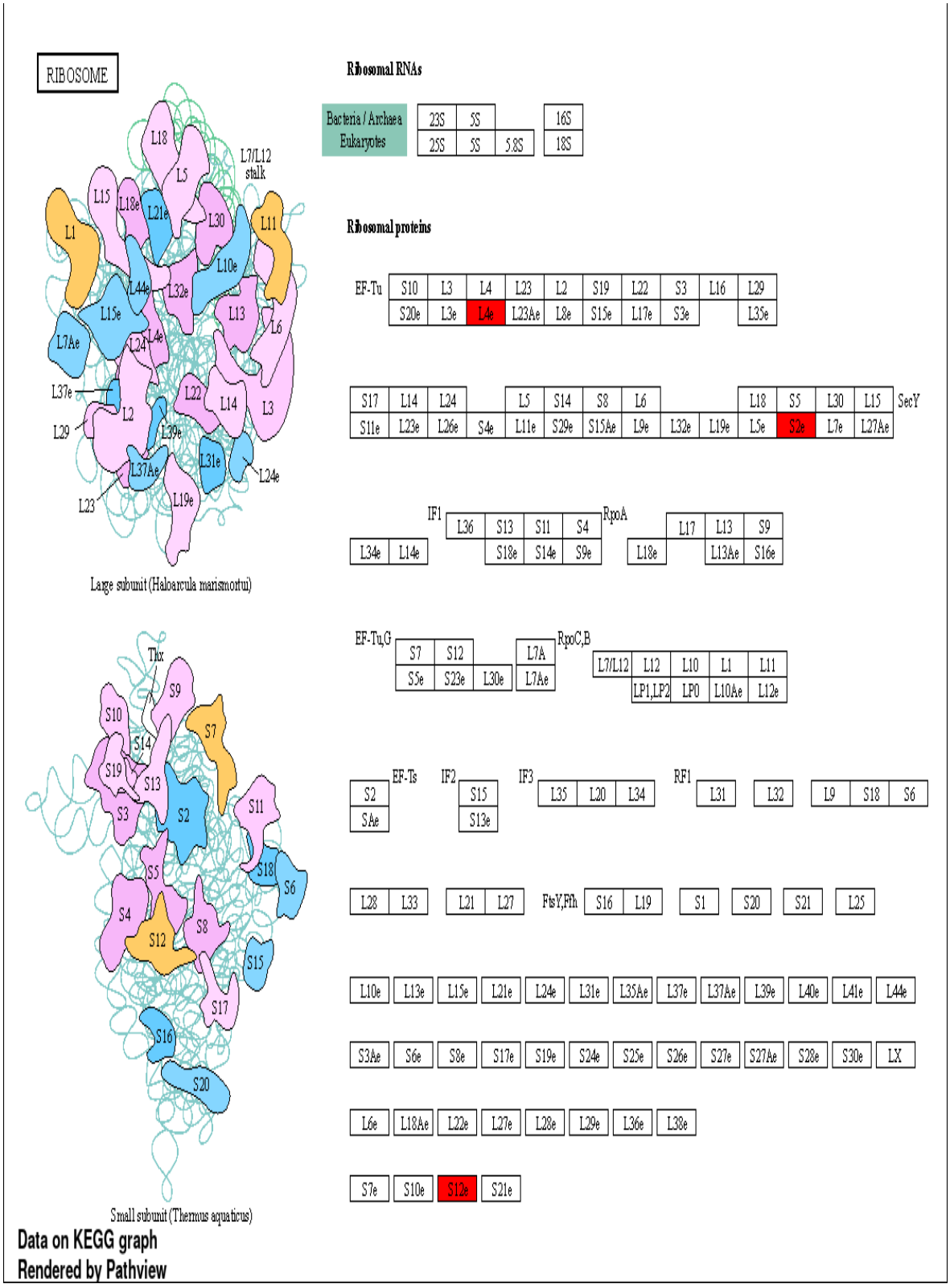

Figure 3. KEGG pathway analysis

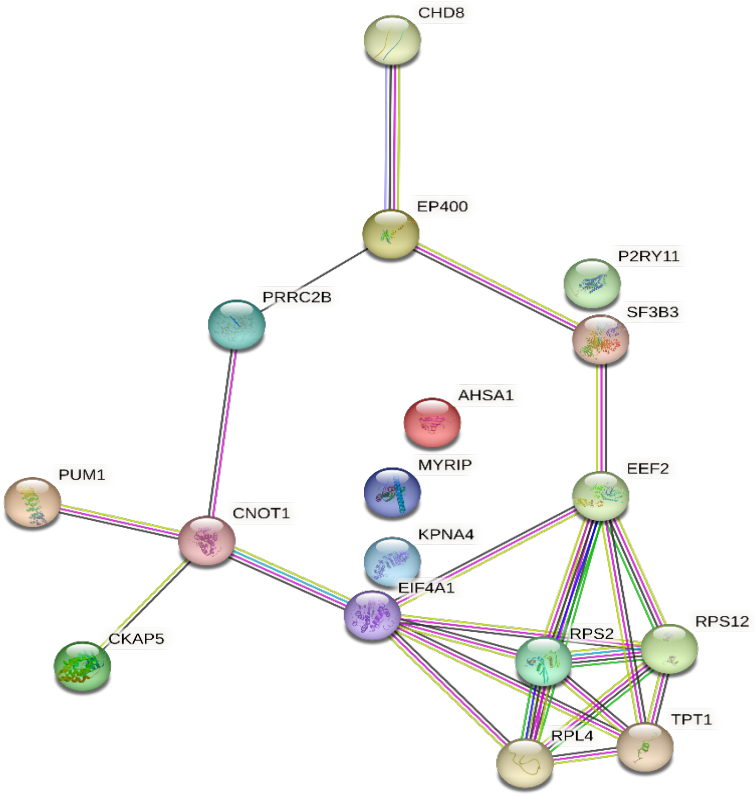

Figure 4. Protein-Protein interactions using STRING Database

Discussion

In our study, we revealed the deregulated expressions of snoRNAs in the PBMCs isolated from patients with PD. GO terms and pathway analysis have shown that snoRNAs are involved in several biological processes, mainly in cytoplasmic translation. With the advance of the in-silico algorithms, it is possible to determine the host genes and target RNAs of snoRNAs as shown in Table 1.

snoRNAs, which are involved in many physiological and pathological processes, also have tumor suppressor and oncogenic functions in various cancer types. In a study, it was reported that snoRNAs are overexpressed in human breast and prostate cancers, and this overexpression supports tumorigenicity both in vitro and in vivo [12]. In a study that investigated the expression of ncRNAs in central nervous system diseases, two snoRNAs whose expression was deregulated prior to amyloid plaque formation were identified in a mouse Alzheimer's model [13]. The role of snoRNAs in Parkinson's disease is unknown, but one study identified four snoRNAs (SNORA52, SNORD15A, SNORD134, and SNORD57) that were significantly upregulated in a model of MPP+-induced Parkinson's disease [14]. Cavaillé et al. reported four snoRNAs (MBII-13, MBII-52, MBII-85, and MBI-36) expressed in the central nervous system of mice [15]. The presence of snoRNAs can also be detected in human cerebrospinal fluid samples [13]. Altered snoRNA expression may result from disease processes and changes in the transcriptional activity of host genes and thus serve as biomarkers for diseases.

Peripheral blood mononuclear cells (PBMCs) are one of the novel sources in many disorders [16] and could mimic the conditions of some tissues [17]. Because PBMCs are subsidiary in the functionalities of the immune system they can be a source of biomarkers [18].

In conclusion, there is a fact that the heterogeneity of PD causes diagnostic difficulties. The limitation of the study is a very limited number of cases with motor movement deficits can be diagnosed as PD. Therefore, here in this study, we evaluated the differential expressions of snoRNAs in patients with a

definitive diagnosis of PD by microarray analysis and observed deregulated expressions of some snoRNAs. We believe that this study can contribute to the literature. More studies on PD patients can help to determine new biomarkers for the disease.

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

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Authors' contributions to the article

P.E.T. and A.G.T. constructed the main idea and hypothesis of the study. P.E.T., A.G.T. and F.G.S. developed the theory and arranged/edited the material and method section. L.S.B. has chosen the patients included in the study. P.E.T., A.G.T. have done the evaluation of the data in the Results section. Discussion section of the article was written by P.E.T., A.G.T.; P.E.T., A.G.T., F.G.S. and L.S.B. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Evaluation of nutritional habits and affecting factors of health care professionals during the Covid-19 pandemic stage: on-line survey study

Sağlık çalışanlarının Covid-19 pandemisi sürecinde beslenme alışkanlıkları ve etkileyen faktörlerin değerlendirilmesi: on-line anket çalışması

İlker Coşkun, Ebru Çanakçı, Zübeyir Cebeci

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Abstract

Purpose: Health workers have been greatly affected by the pandemic, both as a health worker and as a member of the society, and have gone out of their routine lifestyle and habits more than normal individuals. In the pandemic stage; intense, irregular and stressful work pace also disrupted the routine eating habits while increasing the need for nutrition. With this survey study, it is aimed to evaluate the nutritional habits, affecting factors and results of healthcare professionals during the Covid-19 pandemic stage.

Materials and methods: For our study a questionnaire of 49 questions was prepared. It was continued between 01/06/2020 and 01/01/2021. Questionnaires were prepared on Google forms and sent to healthcare professionals via e-mail. Multiple-choice questions were asked about personal information such as the number of meals, whether they gained weight during the pandemic stage, foods believed to protect from Covid-19, nutritional supplements used during the pandemic period, and the reason for using supplements. The questions in the second category are; it mostly includes questions about changes in dietary and lifestyle of health workers during the pandemic period. It includes questions such as: ''My meal count has increased'', ''My water consumption has increased'', ''My night eating behavior has improved'', ''My sleep pattern has been disrupted'', ''I gained weight during the pandemic'', ''I smoke more'', ''I drink more tea and coffee'', ''I try to exercise''. The answers were obtained with a 3-point Likert scale (agree, undecided, disagree).

Results: It was determined that health workers experienced weight gain during the pandemic stage. It was determined that the average weight and average BMI of health professionals showed a statistically significant increase (p<0.01). It was noticed that the participants had an increase in the number of meals during the pandemic stage (p<0.001). It was noticed that the vast majority of the participants took vitamin and mineral supplements.

Conclusion: We found that healthcare workers took additional mineral and vitamin supplements, increased the number of meals, and experienced weight gain during the pandemic. Because of this, health workers should be given healthy snacks with high nutritional value during the pandemic stage. By health managers and administrators; a management and organizational plan including a healthy nutrition program especially in extraordinary situations such as pandemics can be created, for health workers who are exposed to intense, irregular and stressful working conditions and who are in high risk groups.

Key words: Covid-19, pandemic process, nutritional habits, healthcare workers, vitamin mineral supplement.

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Öz

Amaç: Sağlık çalışanları, pandemiden hem bir sağlık çalışanı olarak hem de toplumun bir bireyi olarak fazlasıyla etkilenmiş, rutin yaşam şekli ve alışkanlıklarının dışına normal bireylere göre daha fazla çıkmıştır. Pandemi sürecinde yoğun, düzensiz, stresli çalışma temposu, beslenmeye olan ihtiyacı artırırken bir taraftan da rutin beslenme alışkanlıklarını bozmuştur. Bu anket çalışması ile sağlık çalışanlarının Covid-19 pandemisi sürecinde beslenme alışkanlıkları, etkileyen faktörlerin ve sonuçlarının değerlendirilmesi amaçlanmıştır.

Gereç ve yöntem: Çalışmamız için 49 soruluk anket hazırlanmıştır. 01/06/2020 tarihi ile 01/01/2021 tarihleri arasında sürdürülmüştür. Google formlar üzerinden anket soruları hazırlanmış ve mail yoluyla sağlık çalışanlarına gönderilmiştir. Katılımcıların öğün sayısı, pandemi sürecinde kilo alıp almadıkları, Covid-19'dan koruduğuna inanılan besinler, pandemi döneminde kullanılan besin takviyeleri ve takviye kullanma sebebi gibi kişisel bilgilere yönelik çoktan seçmeli sorular sorulmuştur. İkinci kategorideki sorular ise; daha çok sağlık çalışanlarının pandemi döneminde beslenme ve yaşam tarzındaki değişikliklerle ilgili soruları içermektedir. ''Öğün sayım arttı'', ''su tüketimim arttı'', ''gece yeme davranışım gelişti'', ''uyku düzenim bozuldu'', ''pandemi sürecinde kilo aldım'', ''daha çok sigara içiyorum'', ''daha çok çay-kahve içiyorum'', ''egzersiz yapmaya çalışıyorum'' gibi maddelerden oluşan sorular yer almaktadır. Cevaplar 3'lü likert skalası (katılıyorum, kararsızım, katılmıyorum) ile elde edilmiştir.

İlker Coşkun, Asst. Prof. Ordu University, Faculty of Medicine, Training and Research Hospital, Department of Anesthesiology and Reanimation, Ordu, Turkey, e-mail: drilker75@gmail.com (https://orcid.org/0000-0001-6781-3522) (Corresponding Author)

Ebru Çanakçı, Assoc. Prof. Ordu Üniversitesi, Tıp Fakültesi, Eğitim Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ordu, Turkey, e-mail: canakciebru@gmail.com (https://orcid.org/0000-0003-2093-9229)

Zübeyir Cebeci, Asst. Prof. Ordu Üniversitesi, Tıp Fakültesi, Eğitim Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ordu, Turkey, e-mail: zubeyircebeci@gmail.com (https://orcid.org/0000-0001-7862-4268)

Bulgular: Pandemi sürecinde sağlık çalışanlarının kilo artışı yaşadıkları tespit edildi. Sağlık çalışanlarının, ağırlık ortalamasının ve VKİ ortalamasının istatistiksel olarak anlamlı artış gösterdiği belirlendi (p<0.01). Katılımcıların pandemi sürecinde öğün sayısında artış olduğu tespit edildi (p<0.001). Katılımcıların çok büyük çoğunluğunun vitamin ve mineral takviyesi aldığı tespit edildi.
Sonuç: Sağlık çalışanlarının pandemi süresince ek mineral ve vitamin takviyesi aldıkları, öğün sayısını artırdıkları ve kilo artışı yaşadıklarını tespit ettik. Bu sebeple sağlık çalışanlarına pandemi sürecinde, besleyici değeri yüksek, sağlıklı ara öğünler verilmesi gerekmektedir. Sağlık yönetici ve idarecileri tarafından, özellikle pandemi gibi olağanüstü durumlarda yoğun, düzensiz ve stresli çalışma koşullarına maruz kalan ve yüksek risk grubunda ki sağlık çalışanları için sağlıklı beslenme programını içeren bir yönetim ve organizasyon planı oluşturulabilir.

Anahtar kelimeler: Covid-19, pandemik süreç, beslenme alışkanlıkları, sağlık çalışanları, vitamin mineral takviyesi.

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Introduction

The Covid-19 pandemic has adversely affected the whole world and our country in many areas, especially health. The negative impacts of the pandemic on working life, social life and economy are still increasing. Health workers have been greatly affected by the pandemic, both as a health worker and as a member of the society, and have gone out of their routine lifestyle and habits more than normal individuals. While disrupting routine eating habits, intense, irregular and stressful work pace during the pandemic process increased the need for nutrition. The occupational group with high risk during the pandemic period is healthcare workers. Nutrition, on the other hand, is an important part of health and is effective in shaping our immune system. Having a strong immune system against Covid-19 infection can be considered an important protection mechanism. A balanced and healthy diet plays an effective role in boosting immunity. During the pandemic, the World Health Organization (WHO), the Turkish Dietetic Association and the Food and Agriculture Organization have published nutritional recommendations for Covid-19 [1-4]. In spite of all these warnings and suggestions about nutrition, people have gained different eating habits despite all the recommendations of social organizations due to many psychological factors such as isolation processes, difficulties, fear and stress in people's homes during the pandemic. So that, extremely negative dietary habits increase the incidence of chronic diseases such as obesity and diabetes, which have a high prevalence and adversely affect the quality of human life. In many studies, it has been shown that people's eating habits, eating behaviors and physical activity levels have changed during the pandemic process. The pandemic stage has also directed healthcare workers to take nutritional supplements [5, 6].

With this survey study; it was aimed to evaluate the nutritional habits, influencing factors and results of healthcare professionals during the Covid-19 pandemic stage.

Materials and methods

Ethical approval was obtained from Ordu University Clinical Research Ethics Committee for our study. Questionnaires were prepared on Google forms and sent to healthcare professionals via e-mail. All healthcare professionals who voluntarily participated in the survey were included in our survey. Healthcare workers who did not want to participate in our study were excluded from the study. Our study was carried out between 01/06/2020 and 01/01/2021.

A questionnaire of 48 questions was prepared for our study. The questions in the first category; included personal information questions as gender, age (year), body weight (kg), height (cm), profession and time in the profession, education status, marital status, where and with whom she lives, having received nutrition education and being interested in nutrition, status of having a chronic disease, smoking use, regular physical activity status and frequency. Moreover, there are questions, as number of daily meals related to nutritional status, skipping meals, the most skipped meals/meals and the reason for skipping meals, the most preferred snacks, daily water, tea and coffee consumption (liter), place to eat during working hours and where the food is obtained from, mood effect of changes in diet. It consists of multiple-choice questions for personal information such as

passing Covid-19 and the thought that using nutritional supplements alleviates the course of Covid-19, foods believed to protect from Covid-19, nutritional supplements used during the pandemic period and the reason for using supplements. The questions in the second category are; it mostly includes questions about changes in alimentation and lifestyle of health workers during the pandemic period. It includes questions such as: ‘‘My meal count has increased’’, ‘‘My water consumption has increased’’, ‘‘My night eating behavior has improved’’, ‘‘My sleep pattern has been disrupted’’, ‘‘I gained weight during the pandemic’’, ‘‘I smoke more’’, ‘‘I drink more tea and coffee’’, ‘‘I try to exercise’’. The answers were obtained with a 3-point Likert scale (agree, undecided, disagree).

Statistical analysis

SPSS 22.0 program was used for statistical analysis. The descriptive statistical evaluation of the data is indicated with average, standard deviation, median, min-max, ratio and frequency values. The distribution of variables was checked with the Kolmogorov Smirnov test. ANOVA (Tukey test), Kruskal-Wallis (Mann-Whitney U test) were used in the analysis of quantitative data. Chi-square test was used in the analysis of qualitative data, and Fischerexact and McNemar tests were used when chi-square conditions were not met. A value of $p<0.05$ was considered statistically significant.

Results

A total of 714 people participated in our survey. However, since 3 people answered ‘‘No’’ to the question ‘‘I voluntarily participate in this study and I accept the use of the information I have given in scientific studies’’, the total number of participants was accepted as 711.

The weight and body mass index (BMI) of the participants before and during the pandemic are presented in Table 1.

As a result of the Paired t-test, it was noticed that the mean weight and mean BMI increased statistically significantly during the pandemic period ($p<0.01$). Demographic characteristics of the participants are presented in Table 2.

The chronic disease states of the participants are presented in Table 3. 69.3% of the health workers who participated in the survey do not have any additional diseases.

The use of a vitamin preparation, supplement or immune system-supporting drug or product before and during the pandemic of the participants in the study is presented in Table 4.

The distribution of the answers given by the participants to the question of how often they used nutritional supplement products during the pandemic is presented in Table 5.

It is seen that all of the participants took nutritional supplements during the pandemic. In the study, the number of meals before and after the pandemic and the status of whether the participants had snacks or not are presented in Table 6.

According to the McNemar’s test, in the survey participants increased the number of meals significantly during the pandemic *(p*<0.001). According to McNemar’s test, it was determined that there was no increase in the number of snacks during the pandemic, that is, there was no statistically significant change ($p=0.646$).

Discussion

According to our survey results, it was determined that health workers gained weight and their body mass indexes increased. Similarly, it has been determined that health workers take nutritional supplements during the pandemic and there is an increase in the number of meals. The roles and responsibilities of healthcare professionals in the Covid-19 process have increased over time. In this

Table 1. Average weight and BMI of the participants before and during the pandemic

	Before the pandemic	During the pandemic	*p*
Weight (kg)	72.66±15.36	73.04±15.61	*0.003***
Body Mass Index (BMI)	25.54±4.30	25.67±4.41	*0.002***

Mean±SDPaired t-test**:<0.01

Table 2. Demographic characteristics of the participants in the study

		n	%
Gender	Man	275	38.7
	Woman	436	61.3
Age Groups	20-30	156	21.9
	31-40	198	27.8
	41-50	251	35.3
	51-60	101	14.2
	60+	5	0.7
Educational Status	Graduate	261	36.7
	High school	36	5.1
	University	414	58.2
Marital Status	Single	195	27.4
	Married	516	72.6
Do you have children?	Yes	490	68.9
	No	221	31.1
With how many people do you live at home?	2 people	149	21
	3 people	187	26.3
	4 people	209	29.4
	5 and more	86	12.1
	I am living alone	80	11.3

Table 3. Chronic disease status of the participants in the study

	No		**Yes**	
	n	**%**	**n**	**%**
I don’t have any disease	218	30.7	493	69.3
Diabetes Mellitus	682	95.9	29	4.1
Chronic Obstructive Pulmonary Disease	708	99.6	3	0.4
Asthma	678	95.4	33	4.6
Hypertension	654	92	57	8
Coronary Artery Disease	699	98.3	12	1.7
Heart failure	708	99.6	3	0.4
Thyroid Diseases	655	92.1	56	7.9
Other	615	86.5	96	13.5

Table 4. The use of a vitamin preparation, supplement or immune system-supporting drug or product before and during the pandemic of the study participants

		n	%
Before the pandemic, were you taking a vitamin preparation, supplement or immune system-supporting drug or product?	Yes	153	21.5
	No	558	78.5
Have you used any vitamin preparations, supplements, drugs or products to support immune system during the pandemic?	Yes	316	44.4
	No	395	55.6
When did you start these products?	Unanswered	367	51.6
	Just at the beginning of the pandemic	209	29.4
	The first 15 days of the pandemic	79	11.1
	Second 15 days of the pandemic	33	4.6
	In the second month of the pandemic	18	2.5
	In the third month of the pandemic	5	0.7
Have you made your family use these products during the pandemic process?	Yes	297	41.8
	No	414	58.2

Table 5. Distribution of the answers given by the participants to the question of how often did you use nutritional supplements during the pandemic

	Unanswered		As far as I can think of		1-2 times a month		Every other day		Once a week		Every day	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Vitamin C	443	62.3	61	8.6	8	1.1	54	7.6	32	4.5	113	15.9
Vitamin D	474	66.7	62	8.7	22	3.1	27	3.8	52	7.3	74	10.4
Vitamin E	617	86.8	43	6	6	0.8	10	1.4	10	1.4	25	3.5
Multivitamin complexes	534	75.1	57	8	3	0.4	29	4.1	22	3.1	66	9.3
Omega 3	589	82.8	49	6.9	10	1.4	15	2.1	15	2.1	33	4.6
Mineral content (selenium,zinc)	581	81.7	44	6.2	8	1.1	13	1.8	23	3.2	42	5.9
Herbal teas/products	561	78.9	41	5.8	12	1.7	23	3.2	19	2.7	55	7.7
Antioxidants	617	86.8	40	5.6	8	1.1	13	1.8	7	1	26	3.7
Probiotics	573	80.6	38	5.3	14	2.0	24	3.4	23	3.2	39	5.5
Beta glucans	601	84.5	43	6	8	1.1	13	1.8	14	2	32	4.5
Other	641	90.2	33	4.6	5	0.7	6	0.8	7	1	19	2.7

Table 6. The number of meals before and after the pandemic and whether they have snacks or not

		Before Pandemic		During Pandemic		
		n	**%**	**n**	**%**	***p***
How many meals do you eat?	1 meal	2	0.3	10	1.4	<0.001
	2 meals	192	27	274	38.5	
	3 meals	475	66.8	352	49.5	
	more than 3 meals	42	5.9	75	10.5	
Did you have a snack?	Yes	224	31.5	231	32.5	0.646
	No	487	68.5	480	67.5	

McNemar's test

process, negative effects have been seen on the physical, mental and social well-being of health professionals who are faced with an unprecedented workload. At the same time, this occupational group, which has a higher risk of exposure to the virus, felt under a serious mental stress because they put their families at risk [7].

It is known that healthcare workers are also affected by epidemic diseases such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Ebola, which have been seen recently [8]. In the SARS and MERS epidemics between 2003 and 2015, it is stated that one-fourth of those infected were healthcare professionals [9]. One of the key strategies to promote healthy eating in communities is to advocate for healthy eating through health services [10]. In many countries, physicians provide advice on healthy eating in order to manage their patients' chronic diseases and other conditions in which malnutrition is an important risk factor [11].

It is stated that the mood or characteristic features of individuals affect their eating behaviors. Emotional eating is thought to help people cope with negative emotions. Difficulties identifying or perceiving emotions, on the other hand, can lead to binge eating episodes. Individuals who are experiencing intense emotions may try to distract themselves with food if they are unable to determine the meaning of their emotions [11]. Emotional eating is accepted as a psychological support in coping with negative emotions. However, difficulties in identifying or perceiving emotions can trigger binge eating attacks. Just as individuals experience their emotions intensely, if they have difficulty in determining what their emotions really mean, they try to distract their attention by means of food, thinking that they cannot cope with this emotional state [11]. This situation turns into a situation where people take more energy and consume more fat, carbohydrates and protein [12]. In our survey study, we found that health workers ate more food, increased the number of meals and gained weight as a result, due to the stress and feelings of burnout they experienced during the pandemic. Similarly, in survey studies, it was determined that students studying in the health sciences department increased the number of meals and experienced weight gain during the pandemic stage [13-15]. Our results are consistent with the literature findings.

There is no WHO-approved treatment available to treat Covid-19. One of the general nutritional recommendations for the prevention of viral infections is to ensure adequate intake of nutrients or supplement them with nutritional supplements [16]. Vitamins (A, B_6, B_{12}, C, D, E and folate), trace elements (zinc, iron, selenium, magnesium and copper), omega-3 fatty acids, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are known to play a complementary role to strengthen the immune system [8]. Micronutrients are important for immunomodulation and their deficiency increases susceptibility to viral infections. It is known that, somevitamins, such as vitamins D, C, and E, play an important role in maintaining a healthy immune response [17]. Zinc, selenium etc. trace elements, such as, show antiviral activity by inhibiting virus replication in host cells. Some elements are involved in multiple immunomodulatory pathways by positively affecting the immune system with their antioxidant properties [18]. It has been reported that vitamin D supplementation may be considered in cases where exposure to sunlight, which is the main source of vitamin

D, is reduced due to quarantine conditions and vitamin D-rich foods (including vitamin D-fortified foods) cannot be consumed [19]. Ural et al. [20] found that individuals took nutritional supplements, multivitamins, B, C, D vitamins and mineral supplements during the pandemic in a survey study they conducted with young adults. The author concluded that the utilization of nutritional supplements and functional foods by young adults tends to increase compared to the past during the COVID-19 pandemic. Our study is a survey of healthcare workers in a specific population, and we found that participants were taking vitamin and mineral supplements. Even though the study of Ural et al. [20] was conducted in a more general population, our results are similar. There appears to be an increased intake of vitamin and mineral supplements in young adults, both in healthcare workers and in the general population. Our results are in agreement with the literature findings.

Consequently; We found that healthcare workers took additional mineral and vitamin supplements, increased the number of meals and experienced weight gain during the pandemic. For this reason, health workers should be given healthy snacks with high nutritional value during the pandemic stage. By health managers and administrators; a management and organizational plan including a healthy nutrition program especially in extraordinary situations such as pandemics can be created, for health workers who are exposed to intense, irregular and stressful working conditions and who are in high risk groups.

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Authors' contributions to the article

I.C. constructed the main idea and hypothesis of the study. I.C. developed the theory and edited the material and method section. I.C. and Z.C. collected the data. Z.C. made a statistical analysis of the data and evaluation of the data in the results section. Discussion section of the article was written by E.C. and I.C. In addition, all authors discussed the entire study and approved the final version.

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Left atrial and ventricular longitudinal strain in embolic stroke of undetermined source

Kaynağı belirlenemeyen embolik inmede sol atriyal ve ventriküler longitudinal strain

Emrah Kaya, Yalın Tolga Yaylalı, Eylem Teke, Hande Şenol, Gökay Nar

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Abstract

Purpose: Left atrial (LA) and left ventricular (LV) remodelling may lead to stroke. The aim of this study was to analyze LA function and LV strain in patients with embolic stroke of undetermined source (ESUS).

Material and methods: This prospective study included 35 ESUS patients and 37 age and sex-matched controls. All participants underwent brain computed tomography (CT), conventional and diffusion-weighted magnetic resonance imaging (MRI), CT or MR angiography, 12 lead ECG, transthoracic echocardiography, and 48 hour Holter ECG monitoring. LA volume and function were determined by echocardiography. LA reservoir and LV strains were measured longitudinally by speckle-tracking method. CHA2DS2-VASc, The National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS) scores were calculated.

Results: Major cardiovascular risk factors were similar between the two groups. The mean CHA2DS2-VASc score was 2.6±1.2. NIHSS was 3.9±3.0 and mRS was 1.3±0.8. Atrial electromechanical coupling intervals and delays, LA emptying fraction and volumes were similar between the two groups. LA reservoir strain was lower than controls (25.2±7.2% vs. 29.7±8.8%, *p*=0,019). LV global longitudinal strain was lower than controls (-14.7±4.2% vs -16.4±3.9%, *p*=0,031). There was no correlation between LA, LV strains and the scores (CHA2DS2-VASc, NIHSS, mRS).

Conclusions: ESUS patients had lower LA reservoir and LV longitudinal global strains than controls. Left atrial volume index, LA emptying fraction did not differ between the two groups. Echocardiographic quantification of LA and LV remodelling has great potential for secondary prevention from ESUS. Further studies are needed to confirm our findings.

Key words: Embolic stroke, left atrial function, left ventricular function, left atrial strain, left ventricular strain.

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Öz

Amaç: Sol atriyal ve sol ventriküler yeniden şekillenme inmeye neden olabilir. Bu çalışmanın amacı, kaynağı belirsiz embolik inme (ESUS) hastalarında sol atriyum fonksiyonlarını ve sol ventrikül strain değerlerini analiz etmektir.

Gereç ve yöntem: Bu prospektif çalışma cinsiyet ve yaş açısından benzer olan 35 adet ESUS'lu hasta (61±10 yaşında) ve 37 adet kontrol grubunu (60±10 yaşında) içeriyordu. Tüm hastalara beyin bilgisayarlı tomografisi (BT), konvansiyonel ve difüzyon manyetik rezonans görüntüleme (MRG), BT veya MR anjiyografi, 12 derivasyonlu EKG, transtorasik ekokardiyografi ve 48 saat Holter EKG monitörizasyonu yapıldı. Sol atriyum hacimleri ve fonksiyonları ekokardiyografi ile belirlendi. Sol atriyum rezervuar ve ventrikül strain değerleri speckle-tracking metoduyla longitudinal olarak ölçüldü. CHA2DS2-VASc, Amerikan Ulusal Sağlık Enstitüsü İnme Skalası (NIHSS), Modifiye Rankin Skalası (mRS) skorları hesaplandı.

Bulgular: Major kardiyovasküler risk faktörleri iki grup arasında da benzerdi. ESUS'lu hastaların ortalama CHA2DS2-VASc skoru 2,6±1,2, NIHSS 3,9±3,0 ve mRS 1,3±0,8 saptandı. Atrial elektromekanik süreler ve gecikme zamanları, sol atriyum boşalma fraksiyonu ve hacim indeksleri 2 grup arasında benzer bulundu. Sol atriyal rezervuar strain, kontrol grubuna göre düşük saptandı (25,2±%7,2 vs. 29,7±%8,8, *p*=0.019). Sol ventrikül global longitudinal strain kontrol grubuna göre düşük saptandı (-14,7±%4,2 vs -16,4±%3,9, *p*=0.031). Sol atriyum rezervuar ve sol ventrikül strain değerleri ile skorlar arasında korelasyon saptanmadı (CHA2DS2-VASc, NIHSS, mRS).

Sonuç: ESUS'lu hastalar, kontrol grubuna göre daha düşük sol atriyal rezervuar ve sol ventriküler global longitudinal straine sahipti. Sol atriyal hacim indeksleri, sol atriyum boşalma fraksiyonu ve elektromekanik süreler 2 grup arasında farklılık göstermemektedir. Sol atriyal ve ventriküler yeniden şekillenmesinin ekokardiyografik ölçümü, ESUS'tan ikincil koruma için büyük bir potansiyele sahiptir. Bulgularımızın doğrulanması için daha fazla çalışmaya ihtiyaç vardır.

Emrah Kaya, M.D. Department of Cardiology, Kütahya Health Sciences University, Evliya Çelebi Training and Research Hospital, Kütahya, Turkey, e-mail: dremrah68@gmail.com (https://orcid.org/0000-0003-0457-3124) (Corresponding Author)

Yalın Tolga Yaylalı, Prof. Department of Cardiology, Pamukkale University, Faculty of Medicine, Denizli, Turkey, e-mail: yaylalimd@gmail.com (https://orcid.org/0000-0002-8452-923X)

Eylem Teke, Prof. Department of Neurology, Pamukkale University, Faculty of Medicine, Denizli, Turkey, e-mail: eylemteke@yahoo.com (https://orcid.org/0000-0002-5834-7563)

Hande Şenol, Asst. Prof. Department of Biostatistics, Pamukkale University, Faculty of Medicine, Denizli, Turkey, e-mail: handesenol@gmail.com (https://orcid.org/0000-0001-6395-7924)

Gökay Nar, Assoc. Prof. Department of Cardiology, Pamukkale University, Faculty of Medicine, Denizli, Turkey, e-mail: gokay_nar@yahoo.com (https://orcid.org/0000-0001-6159-7785

Anahtar kelimeler: Embolik inme, sol atriyal fonksiyon, sol ventriküler fonksiyon, sol atriyal strain, sol ventriküler strain.

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Introduction

Stroke is a clinical syndrome of vascular origin, characterized by signs of focal cerebral function loss and rapid localization of symptoms (within seconds or hours) without any apparent causes other than vascular causes. Approximately 85% of strokes are ischemic, while 15% are hemorrhagic. Stroke is the third most common life-threatening cause of mortality after heart disease and cancer, not only in developed countries but worldwide [1]. Cryptogenic mechanisms constitute 10-40% of all ischemic strokes [2]. Investigation of cryptogenic stroke patients includes evaluation of atherosclerotic and non-atherosclerotic diseases, cardiac embolism, and coagulopathies [3]. Embolic stroke of undetermined source (ESUS) is a new concept used as a functional definition of non-lacunar stroke of presumed embolic or thromboembolic origin, unlike cryptogenic stroke [4]. Myocardial strain analysis may offer insights into left atrial (LA) and left ventricular (LV) pathophysiology. This study aimed to determine whether or not ESUS patients might have atrial or ventricular dysfunction. We also examined atrial volumes of ESUS patients using echocardiography.

Materials and methods

The study protocol was approved by the Medical Ethics Committee of the Pamukkale University, written informed consent was obtained from the participants and was conducted in accordance with the Helsinki Declaration.

The study design was prospective. This study included 35 patients and 37 controls between September 2016 and March 2018. The patient group consisted of patients over age 45, diagnosed with embolic stroke of undetermined source, with cardioembolic risk ruled out. Demographic data, nicotine and alcohol use, history of cerebrovascular disease, medication use, comorbid coronary artery disease, and the presence of diabetes mellitus or hypertension were questioned and documented. The CHA_2DS_2-VASc, National Institutes of Health Stroke Scale (NIHSS), and modified Rankin Scale (mRS) scores were calculated on admission. In this study, electrocardiography (ECG), 48 hour Holter ECG and transthoracic echocardiography, computerized tomography (CT) of the brain, conventional and diffusion cerebral magnetic resonance imaging (MRI), cervical CT angiography of the carotid and vertebral arteries or cervical MRI angiography, and Doppler ultrasound were performed on ESUS patients. Also we did perform transesophageal echocardiography (TEE) to rule out patent foramen ovale, aortic arch atheroma, and LA appendage thrombus on all our patients. ECG, 48 hour Holter ECG and transthoracic echocardiography were performed on controls. Exclusion criteria for both groups were: 1) ischemic or valvular heart disease, 2) left ventricle ejection fraction (LVEF) <50%, 3) acute or chronic kidney failure (serum creatinine >1.5 mg/dl), 4) liver disease (bilirubin >2 mg/dl, AST two times higher than normal upper limit), 5) age younger than 45 years, 6) the presence of cardioembolic conditions that could cause cerebrovascular disease (for instance LA dilatation), 7) the presence of lacuna on CT or MRI imaging, 8) intra- or extra-cranial atherosclerosis (more than 50% stenosis on angiography) compatible with ischemic site, 9) active smoker or history of smoking, 10) obesity (BMI>30 kg/m^2), 11) use of statins or other anti-inflammatory drugs, 12) moderate or severe valvular disease, 13) ventricular hypertrophy, 14) history of acute coronary syndrome, cardiac operation, slow coronary flow, pacemaker implantation, left bundle branch block, and variant angina.

Echocardiography of all patients were performed using a 1-5 MHz transducer with a Phillips CX50 xMATRIX device. 2-D, M-mode, pulsed and color flow Doppler and tissue Doppler echocardiography were performed on all participants. During the examination, a continuous 1-lead ECG was recorded. Apical 2-chamber (A2C), apical 4-chamber (A4C), and apical 3-chamber (A3C) imaging were obtained on all participants. Left atrium volumes (maximum, minimum, presystolic, and emptying) were measured with A4C and A2C windows using the biplane method and indexed to body surface

area. Maximum LA volume was measured at LV end-systole, while minimal LA volume was measured at LV end-diastole. Left atrium emptying fraction was calculated as percentage with the formula {[(LA maximum volume - LA minimum volume)/LA maximum volume] × 100%} using biplane volumes measured from A4C and A2C imaging. Emptying volume was calculated using the formula (LA maximum volume - LA minimum volume) acquired from biplane volume. Pre-atrial contraction volume was measured at the start of P wave in ECG. Volume indices were calculated by dividing the calculated volumes by body surface area. Atrial electromechanical coupling (PA) was defined as the time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wave (Am wave) on tissue Doppler imaging. PA was obtained from the lateral mitral annulus (PA lateral), septal mitral annulus (PA septum), and right ventricular tricuspid annulus (PA tricuspid). Values were averaged over three consecutive beats. The difference between PA lateral and PA tricuspid was defined as inter-atrial electromechanical delay (EMD), the difference between PA lateral and PA septum was defined as left intra-atrial EMD, and the difference between PA septum and PA tricuspid was defined as right intra-atrial EMD.

In order to measure optimal strain, myocardial walls were clearly determined and myocardium and neighboring structures were distinguished from one another. When myocardial velocity and deformation curves varied between different speeds, it was ensured that transducer axis was parallel to the myocardium wall to obtain better results. All routine echocardiographic studies were performed according to current recommendations [5, 6]. Images for strain analysis were obtained with 60-90 frames/sec [7]. These values were accessed by narrowing the viewing window to only include the wall segment to be measured. At least three consecutive strokes were recorded and digitally processed data were analyzed with the software program incorporated in the equipment. Longitudinal strain values of LV and LA reservoir were calculated using the speckle-tracking method from A4C, A2C, and A3C imaging. LV global longitudinal strain values were also calculated. Holter ECG monitoring was performed for 48 hours in all patients. There was no arrhythmia detected.

Statistical analysis

When parametric test hypotheses were established, Independent Samples t test was used to compare differences between independent groups; when parametric test hypotheses could not be established, Mann-Whitney U test was used for comparing differences between independent groups. In addition, relationships between continuous variables were assessed with Spearman correlation analysis while Chi-square was used to assess differences between categorical variables. Data were analyzed with SPSS 25.0 (SPSS, Chicago, IL, USA). The value of $p<0.05$ was considered statistically significant.

Results

35 patients with ESUS and 37 controls participated in the study (Table 1). There was no significant age or gender difference between the two groups. Both groups had the same cardiovascular risk factors. PA septal, PA lateral, PA tricuspid, right intra-atrial (EMD; PA septum - PA tricuspid) and inter-atrial (EMD; PA lateral - PA tricuspid) intervals were compared and no significant difference was found. PA and EMD of the patient group tended to be longer than the control group (Table 2). LA maximum volume index (maxVI), minimum volume index (minVI), pre-atrial contraction volume index (pVI), systolic volume index (sVI), and emptying fractions of the patient and control groups were compared. There was no significant difference between the groups. LA emptying fraction of the patient group tended to be lower compared to the control group (Table 3). LA reservoir strain, LV apical 4-chamber longitudinal strain (4CLS), apical 3-chamber longitudinal strain (3CLS), apical 2-chamber longitudinal strain (2CLS), and LV global longitudinal strain (GLS) measurements were compared between the patient and control groups. There was a significant difference in terms of LV 4CLS, LV global longitudinal strain, LA reservoir 4CLS and LA reservoir 3CLS values; these values were lower in the patient group (Table 4). In the patient group, mean CHA_2DS_2-VASc score was 2.6±1.2, mean NIHSS score was 3.9±3.0, and mean mRS score was 1.3±0.8. There was no correlation between LA, LV strain values and the scores (CHA_2DS_2-VASc, NIHSS, mRS) (Table 5).

Table 1. Demographic data of the study population

	Gender			Age			
	Female	**Male**	***p***	**Mean±S.D.**	**min**	**max**	***p***
Patients n=35	11 (31%)	24 (69%)	0,568	61±10	45	82	0,964
Controls n=37	14 (37%)	23 (63%)		60±10	46	79	

max: maximum, min: minimum; S.D.: standard deviation

Table 2. Atrial electromechanical coupling findings measured by tissue Doppler imaging

	Patients n=35	**Controls n=37**	
	Mean ± S.D.	**Mean ± S.D.**	***p***
PA Lateral (ms)	43.94±14.33	38.57±14.81	0.178
PA Septum (ms)	33.03±12.99	28.08±11.85	0.096
PA Tricuspid (ms)	24±11.4	21.11±8.38	0.222
EMD Right Intra-atrial (ms)	8.8±7.27	6.97±5.59	0.344
EMD Inter-atrial (ms)	19.94±9.07	17.46±10.54	0.351

EMD: electromechanical delay, PA: the time interval from the onset of the P wave on surface ECG to the beginning of the late diastolic wawe (Am wawe) on tissue Doppler imaging
S.D.: standard deviation

Table 3. Left and right atrial volume measurements

	Patients (n=35)		**Controls (n=37)**		
	Mean±S.D.	**Median [min-max]**	**Mean±S.D.**	**Median [min-max]**	***p***
LA maxVI A4C (ml/m²)	24.34±7.42	22.79 [12.12-41.49]	24.83±7.13	23.72 [12.41-40.99]	0,640
LA minVI A4C (ml/m²)	10.41±5.04	8.41 [3.82-25.51]	9.42±4.34	8.52 [2.28-20.22]	0,488
LA pVI A4C (ml/m²)	16.34±5.85	14.62 [5.75-32.6]	14.7±5.7	13.46 [5.36-27.53]	0,234
LA maxVI A2C (ml/m²)	23.23±6.7	22.66 [13.88-47.21]	23.68±5.42	23.17 [12.2-34.75]	0,569
LA minVI A2C (ml/m²)	10.49±4.59	9.54 [4.65-23.18]	9.45±3.56	8.74 [2.74-17.54]	0,450
LA pVI A2C (ml/m²)	16.02±5.42	15.54 [7.65-31.84]	14.52±4.25	14.22 [6.24-24.34]	0,195
RA maxVI A4C (ml/m²)	19.33±5.44	19.8 [9.44-31.45]	19.33±5.39	18.93 [8.65-29.73]	0,997
RA minVI A4C (ml/m²)	8.46±3.26	8.12 [3.39-15.99]	8.25±3.01	8.19 [3.18-15.51]	0,773
RA pVI A4C (ml/m²)	13.23±4.58	12.99 [6.63-22.14]	12.33±4	11.95 [5.64-21.43]	0,550
LA Emptying Fraction Biplane(%)	56.7±9.8	58.7 [34.5-68.9]	61.2±8.6	61 [39.8-78.6]	0,137
LA maxVI Biplane (ml/m²)	24.17±6.5	23.29 [14.15-42.96]	25.18±5.8	24.03 [13.8-39.5]	0,489
LA sVI Biplane (ml/m²)	13.61±3.67	13.37 [7.68-23.07]	15.43±3.48	15.05 [8.69-24.19]	0,013*
LA minVI Biplane (ml/m²)	10.73±4.38	9.28 [4.75-20.41]	9.75±3.74	9.03 [2.95-18.57]	0,414

A2C: apical two-chamber, A4C: apical four-chamber, EF: emptying fraction, LA: left atrial
max: maximum, maxVi: maximal volume index, min: minumum, minVi: minimum volume index
pVi: pre-atrial contraction volume index, RA: right atrial, S.D.: standard deviation
sVi: stroke volume index

Table 4. Left atrial and left ventricular strain values

	Patients (n=35)		Controls (n=37)		
	Mean±S.D.	**Median (min-max)**	**Mean±S.D.**	**Median (min-max)**	***p***
LV 4CLS (%)	-14.94±3.96	-14 [-27--10]	-17.11±4.25	-17 [-25--9]	0,015*
LV 2CLS (%)	-14.34±5.02	-14 [-26--6]	-16.38±4.41	-16 [-24--9]	0,072
LV 3CLS (%)	-14.66±4.77	-14 [-27--8]	-16.05±4.14	-15 [-25--8]	0,188
LV GLS (%)	-14.66±4.16	-14 [-26--9]	-16.41±3.86	-16 [-24--8]	0,031*
LA reservoir strain A4C (%)	24.11±7.16	24 [13-44]	32.35±13.06	29 [6-61]	0,003*
LA reservoir strain A2C (%)	25.69±9.61	26 [5-50]	26.84±7.72	27 [14-50]	0,576
LA reservoir strain A3C (%)	26.66±9.06	27 [3-48]	30.43±8.64	30 [5-45]	0,050*

2CLS: Apical two-chamber longitudinal strain, 3CLS: Apical three-chamber longitudinal strain 4CLS: Apical four-chamber longitudinal strain A4C: Apical four-chamber
A2C: Apical two-chamber, A3C: Apical 3-chamber, GLS: Global longitudinal strain
LA: Left atrial, LV: Left ventricular, max: maximum, min: minumum, S.D.: Standard deviation

Table 5. Correlation of LA, LV strain values with CHA2DS2-VASc, NIHSS, mRS

		CHA2DS2-VASc	**NIHSS**	**mRS**
LV 4CLS	r	,237	,151	,128
	p	,171	,387	,463
LV 2CLS	r	,232	-,053	,110
	p	,179	,763	,530
LV 3CLS	r	,066	,224	,309
	p	,705	,195	,071
LV GLS	r	,213	,166	,277
	p	,219	,341	,107
LA reservoir strain A4C	r	,098	-,139	-,277
	p	,576	,427	,107
LA reservoir strain A2C	r	-,209	,026	-,142
	p	,229	,882	,417
LA reservoir strain A3C	r	-,233	,034	-,004
	p	,178	,848	,981

2CLS: Apical two-chamber longitudinal strain, 3CLS: Apical three-chamber longitudinal strain 4CLS: Apical four-chamber longitudinal strain, A4C: Apical four-chamber
A2C: Apical two-chamber, A3C: Apical 3-chamber, GLS: Global longitudinal strain
LA: Left atrial, LV: Left ventricular, mRS: modified Rankin Scale
NIHSS: The National Institutes of Health Stroke Scale

Discussion

The main findings of this study are: 1) LA reservoir and LV global longitudinal strains were lower in ESUS; 2) Left atrial volume index (LAVI) and EMD did not differ between ESUS and controls; and patients did not show any episode of AF on 48-hour Holter ECG monitoring. These results suggest that atrial and ventricular remodelling may themselves play a role in ESUS patients.

One out of four patients who have had stroke fall in the category of stroke of undetermined source. Asymptomatic AF episodes might be the cause. Therefore, various tools have been used to identify silent AF episodes to clarify the etiology of this patient group. In this study, we did not observe any AF episode on 48-hour Holter ECG monitoring. In contrast, EMBRACE and CRYSTAL studies found that patients had more frequent AF episodes on long-term rhythm monitoring than 24-hour Holter ECG monitoring [8, 9]. Both studies enrolled patients with cryptogenic stroke. EMBRACE study used 30-day event recorder and CRYSTAL study used implantable cardiac monitor.

In this study, EMD did not differ between ESUS patients and controls. No significant correlation was found between ESUS and EMD. In contrast, Bayar et al. [10] demonstrated that longer EMD was associated with stroke/TIA in

patients with paroxysmal AF. They suggested that longer EMD predicts atrial conduction heterogeneity which is associated with stroke; therefore, evaluation of EMD could be helpful in determining patients at high-risk of stroke/ TIA in PAF patients. We excluded patients with paroxysmal AF.

In this study, LAVI and LA emptying fraction did not differ between ESUS patients and controls. Skaarup et al. [11] investigated whether or not left atrial parameters were predictive in paroxysmal AF diagnosis in patients with stroke or TIA. They demonstrated that LA function measurements (minimum LA volume and LA emptying fraction) were independently correlated with paroxysmal AF and that the presence of PAF after ischemic stroke or TIA increased risk. Recently, Jordan et al. [12] sought to determine the association between LAVI and cardioembolic stroke and ESUS subtypes. They demonstrated that LAVI was associated with cardioembolic stroke as well as AF detection in ESUS. In line with their findings, LAVI was similar in both our patients and controls. We did not observe any AF episode on Holter ECG monitoring either. LA emptying fraction did not differ between our patients and controls either. Recent work demonstrated that risk of cardioembolism or PAF increased as LA emptying fraction decreased [13-15].

In this study, LA reservoir strain was significantly decreased in ESUS patients compared to controls. Similarly, Leong et al. [16] demonstrated that LA strain was significantly decreased in cryptogenic stroke patients compared to controls. LV global longitudinal strain (LVGLS) was also decreased in our patients compared to controls. Russo et al. [17] recently demonstrated that decreased LVGLS was associated with AF risk. However, we did not observe any AF episodes on 48-hour Holter ECG monitoring. Sade et al. [18] demonstrated ESUS patients had significantly worse LA strain than control patients. Echocardiographic quantification of LA remodelling has great potential for secondary prevention from ESUS.

Our findings highlight the important interplay between LA/LV remodelling and ESUS. The exact mechanism remains unclear. LAVI, EMD, and LA emptying fraction were similar between patients and controls. Atrial remodelling may start with fibrotic changes in LA. Atrial remodelling may itself be an independent risk factor [19]. AF may not be the only prerequisite for atrial thromboembolism.

As a result, our study demonstrates LA and LV remodelling in ESUS as well as similar LAVI, EMD, and LA emptying fraction between patients and controls. LA and LV remodelling may play a role in ESUS. Echocardiographic quantification of LA and LV remodelling has great potential for secondary prevention from ESUS. More studies are needed to confirm our findings.

Study limitations

This study is single-centered also we were not able to do more than 48-hour Holter ECG monitoring.

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

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Parts of the results of this study have recently been presented as an oral presentation at the 34th Annual Congress of the Turkish Cardiac Society held on October 20-23, 2018 in Antalya.

Ethics committee approval: The study protocol was approved by the Medical Ethics Committee of the Pamukkale University (the registry number 60116787-020/50307, 17 Aug 2016).

Author contributions

Conception and design of the research, analysis and interpretation of the data and critical revision of the manuscript for intellectual content: E.K., Y.T.Y., E.T., H.S., G.N.; Acquisition of data: E.K., Y.T.Y., E.T.; Statistical analysis: H.S.; Writing of the manuscript: E.K., Y.T.Y.

Research Article

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Evaluation of the relationship between surfactant protein D levels and COVID-19 clinical severity: a case-control study

Sürfaktan protein D düzeyleri ile COVID-19 klinik şiddeti arasindaki ilişkinin değerlendirilmesi: bir vaka kontrol çalışması

Emre Karslı, Ramazan Sabırlı, Tarık Gören, Aykut Kemancı, Denizhan Karış, İbrahim Türkçüer, Özgür Kurt, Philippe Bertrand, Aylin Köseler

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Abstract

Purpose: Serum surfactant protein D (SP-D) plays roles in the body such as protection against viral infection, bacterial and fungal clearance, clearance of apoptotic cells and suppression of inflammation. This study aims to examine the relationship between SP-D level and coronavirus disease (COVID-19) severity.

Methods: 80 patients (30 with mild disease and 50 with severe/critical COVID-19), and 50 healthy volunteers were enrolled in the study. SP-D levels were analyzed by ELISA in serum samples.

Results: The median of SP-D was found to be 2.47 (1.67-7.79) ng/ml in mild disease and 5.65 (3.09-16.55) ng/ml in severe/critical disease groups, while 2.89 (10.8-6.24) ng/ml in the healthy controls. The differences in SP-D levels between the severe/critical disease group compared to both mild disease and control groups were found statistically significant (p=0.007 and 0.001, respectively). ROC analysis showed greater AUC for the serum SP-D levels of the severe/critical COVID-19 patients compared to mild COVID-19 disease patients (AUC=0,691, 95% CI=0.56-0,822; p=0.004). Furthermore, SP-D levels were 86% sensitive and 51.6% specific at 2.44 ng/ml level (p=0.004) to detect severe/critical patients.

Conclusion: SP-D levels is useful for COVID-19 patients in the prediction of clinical severity and prognosis. SP-D is a valuable biomarker for predicting the clinical severity and prognosis.

Key words: Serum surfactant protein D, COVID-19, pneumonia.

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Öz

Amaç: Serum surfaktan protein D (SP-D) vücutta viral enfeksiyona karşı koruma, bakteriyel ve fungal klirens, apoptotik hücrelerin temizlenmesi ve inflamasyonun baskılanması gibi roller oynar. Bu çalışma, SP-D düzeyi ile koronavirüs hastalığı (COVID-19) şiddeti arasındaki ilişkiyi incelemeyi amaçlamaktadır.

Gereç ve yöntem: Çalışmaya 80 hasta (30 hafif hastalığı ve 50 ağır/kritik COVID-19) ve 50 sağlıklı gönüllü dahil edildi. Serum örneklerinde SP-D seviyeleri ELISA ile analiz edildi.

Bulgular: SP-D düzeyi ortanca değeri hafif hastalıkta 2,47 (1,67-7,79) ng/ml, ağır/kritik hastalık gruplarında 5,65 (3,09-16,55) ng/ml iken, sağlıklı control grubunda 2,89 (10,8-6,24) ng/ml olarak bulundu. Ağır/kritik hastalık grubu hem hafif hastalık hem de kontrol grubu ile karşılaştırıldığında SP-D düzeylerindeki farklılıklar istatistiksel olarak anlamlı bulundu (sırasıyla p=0,007 ve 0,001). ROC analizi, hafif COVID-19 hastalığı hastalarına kıyasla şiddetli/kritik COVID-19 hastalarında serum SP-D seviyeleri için eğri altında kalan alan daha yüksek saptandı (AUC=0.691, %95 CI=0,56-0.822; p=0,004). Ayrıca, ağır/kritik hastaları saptamak için SP-D düzeyleri 2,44 ng/ml düzeyinde (p=0,004) %86 duyarlı ve %51,6 özgül saptandı.

Sonuç: SP-D seviyeleri, COVID-19 hastaları için klinik şiddeti ve prognozu tahmin etmede faydalıdır. SP-D, klinik şiddeti ve prognozu tahmin etmek için değerli bir biyobelirteçtir.

Emre Karslı, Assist. Prof. Department of Emergency Medicine, Kafkas University Faculty of Medicine, Kars, Turkey, e-mail: dremrekarsli@gmail.com (https://orcid.org/0000-0002-0441-3019)

Ramazan Sabırlı, Assoc. Prof. Department of Emergency Medicine, Kafkas University Faculty of Medicine, Kars, Turkey, e-mail: ramazan_sabirli@hotmail.com (https://orcid.org/0000-0003-4599-5833)

Tarık Gören, MD. Department of Emergency Medicine, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: tarikgoren92@hotmail.com (https://orcid.org/0000-0002-8292-6717)

Aykut Kemancı, MD. Department of Emergency Medicine, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: aykemanci@gmail.com (https://orcid.org/0000-0002-6308-3830)

Denizhan Karış, Assist. Prof. Department of Biophysics, Istinye University Faculty of Medicine, Istanbul, Turkey, e-mail: denizhankar@yahoo.com (https://orcid.org/0000-0002-5976-4107)

İbrahim Türkçüer, Prof. Department of Emergency Medicine, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: iturkcuer@pau.edu.tr (https://orcid.org/0000-0001-8342-4615)

Özgür Kurt, Prof. Department of Medical Microbiology, Acibadem Mehmet Ali Aydinlar University School of Medicine, Istanbul, Turkey, e-mail: ozgur.kurt@acibadem.edu.tr (https://orcid.org/0000-0001-5575-588X)

Philippe Bertrand, M.D. University of Poitiers IC2MP UMR CNRS 7285 4, rue Michel Brunet - B27, TSA 51106, 86073 Poitiers cedex 9, France, e-mail: philippe.bertrand@univ.poitiers.fr (https://orcid.org/0000-0001-8171-2031)

Aylin Köseler, Prof. Department of Biophysics, Pamukkale University Faculty of Medicine, Denizli, Turkey, e-mail: aylinkoseler@gmail.com (https://orcid.org/0000-0003-4832-0436) (Corresponding Author)

Anahtar kelimeler: Sürfaktan protein D, COVID-19, pnömoni.

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Introduction

SARS-CoV-2 virus infection was reported by World Health Organization (WHO) in the beginning of March 2020 as a world-wide pandemic and SARS-CoV-2 virus infection were called as coronavirus disease (COVID-19) [1, 2].

Studies on COVID-19 disease have documented that COVID-19 patients can develop symptoms of mild or severe acute respiratory infection. Mild symptoms include upper respiratory tract symptoms such as fever, dry cough, and fatigue. Severe symptoms include dyspnea, diarrhea, clinical onset of serious pneumonia, acute respiratory distress syndrome (ARDS) or multiple organ dysfunction [3, 4].

In lung tissue, type II alveolar cells produce functional substances such as surfactants and release them onto the surface, thereby helping with gas exchange [5]. Lung surfactant is a unique compound enriched with phospholipids and four surfactant protein (SP) types. Two of these proteins hydrophilic are the surfactant protein D (SP-D) and surfactant protein A (SP-A), also called as collectins, and the other two have lipophilic structure named as surfactant protein B (SP-B) and surfactant protein C (SP-C) [6]. Being a member of collagen-containing C-type lectins, serum SP-D is a hydrophilic structured protein [7]. SP-D is secreted from alveolar type II pneumocytes and secretory bronchiolar epithelial cells named as Clara cells [8].

SP-D is preliminarily produced inside the respiratory system, thus it has been assessed as a potential biomarker in some subjects having allergic bronchopulmonary aspergillosis in pneumonia, drug-induced lung disease, cystic disease and interstitial fibrosis [9-11]. It has been also shown to decrease in bronchoalveolar lavage in individuals having chronic obstructive pulmonary disease (COPD) [12].

Our study aimed to enlighten the variations of levels of SP-D protein in cases diagnosed with mild COVID-19 disease and severe/critical COVID-19 (+) disease compared with the healthy population within a high number of individuals. The secondary aim of this study was to determine the diagnostic and prognostic features of SP-D as a biomarker.

Materials and methods

Study population

The ethics approval for our prospective case-control study was received from the Pamukkale University Non-Invasive Clinical Trials Ethics Committee. The study was carried out between 01.11.2020 and 15.12.2020. After being informed concerning with the study, all of the individuals were asked to give written consent to be admitted in the study. The individuals were assessed by means of inclusion and exclusion criteria. COVID-19 infection was diagnosed and assessed clinically according to WHO guideline as a result of clinical assessment in the emergency department (ED). As the diagnosis of the patients were confirmed by reverse transcription polymerase chain reaction (RT-PCR) [13]. 80 patients (30 patients mild COVID-19 disease; 50 patients severe/critical COVID-19 disease) and 30 healthy controls without symptoms were included in the study.

Mild COVID-19 disease group

This group involved the patients (a) who admitted to the COVID-19 outpatient clinic (b) whose CT imagings were normal and PCR tests were positive.

Severe/Critical COVID-19 disease group

This group involved the patients (a) who admitted to the ED with symptoms and was diagnosed with severe/critical COVID-19 infection according to WHO guideline [13] (b) who had positive RT-PCR nasopharyngeal swab samples collected in ED included in the study.

Control group

This group involved the volunteers who not having a history of acute, subacute or chronic

disease; no infection in the last fortnight; no particular medication and have no contact with people infected with COVID-19 admitted to ED with non-infectious complaints.

The exclusion criteria for the present study were kidney failure, liver failure, chronic inflammatory disease history, confirmation of any cancer onset, history of cerebrovascular disease, respiratory diseases such as acute pulmonary embolism, asthma disease and COPD, and pregrancy. Moreover, the patients having CT imaging results evaluated as COVID-19 pnemonia and negative PCR tests were not involved in the study.

Data collection

Medical history, demographic data, vital findings, biochemical parameters (hemogram, C-reactive protein (CRP), ferritin, D-dimer, and high-sensitivity troponin T (hsTnT)) and radiological findings, time to onset of symptoms, CT severity scores were collected for statistical analysis.

Computerized Tomography (CT) evaluation

The thoracic CT severity scores were calculated, as cited in the literature, by an emergency medicine specialist blinded to the study [14].

Clinical evaluation and management

The individuals were evaluated clinically based on guidelines of WHO used for COVID-19 diagnosis and treatment [13]. On the basis of the up-date of this guide, the algorithm used for patient management was also edited.

The complications of the patients after 6 months and the drugs used in the treatment of COVID-19 infection were also screened. It was also recorded whether they received non-macrolide antibiotic treatment due to superinfection.

It was observed that Hydroxyqloroquin, Favipiravir, Clarithromycin (for patients who had pneumonia findings) and Enoxaparin treatment were started at ED in all patients according to the current treatment guideline of the Turkish Ministry of Health [15], and pulse steroid therapy was given in addition to this treatment in severe/critical patients.

Blood samples and laboratory parameters

Routinely checked parameters of hemogram, and serum CRP, ferritin, creatinine, urea and D-dimer during their examination in ED were evaluated. Blood sample of 2 cc drawn from antecubital vein into a dry test tube was centrifugated for 15 minutes at 5000 rpm and its serum component was separated for measurement of SP-D level. Then, serum SP-D level was meassured using the Enzyme-Linked Immunosorbent Assay (ELISA) method. The SP-D levels was measures via same protocol in that laboratory. The laboratory results obtained from the patients admitted to ED were recorded for statistical analysis.

Surfactant Protein D (SP-D) level measurement

A commercial ELISA kit (Human SP-D ELISA Kit, Elabscience, E-EL-H1269, USA), was used to measure serum SP-D levels.

Data analysis

As a planned reference study was not established in the literature, a power analysis was conducted prior to the present study. The power analysis presented that minimum 112 individuals (minimum 28 for each group) were required to obtain 95% power at 95% confidence interval, predicting a medium-high effect size (f=0.4). SPSS software program was used for statistical analysis of the data set. The continuous variables were expressed as median (IQR), while numbers and percentages were used for the categorical variables. Kolmogrov-Smirnov test was used for calculation of parametric distribution for the continuous data Mann-Whitney U test and Kruskal-Wallis variance analysis and were conducted to compare the differences in independent groups. The relationships among continuous variables were evaluated with Spearman correlation. Chi-square test was used for the analysis of categorical variables. To measure the discriminant performance of SP-D levels ROC curve analysis was conducted. Binary logistic regression analysis was performed for evaluating of effects of the parameters on disease severity. $P<0.05$ was evaluated as statistically significant.

Results

The gender distribution and mean age were similar in the groups (p=0.491 and p=0.609 respectively).

Vital parameters of the groups were given in Table 1.

SP-D level median values were 2.89 (10.8-6.24) ng/ml in control group, 2.47 (1.67-7.79) ng/ml in mild disease group, 5.65 (3.09-16.55) ng/ml in severe/critical disease group (Table 2). There was a statistical significance between the SP-D levels among the groups (p=0.001). Serum SP-D level was determined higher in the severe/critical disease group compared to both the control group and the mild disease group (p=0.007 and 0.001) (Table 1) (Figure 1).

Hemogram, biochemical and blood gas analysis parameters in the study groups are given in Table 2.

The correlations between serum surfactant associated protein D level and clinical and laboratory parameters were examined in patients who have COVID-19 infection. SP-D level and sPO_2 level were found mild negative correlated (rho=-0.248 and p=0.026).

CT severity and SP-D levels were found moderate positive correlated (rho=0.42 and p=0.002) (Table 3)

Table 1. Clinical and demographical datas of the groups

		Control (N=30)	**Mild Disease** (N=30)	**Severe-Critical Disease** (N=50)	***p*-Value**
		Median (IQR)	*Median (IQR)*	*Median (IQR)*	
Symptom Duration (Day)			2 (0-3)	3 (2-6.25)	***[1]p=0.003***
Fever (^{0}C)		36.6 (36.5-36.75)	36.7 (36.5-37.1)	36.7 (36.5-37.2)	*p=0.071*
sPO_2		96 (95-98)	97.5 (96-98)	95 (93.75-96)	***p=0.0001***
SBP (mm/Hg)		120 (112-150)	120 (110-137)	125 (110-140)	*p=0.418*
DBP (mm/Hg)		80 (70-85)	80 (70-80)	80 (70-80.5)	*p=0.503*
Age (Year)		57 (40.75-46.5)	50.5 (46-56)	54 (37.75-68)	*p=0.428*
Gender	**Male**	14 (46.7%)	16 (53.3%)	21 (42%)	
	Female	16 (53.3%)	14(46.7%)	29 (58%)	*[5]p=0.616*
SP-D (ng/mL)		2.89 (1.08-6.24)	2.47 (1.67-7.79)	5.65 (3.09-16.55)	***p=0.001 [1]p=0.007 [3]p=0.387 [4]p=0.001***
Comorbidities					
Hypertension N(%)			12 (40%)	21 (42%)	*[5]p=1*
Diabetes Mellitus, N(%)			9 (30%)	19(38%)	*[5]p=0.629*
Coronary Artery Disease, N(%)			10 (33.3%)	22 (36%)	*[5]p=0.48*

p-values are derived from Kruskal Wallis test, [1]*p*-values are derived from Mann Whitney U test
[3]*p*-value is derived from Mann Whitney U test and refers to the comparison between Control and mild disease groups
[4]*p*-value is derived from Mann Whitney U test and refers to the comparison between Control and severe-critical disease groups
[5]*p*-values are derived from chi square test
IQR: Interquartile range, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure
SP-D: surfactant proten D

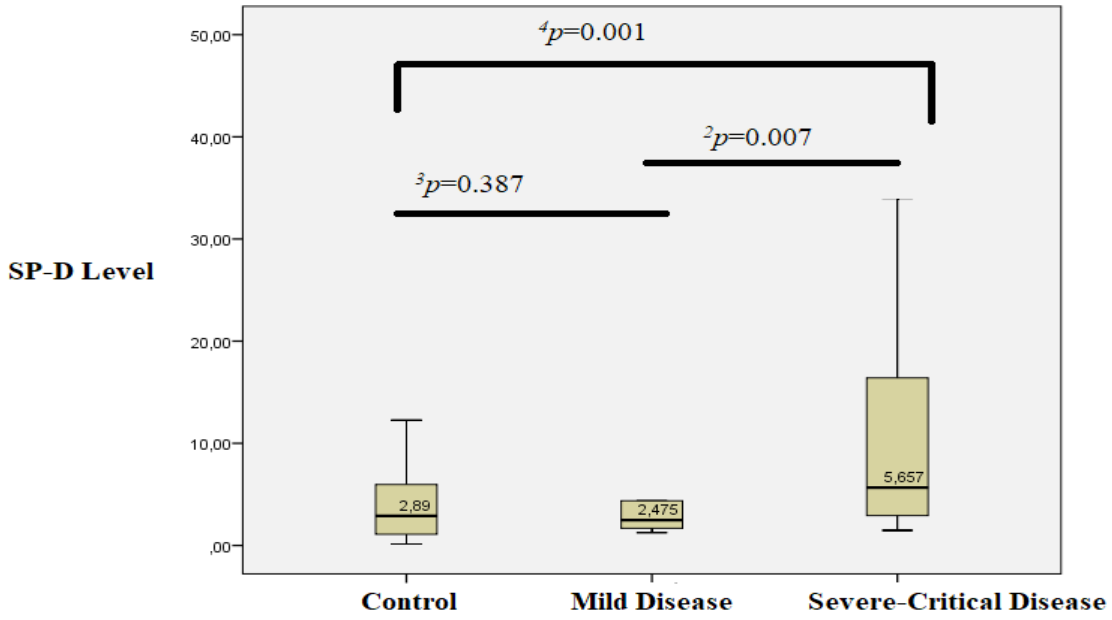

Figure 1. SP-D levels

Table 2. Laboratory parameters of the groups

	Control (N=30)	**Mild Disease** (N=30)	**Severe-Critical Disease** (N=50)	***p*-Value**
	Median (IQR)	*Median (IQR)*	*Median (IQR)*	
WBC (K/µL)	7.62 (5.23-11.24)	7.57 (5.39-10.04)	7.14 (4.74-10.79)	[1]*p*=0.681
Hb (g/dL)	11.7 (11.07-13.47)	14.2 (12.07-15.95)	13.85 (11.67-15.22)	[1]*p*=0.003
Neu. (K/µL)	4.49 (3.05-7.68)	3.97 (3.04-6.74)	4.54 (2.86-7.6)	[1]*p*=0.83
Lymph. (K/µL)	1.4 (0.84-1.94)	1.88 (1.46-3.26)	1.4 (1.09-2.14)	[1]*p*=0.015 [2]*p*=0.008
Plt. (K/µL)	211 (163.5-293.2)	254 (224.5-299.2)	228 (181.7-294.5)	[1]*p*=0.374
CRP (mg/L)	1.8 (1.08-2.91)	1.67 (0.38-6.74)	21.34 (4.71-65.99)	[1]*p*=0.0001 [2]*p*=0.0001
D-Dimer (ng/mL)		161 (56-288)	238 (141.5-599.25)	[2]*p*=0.015
Ferritin (ug/L)		55.59 (18.6-152.87)	170.3 (62.7-311)	[2]*p*=0.008
hsTnT (µg/L)		3.66 (3-5.49)	5 (3.12-13)	[2]*p*=0.054

[1]*p*-values are derived from Kruskal-Wallis test
[2]*p*-values are derived from Mann-Whitney U test and refers to the comparison between mild disease and severe-critical disease groups
WBC: White blood cell, hb: hemoglobin, Neu: neutrophil count, Lymph: lymphocyte count
Plt: platelet count, CRP: C-Reactive Protein, hsTnT: high sensitive troponin T

Table 3. Correlations between Surfactant Associated Protein (SP-D) levels and laboratory and clinical parameters in patients groups

		SP-D
Fever	*rho*	0.1
	p Value	0,301
sPO_2	*rho*	**-0.248**
	p Value	**0,026**
SBP	*rho*	-0.018
	p Value	0,873
DBP	*rho*	-0.08
	p Value	0,479
WBC Count	*rho*	-0.9
	p Value	0,425
Hb	*rho*	-0.036
	p Value	0,751
Neu.	*rho*	-0.005
	p Value	0,966
Lymph.	*rho*	-0.142
	p Value	0,205
Plt.	*rho*	-0.17
	p Value	0,128
CRP	*rho*	0.172
	p Value	0,124
D-Dimer	*rho*	0.043
	p Value	0,720
Ferritin	*rho*	0.139
	p Value	0,263
hsTnT	*rho*	0.026
	p Value	0,845
CT Severity Score	*rho*	**0.42**
	p Value	**0,002**
Symptom Duration	*rho*	0.02
	p Value	0,863

p and rho values are derived from Spearman Correlation test, SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure, WBC: White blood cell, Hb: hemoglobin, Neu: neutrophil count
Lymph: lymphocyte count, Plt: platelete count, CRP: C-Reactive Protein, hsTnT: high sensitive troponin T

ROC analysis presented greater AUC for the serum SP-D levels of the severe/critical COVID-19 patients compared to mild COVID-19 disease patients (AUC=0.691, 95% CI=0.56-0.822; *p*=0.004). Furthermore, the SP-D level was evaluated to be 86% sensitive and 51.6% specific at 2.44 ng/ml level (*p*=0.004) (Figure 2) to detect severe/critical patients.

When the data whether the patients received antibiotherapy for superinfection after being evaluated at ED were considered, only 4 (13.3%) patients in the mild disease group and 21 (42%) patients in the severe/critical disease group were reported to have received antibiotherapy. The median level of serum SP-D was found to be higher in patients who needed antibiotic therapy than in patients who did not need antibiotics in the severe/critical disease group (Figure 3).

Regression analysis results were given in Table 4.

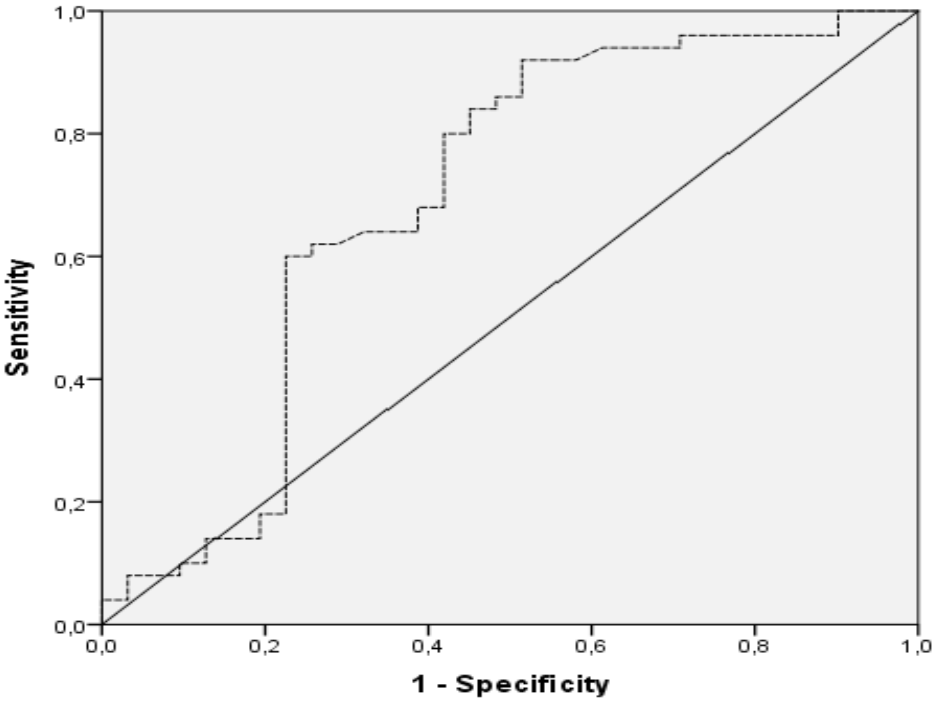

Figure 2. ROC curve analysis for predicting clinical severity

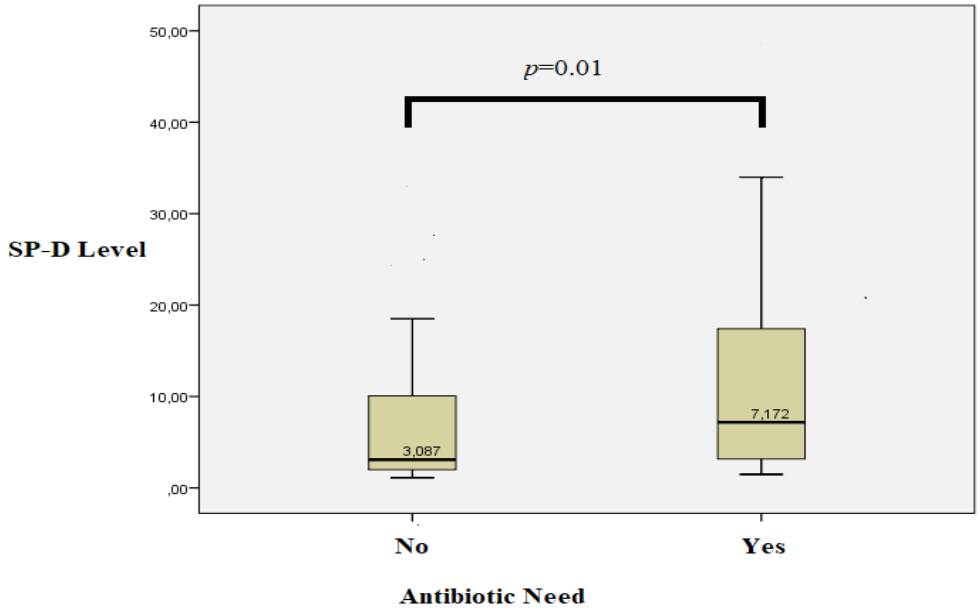

Figure 3. Serum SP-D levels in patient who have antibiotic need or not in severe-critical group

Table 4. Regression analysis between the parameters and disease severity of the patients

	B	S.E	Wald	*p*-Value	OR	95% CI	
						Lower	Upper
SP-D Level	0.067	0.034	3.885	0.049	1.069	1.000	1.142
Fever	0.148	0.475	0.097	0.755	1.160	0.457	2.944
SpO_2	-0.161	0.075	4.609	0.032	0.852	0.735	0.986
Systolic BP	0.001	0.017	0.001	0.972	1.001	0.968	1.034
Diastolic BP	0.021	0.030	0.495	0.482	1.021	0.964	1.082
WBC	0.435	0.504	0.747	0.388	1.545	0.576	4.146
Hemoglobin	-0.037	0.117	0.100	0.752	0.964	0.767	1.212
Neutrophil counts	-0.305	0.578	0.278	0.598	0.737	0.238	2.289
%Neu	0.149	0.103	2.108	0.147	1.161	0.949	1.421
Lymphocyte counts	-1.552	0.675	5.286	0.022	0.212	0.056	0.795
%Lymphocyte	0.276	0.115	5.726	0.017	1.317	1.051	1.651
Platelete	0.000	0.001	.012	0.912	1.000	0.998	1.002
Monocyte counts	-0.183	0.372	.243	0.622	0.833	0.402	1.725
Gender	1.082	0.564	3.684	0.055	2.951	0.977	8.910
Comorbidity existence	-2.173	0.586	13.775	0.0001	0.114	0.036	0.359

WBC: White blood cell

Discussion

SP-D, possesses a key role in lungs, in the system of humoral and innate immunity; binds a wide range of pathogenic microorganisms, inhibits the growth of microorganisms, is involved in damage bacterial membrane, stimulates phagocytosis, chemotaxis, regulates the expression of cytokines and the production of free radicals [7].

SP-D provides interaction with pathogenic microorganisms (both gram-negative, such as Klebsiella pneumoniae, Haemophilus influenza, Pseudomonas aeruginosa and Escherichia coli, and gram-positive, mycobacteria, viruses, including influenza virus, fungi), acting as an attractant for immune cells, thereby performing the classic opsonizing functions [7, 16]. SP-D play crucial a role in the cascade and modeling of inflammatory responses. SP-D regulates the scavenging of apoptotic cells and bodies and inhibits the release of cytokines and other pro-inflammatory products [16, 17].

To date, there are many indications of how the structure of the surfactant and its components, in particular its proteins SP-D, changes during a respiratory infection [16, 18-20]. Pathogenic microorganisms, entering the respiratory tract, change the surface balance by several mechanisms, which leads to a direct decrease in the content of apoprotein and lipid components inside the alveoli, as well as to the degradation of collectins [20-22].

Most of the studies (more than 200 publications over the past 10 years) concern the levels of surfactant proteins SP-D in ARDS of various etiologies (it is important that up to 80% of ARDS associated with pneumonia), a significantly smaller number of publications - for chronic lung diseases and isolated ones for community-acquired pneumonia (CAP) [23, 24]. Serum levels of SP-D have been determined as biomarkers for other respiratory diseases, including COPD [25], systemic sclerosis [26] and interstitial lung diseases (including those associated with rheumatoid arthritis) [27], sarcoidosis [10], play an important role in differential diagnosis and have prognostic value.

Higher baseline concentrations of SP-D in blood plasma were associated with higher mortality and severe course of lower respiratory tract infection complicated by mechanical ventilation and the addition of organ failure [28]. In single studies of the SP-D protein level in patients with CAP compared with healthy patients, not only the presence of a higher indicator, but also a direct relationship of this

protein in the development of life-threatening complications and mortality in CAP has been shown [29, 30].

In a similar study, severe COVID-19 had higher SP-D levels than non-severe group according to the CT imaging results [30]. Saito et al. [31] also suggested that SP-D levels might be a distinctive biomarker in the diagnosis of COVID-19 infection, where CT image findings were not present [31]. In addition, in a study, it was observed that mortality decreased and the need for mechanical ventilation decreased after bronchoscopy was performed in ARDS cases caused by COVID-19 [32].

Kerget et al. [33] identified higher levels of SP-D in non-survivors compared to surviving patients from COVID-19. In another study conducted by Choreno-Parra and colleagues, SP-D levels were assessed in serious H1N1 and COVID-19 patients and declared SP-D levels as good prognostic markers in severe H1N1, but it is not a good biomarker for differentiation COVID-19 and H1N1 patients [34].

In the present study, we identified higher levels of SP-D in COVID-19 patients (both mild and severe/critical patients) compared to healthy controls; however, despite the mean values were higher, the difference between the mild patients and control were not statistically significant and thus, it is unlikely to indicate SP-D as a good diagnostic marker for COVID-19. And also we have determined increased SP-D levels in patients who have superinfection during the COVID-19 treatment in hospital. These results may show that SP-D levels might be a prognostic marker for predicting superinfected patients.

Furthermore, SP-D might be evaluated as a prognostic determinant after clinical diagnosis of severe/clinical patients with 86% of sensitivity and 51.6% specificity, which are parallel to previous studies in the literature. In addition, we identified a significant correlation between serum SP-D levels and CT severity score in COVID-19 patients. This finding contributes to the prognostic value of SP-D for COVID-19 patients, as well.

In conclusion, our findings clearly demonstrate the value of serum SP-D levels in predicting the clinical severity and prognosis of COVID-19 patients. SP-D is a valuable marker for predicting the clinical severity, prognosis and superinfections. Development of new methods for the optimization of these proteins will also improve differential diagnosis of COVID-19.

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

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Ethics committee approval: The ethics approval for our prospective case-control study was received from the Pamukkale University Non-Invasive Clinical Trials Ethics Committee (date 13.10.2020 and number 63692).

Author contributions

Conception: R.S. and A.K.; Study design: R.S., A.K., E.K., P.B., and O.K.; Funding: A.K.; Materials: T.G., A.K., I.T. and O.K.; Data collection and processing: E.K., T.G., A.K., I.T. and R.S.; Literature review: E.K., R.S., A.K. and A.K.; Writers: E.K., R.S., A.K., P.B. and A.K.; Critical review: O.K.

Case Report

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Our clinical experience and case series of Takotsubo cardiomyopathy

Takotsubo kardiyomiyopati üzerine klinik deneyimimiz ve vaka serimiz

Abdi Sağcan, Mustafa Zungur, M. Murat Tümüklü, Seyid Hamid Moghanchizade

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Abstract

In this study we aimed to evaluate the clinical course and prognosis of Takotsubo Cardiomyopathy cases diagnosed and treated in our clinic.

Takotsubo Cardiomyopathy was first described in 1990 by Dote et al. The reason why it is called Tako-tsubo cardiomyopathy; This is due to the appearance of the left ventricle resembling the narrow-necked, broad-bottomed container used by Japanese fishermen to catch octopuses. In addition to Takotsubo cardiomyopathy, this syndrome is also called ampulla cardiomyopathy, Human stress cardiomyopathy and Broken heart syndrome. In this study, a series of 7 cases of Takotsubo Cardiomyopathy diagnosed and treated in our clinic are presented and the clinical course and prognosis of the disease are examined.

The age range of the series, consisting of six female and one male patients, ranged from 57 to 81 years (median age 70). All of the female patients were in the postmenopausal period and physical or emotional stress was found in four of them. Moderate-to-moderate cardiac enzyme elevation was found in all of the patients. While noncritical plaques were detected in the angiography of six patients who underwent coronary angiography and ventriculography, one patient had normal coronaries. During the follow-up, in-hospital death due to non-cardiac causes (Acute Myeloblastic Leukemia) was observed in one of the patients. In the echocardiographic follow-up of six surviving patients, it was observed that the LV ejection fraction was normalized and ballooning regressed within two months.

The awareness of Takotsubo Cardiomyopathy among cardiology physicians in the world and in our country is increasing. However, information about its prevalence, clinical course and short-term prognosis in our country is insufficient. In the study, a new series was presented in addition to the first data of our country. It is thought that there may be some different physical risk factors that have not yet been identified.

Key words: Acute myocardial infarction, emotinal stress, takotsubo cardiomyopathy.

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Öz

Bu çalışmada kliniğimizde teşhis ve tedavi edilen Takotsubo Kardiyomiyopati olgularının klinik seyrini ve prognozunu değerlendirmeyi amaçladık.

Takotsubo Kardiyomiyopati ilk olarak 1990 yılında Dote ve ark. Tako-tsubo kardiyomiyopati olarak adlandırılmasının nedeni; sol ventrikülün görünüşünün, Japon balıkçılarının ahtapot yakalamak için kullandığı dar boyunlu, geniş tabanlı kaba benzemesinden dolayıdır. Bu sendroma Takotsubo kardiyomiyopatisinin yanı sıra ampulla kardiyomiyopatisi, insan stres kardiyomiyopatisi ve kırık kalp sendromu da denir. Bu çalışmada kliniğimizde teşhis ve tedavi edilen 7 Takotsubo Kardiyomiyopati olgusu sunulmakta ve hastalığın klinik seyri ve prognozu incelenmektedir.

Altı kadın ve bir erkek hastadan oluşan serinin yaş aralığı 57 ile 81 yıl (ortalama yaş 70) arasında değişmekteydi. Kadın hastaların tamamı postmenopozal dönemdeydi ve dördünde fiziksel veya emosyonel stres saptandı. Tüm hastalarda orta-orta düzeyde kardiyak enzim yüksekliği saptandı. Koroner anjiyografi ve ventrikülografi yapılan altı hastanın anjiyografisinde kritik olmayan plaklar tespit edilirken, bir hastada koroner arterler normaldi. Takiplerde hastalardan birinde kalp dışı nedenlere bağlı hastane içi ölüm (Akut Miyeloblastik Lösemi) gözlendi. Yaşayan altı hastanın ekokardiyografik takibinde iki ay içinde LV ejeksiyon fraksiyonunun normale döndüğü ve balonlaşmanın gerilediği görüldü.

Dünyada ve ülkemizde kardiyoloji hekimleri arasında Takotsubo Kardiyomiyopati farkındalığı giderek artmaktadır. Ancak ülkemizde prevalansı, klinik seyri ve kısa dönem prognozu ile ilgili bilgiler yetersizdir. Çalışmada ülkemizin ilk verilerine ek olarak yeni bir seri sunulmuştur. Henüz tanımlanmamış bazı farklı fiziksel risk faktörlerinin olabileceği düşünülmektedir.

Abdi Sağcan, Prof. KTO Karatay University School of Health Sciences, Konya, Turkey, e-mail: abdisagcan@gmail.com (https://orcid.org/0000-0002-1441-3653 (Corresponding Author)

Mustafa Zungur, Assoc. Prof. Departments of Cardiology, Kent Hospital, Izmir, Turkey, e-mail: drzungur@yahoo.com (https://orcid.org/0000-0003-2908-2778)

M. Murat Tümüklü, Assoc. Prof. Departments of Cardiology, Kent Hospital, Izmir, Turkey, e-mail: tumuklu17@yahoo.com (https://orcid.org/0000-0001-5029-1991)

Seyid Hamid Moghanchizade, M.D. Departments of Cardiology, Kent Hospital, Izmir, Turkey, e-mail: hmoghanchi@yahoo.com (https://orcid.org/0000-0002-6652-3790)

Anahtar kelimeler: Akut miyokard enfarktüsü, duygusal stres, takotsubo kardiyomiyopati.

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Introduction

Takotsubo Cardiomyopathy (TC) was first described in 1990 by Dote et al. [1]. The reason why it is called tako-tsubo cardiomyopathy; This is because the appearance of the left ventricle is similar to the narrow-necked, broad-based vessel used by Japanese fishermen to catch octopuses. Apart from Takotsubo cardiomyopathy, this syndrome is also called Ampulla cardiomyopathy, Human stress cardiomyopathy and Broken heart syndrome. TC is one of the most common causes of MINOCA (Myocardial infarction non-obstructive coronary arteries) [2].

Ventriculography and echocardiography are important in the diagnosis of Takotsubo cardiomyopathy. According to the differences in wall movements, Shimizu et al [3]. They made the TC classification.

Shimizu TC classification: 1. Takotsubo type: Apical akinesia and basal hyperkinesia 2. Reverse Takotsubo: Basal akinesia and apical hyperkinesia 3. Mid-ventricular type: Mid-ventricular ballooning accompanied by basal and apical hyperkinesia 4. Localized type: Takotsubo- ballooning in any part of the left ventricle accompanied by clinical findings of similar left ventricular dysfunction [3].

There are often stressful physical and emotional events in the history of the cases before the onset of symptoms. Most patients present with chest pain similar to angina at rest. Dyspnea may also be an accompanying initial symptom. Patients who usually present with acute coronary syndrome and ST segment changes [4, 5] may sometimes progress asymptomatically [6]. Syncope, cardiac arrest, heart failure, supraventricular and ventricular arrhythmias are less common forms of presentation. Cardiogenic shock, respiratory failure, and pulmonary edema can be seen in the acute phase. Left ventricular rupture resulting in death has been observed [7]. Sometimes, cerebral or peripheral embolism may develop due to thrombi formed in the left ventricular aneurysmatic or dyskinetic segments [8].

Its clinical presentation is acute reversible heart failure without occlusive coronary artery disease and myocardial stunning [9]. Although there is no definitively agreed clinical criteria for Takotsubo cardiomyopathy, the Mayo clinical criteria are still used in the diagnosis.

1) Transient midventricular akinesia / dyskinesia in an area larger than the area fed by a single vessel (may accompany apical involvement), often (not necessarily) triggering stress factor is present.

2) ECG changes such as newly developing ST segment elevation or T wave negativity or moderate troponin elevation.

3) No significant stenosis (≥50%) or acute plaque rupture on coronary angiography.

4) The absence of myocarditis and pheochromocytoma.

Cases

In our clinic, seven patients were diagnosed with TC in the last four years. The age range of the series consisting of six female and one male patients ranged from 57 to 81 years (median age 70). All of the female patients were in the postmenopausal period and physical or emotional stress was detected in four of them. Five patients had ST-T changes in the anterior leads (Figure 1), one patient had pacemaker rhythm and one patient had non-specific ST segment elevation. Moderate cardiac enzyme elevation was found in all cases. Color Doppler Echocardiography was performed in all cases on arrival and at the controls and the data were recorded (Figure 2). Non-critical plaques were detected in the angiography of six patients who underwent coronary angiography and ventriculography, while one patient had normal coronary arteries (Figure 3). In-hospital death due to non-cardiac causes (Acute Myeloblastic Leukemia) was observed in one of the patients during follow-up. In the echocardiographic follow-up of six survivors, it was observed that the LV ejection fraction normalized and ballooning regressed within two months. No

recurrent cardiovascular events were observed in the mean 2-year follow-up of our patients (Table 1-3).

Patient Confirmation: Information about the diagnosis and the procedure to be performed was provided to the patient or relatives of the patients, and a confirmation document was signed.

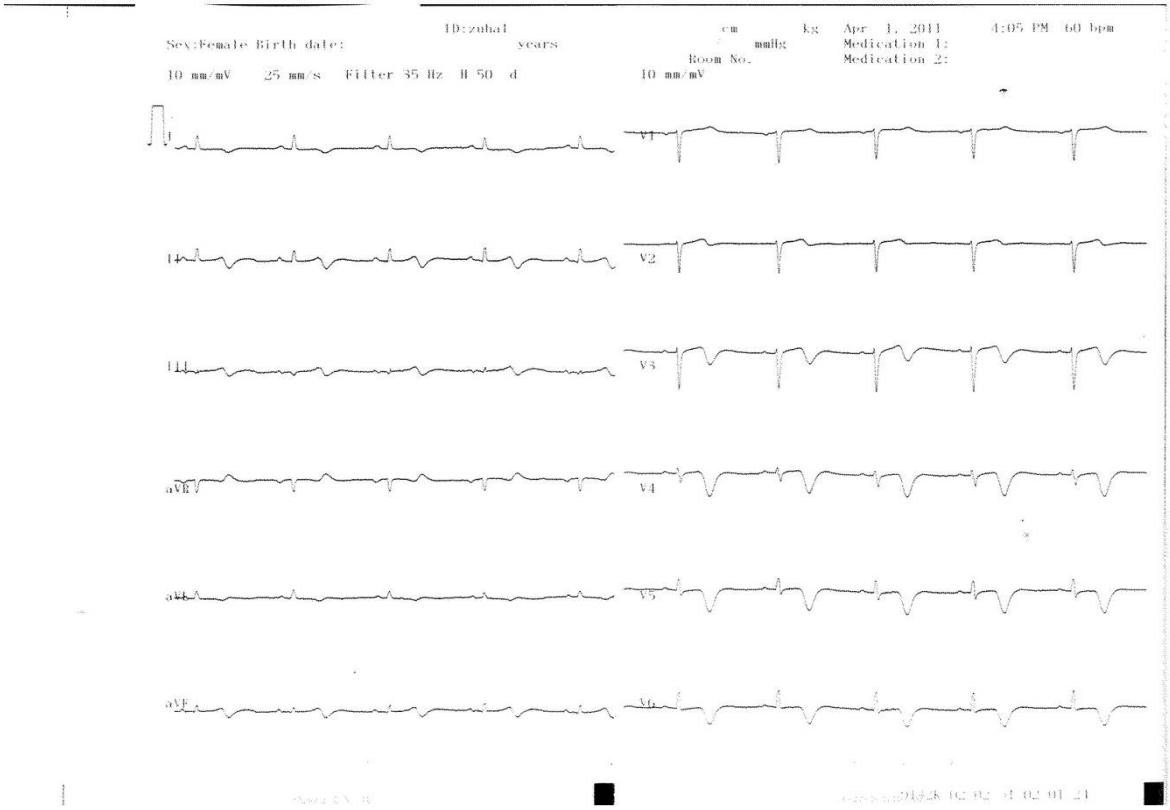

Figure 1. Electrocardiography

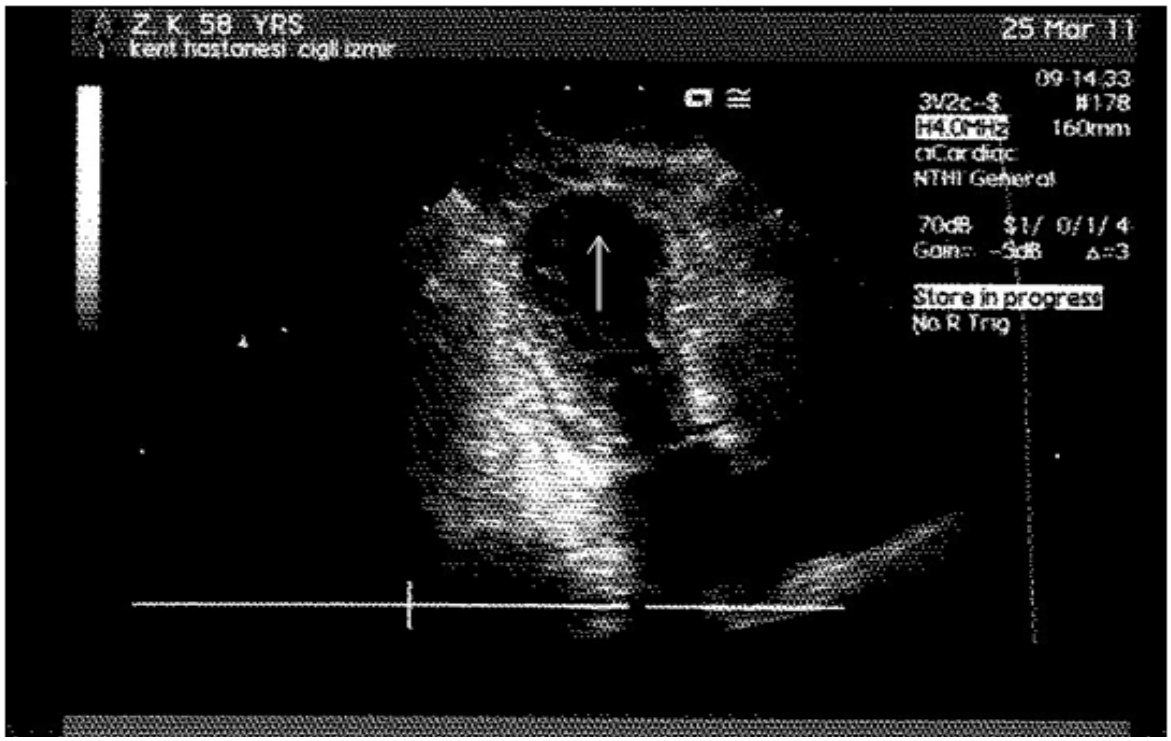

Figure 2. Echocardiography

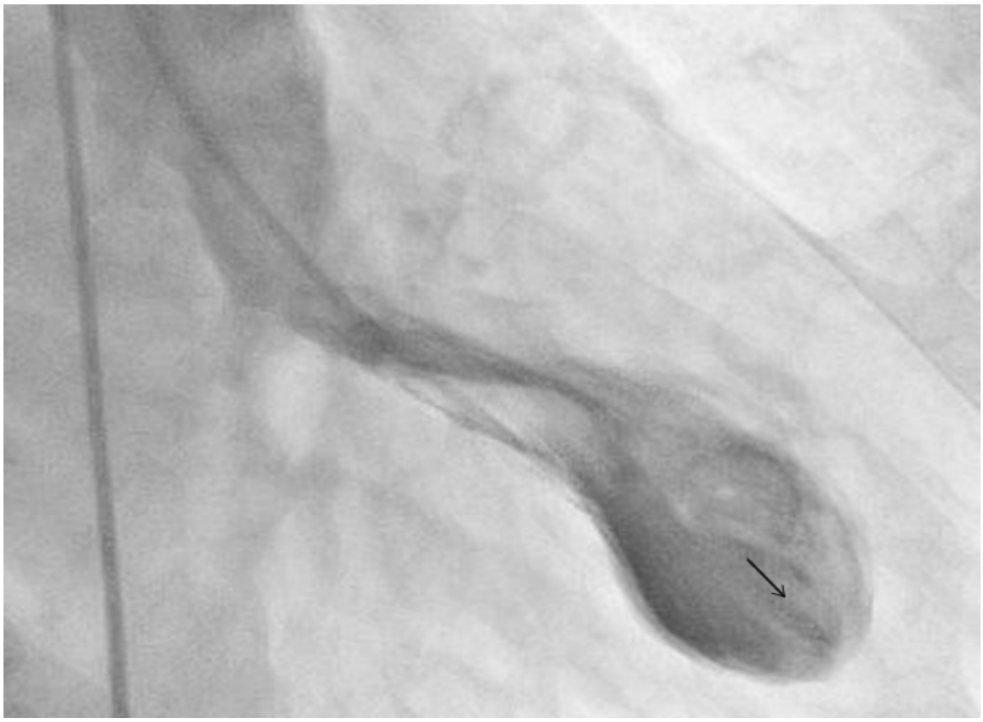

Figure 3. Ventriculography

Table 1. Clinical and demographic characteristics of patients

Age	Gender	Cardiovascular Risk Factors	ECG	Echocardiography
71	Female	HT, HPL		Apex hypokinetic
66	Female	HT, DM	V1-4 ST elevation	Apex dyskinetic, anterior apical akinetic
81	Female	OSAS	V1-4 ST elevation	Apex mild aneurysm, Inferior apical aneurysmatic
57	Male	-	V1-4 ST elevation	1/3 apical of all hypokinetic
77	Female	HT, HPL	Pace rhythm	Progressive hypokinesia to be more apex
58	Female	HT	V1-4 ST elevation	Apex dyskinetic
63	Female	-	V2-4 ST elevation	Anteroapical aneurysmatic

HT: Hypertension, HPL: Hyperlipidemia, DM: Diabetes Mellitus Type 2,
OSAS: Obstructive sleep apnea syndrome

Table 2. Troponin level and coronary angiography of patients

Trigger Factor	TnT ng/mlt	Coronary Angiography	Conclusion
Emotional Stress	0.028	Normal Coronary arteries	Healing
Emotional Stress	0.089	Noncritical stenosis	Healing
COPD, Pneumonia	3.020	Noncritical stenosis	Healing
AML, Pulmonary Aspergillous	2.600	Plaque	Exitus (non-cardiac reason)
---	0.182	Plaque	Healing
Emotional Stress, Stomach Ca	0.244	Plaque	Healing
----	0.458	Plaque	Healing

TnT: Troponin T, COPD: Chronic Obstructive Pulmonary Disease
AML: Acute Myeloblastic Leukemia

Table 3. Echocardiography of patients

Before Treatment			After Treatment		
LVD (mm)	**LVS (mm)**	**EF%**	**LVD (mm)**	**LVS (mm)**	**EF%**
49	29	45	46	24	60
45	30	30	43	25	60
41	25	45	42	23	60
48	35	30	-EX	-EX	-EX
52	37	35	46	37	50
47	29	45	40	25	60
50	32	30	44	28	60

LVD: Left Ventricul Diastolic, LVS: Left Ventricul Systolic

Discussion

Approximately 90% of Takotsubo cardiomyopathy cases are postmenopausal women [10]. All six female cases were in the postmenopausal period and one case had a history of early menopause. All of the patients met the criteria for Takotusubo cardiomyopathy with clinical, ECG, echocardiographic and angiographic findings. In addition to ST segment elevation, T wave reversal or QT prolongation can also be seen on ECG [11]. Six of the seven patients in our series had ST-T changes in the precordial leads, while one case had a pacemaker rhythm.

Cardiac enzymes are often moderately elevated. For these reasons, it is often misdiagnosed as ST-elevation myocardial infarction (STEMI). The correct diagnosis can be made after further investigations by echocardiography or ventriculography with typical hypokinetic and ballooning visualization of the apex of the left ventricle, performing coronary angiography to show normal flow in the coronary arteries, and detecting the absence of late gadolinum involvement in cardiac magnetic resonance imaging, although it is not found in most clinics [12]. Moderate enzyme elevation was observed in all our cases. Coronary angiography revealed normal coronary arteries or plaques with noncritical stenosis. While apical bubbling was demonstrated by venticulography in six cases, ventriculography was not performed in one case due to renal dysfunction. In this case, apical dysfunction was confirmed by echocardiography.

Takotsubo cardiomyopathy is known as a stress-induced disease. Emotional stress has been described in 30-40% of patients [13]. Maekawa et al. [14] found a psychological or physical stress in more than 50% of the patients in their study. Emotional or physical stress was detected in five (71%) of our patients. While emotional stress was present in three cases, no stress factor was found in two cases. COPD is also considered in the etiology of TC. A history of COPD or bronchial asthma was reported in half of 32 patients who met the criteria and were diagnosed with TC, out of 17 thousand patients with normal coronary angiography [15]. In our series, one case had a history of COPD and it was observed that the case became complicated with pneumonia. OSAS was present in one of our cases. There is not yet a study investigating the frequency or relationship of TC in OSAS cases. In another study, a high rate of arterial hypertension was reported in 76% of patients with acute TC [16]. Hypertension was present in 57% of our cases. MVP was found in one of our patients. There is no literature data on a causal relationship between MVP and TC. It has been reported that severe transient mitral regurgitation and related acute pulmonary edema developed in a TC case [17]. In our series, an increase in the degree of mitral regurgitation was observed with the decrease in EF in a female TC patient who was also diagnosed with MVP. In our case, there was no wall motion defect other than apical ballooning. We observed that mitral regurgitation regressed in parallel with the increase in EF following medical treatment. Therefore, we think that MVP may be a facilitating factor with a different mechanism in the etiology of TC, even if it is a single case. In our female case, a milder TC clinic with another emotional stress attack occurred 6 months later, following complete

clinical recovery. Our patient was relieved by increasing the dose of beta blocker. This one case observation suggests the hypothesis that the beta blocker dose should be maintained at the optimal dose to prevent recurrences.

Initial medical treatment of the patients was arranged as the treatment of acute coronary syndrome. Drug preferences and doses (beta blocker, ACEI and diuretic, etc.) were adjusted according to the presence of additional problems.

The short, medium and long-term prognosis of these patients is close to perfect, except for those presenting with cardiogenic shock [18, 19]. Complications of Takotsubo cardiomyopathy include apical thrombus formation, cardiac rupture, embolic events and conduction disorders [20]. No conduction disorder or malignant arrhythmia was observed in any of our patients. Aphasia was observed in one of our patients during his hospitalization. In this case, thrombus was not detected with TTE and it was observed that completely regressed in the follow-up after the addition of anticoagulant treatment. No serious shock requiring IABP was observed in any of the patients.

Although left ventricular functions may be severely reduced at first admission and they recover within a few days. They return to their normal function within a few months [21]. In a study conducted by the French, death in hospital was reported in 1 out of 10 patients [22] and in 1 case in Desmet's 13 disease series [23]. In the American study, death was not observed in any of the 19 patients [24]. One of our TC cases (14%) was lost. This patient was receiving chemotherapy due to hematological malignancy (AML) and died due to non-cardiac causes. Except for this patient who died, recovery was observed in all patients who applied to our clinic. In the RETEKO (National Registry on TAKOtsubo syndrome) Registry, malignancy was reported in 129 (11.8%) of 1097 TC cases followed in 38 centers between 2002 and 2019 [25]. There was malignancy in 2 cases (28.5%) in our series. In one case, recurrent clinic appeared after 6 months and with milder symptoms but treatment was performed without the need for hospitalization.

In conclusion, the awareness of TC among cardiologists in the world and in our country is increasing. However, information about its frequency, clinical course and short-term prognosis in our country is insufficient. In the study, a new series was presented in addition to the first data of our country. It is thought that there may be some other physical risk factors that have not yet been determined.

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Informed consent: Information about the diagnosis and the procedure to be performed was provided to the patient or relatives of the patients, and a confirmation document was signed.

Authors’ contributions to the article

A.S. and M.Z., have constructed the main idea and hypothesis of the study. A.S., M.Z., M.M.T. and S.H.M. developed the theory and arranged/edited the material and method section. A.S. and M.Z., have done the evaluation of the data in the results section. Discussion section of the article written by A.S., M.Z., M.M.T. and S.H.M. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Review Article

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Time is skin: what does the emergency physician need to know about DRESS?

Zaman cilttir: Acil servis hekimleri DRESS sendromu hakkında ne bilmeli?

Reşad Beyoğlu

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Abstract

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, also known as Drug Induced Hypersensitivity Syndrome (DIHS), is an acute drug-induced hypersensitivity reaction. The pathogenesis of this syndrome, which can develop due to many drugs, especially antiepileptic agents, is not known exactly. This syndrome, which was denominated “hydantoin hypersensitivity” in 1950, was renamed as “DRESS syndrome” by Bocquet and his colleagues in 1996 and the first diagnostic criteria were determined. It is estimated that increased reactive metabolites due to inadequate detoxification of some drugs cause immunological reaction and it is thought that a similar reaction such as herpesvirus and Ebstein Barr Virus, as well as drugs, can cause DRESS syndrome.

Unlike syndromes that may develop due to other drugs, DRESS syndrome customarily commences 2-8 weeks after the commencement of the drug, and symptoms perpetuate to progress after discontinuation of the responsible drug. Symptoms such as fever, lymphadenopathy, hematological disorders, maculopapular rash and internal organ involvement are common in this syndrome.

Diagnosis of DRESS syndrome is often difficult, as the clinical manifestations are varied and the latent period after the initiation of drug use can be up to 3 months. Thus, it is thought that the diagnosis of DRESS should be in the minds of all doctors, especially emergency physicians because when this diagnosis is overlooked, its mortality is around 10-20% and it is a very serious clinical condition.

Key words: DRESS, drug rash with eosinophilia systemic symptoms, ED.

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Öz

Drug Rash with Eoshinophilia and Systemic Symptoms (DRESS) sendromu veya diğer adıyla da bilinen İlaçla indüklenen hipersensitivite sendromu (Drug Induced Hypersensitivity Syndrome (DIHS), ilaca bağlı akut bir hipersensitivite reaksiyonudur.

Başta antiepileptik ajanlar olmak üzere birçok ilaca bağlı gelişebilen bu sendromun patogenezi tam olarak bilinmemektedir. 1950 yılında “hidantoin hipersensitivitesi” olarak adlandırılan bu sendrom, 1996 yılında Bocquet ve arkadaşları tarafından “DRESS sendromu” olarak yeniden adlandırılmış ve ilk tanı kriterleri belirlenmiştir. Bazı ilaçların detoksifikasyonundaki yetersizliğe bağlı artan reaktif metabolitlerin immünolojik reaksiyona neden olduğu tahmin edilmektedir. İlaçların yanısıra herpesvirüs ve Ebstein Barr Virüsü gibi benzer bir reaksyonlar DRESS sendromuna yola açabildiği düşünülmektedir.

DRESS sendromunun diğer ilaçlara bağlı gelişebilen sendromlardan farklı olarak Klinik bulgularının genellikle ilacın kullanılmaya başlanmasından 2-8 hafta sonrasında başlaması ve sorumlu ilacın kesilmesiyle semptomların ilerlemeye devam etmesidir.

Ateş, lenfadenopati, hematolojik bozukluklar, makülopapüler döküntü ve ve iç organ tutulumları gibi bulgular bu sendromda rastlamak sıktır.

Klinik bulguların çeşitli olması ve ilaç kullanımının başlaması sonrasındaki latent periyodun 3 aya kadar uzun olabilmesi nedeniyle DRESS sendromunun tanısı sıklıkla güçtür. Bu nedenle DRESS sendromunun, başta acil servis hekimleri olmak üzere tüm doktorların aklında tutulması gerektiği düşünülmektedir. Tanısı gözden kaçtığında mortalitesi %10-20 civarında olup oldukça önemli bir klinik tablodur.

Anahtar kelimeler: DRESS, eozinofili ve sistemik semptomlarla seyreden ilaç reaksiyonu, acil servis.

Beyoğlu R. Zaman cilttir: Acil servis hekimleri DRESS sendromu hakkında ne bilmeli? Pam Tıp Derg 2023;16:157-161.

Reşad Beyoğlu, M.D. Emergency Medicine Specialist, Servergazi State Hospital, Department of Emergency Medicine, Denizli, Turkey, e-mail: resadbeyoglu@gmail.com (https://orcid.org/0000-0001-7321-5131) (Corresponding Author)

Introduction

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, also known as Drug Induced Hypersensitivity Syndrome (DIHS), is an acute drug-induced hypersensitivity reaction. The pathogenesis of this syndrome, which can develop due to many drugs, especially antiepileptic agents, is not known exactly. Increased reactive metabolites due to inadequate detoxification of some drugs are predicted to cause an immunological reaction. It is thought that similar reactions such as herpesvirus and Epstein Barr Virus, as well as drugs, can cause DRESS syndrome. This syndrome, which was denominated “hydantoin hypersensitivity” in 1950, was renamed as “DRESS syndrome” by Bocquet and his colleagues in 1996 and the first diagnostic criteria were determined.

Unlike syndromes that may develop due to other drugs, DRESS syndrome customarily commences 2-8 weeks after the commencement of the drug, and symptoms perpetuate to progress after discontinuation of the responsible drug. Symptoms such as fever, lymphadenopathy, hematological disorders, maculopapular rash and internal organ involvement are common in this syndrome.

Diagnosis of DRESS syndrome is often difficult, as the clinical manifestations are varied and the latent period after the initiation of drug use can be up to 3 months. Therefore, it is thought that the diagnosis of DRESS should be in the minds of all doctors, especially emergency physicians.

Literature review

Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome, additionally kenned as Drug Induced Hypersensitivity Syndrome (DIHS), is an acute drug-induced hypersensitivity reaction [1, 2]. The pathogenesis of this syndrome, which can develop due to many drugs, especially antiepileptic agents, is not known precisely [1]. Incremented reactive metabolites due to inadequate detoxification of some drugs are predicted to cause an immunological reaction [3]. It is thought that similar reactions such as herpesvirus and Epstein Barr Virus, as well as drugs, can cause DRESS syndrome [1, 3-5]. This syndrome, which was denominated “hydantoin hypersensitivity” in 1950, was renamed as “DRESS syndrome” by Bocquet and his colleagues in 1996 and the first diagnostic criteria were determined [3, 6, 7].

Unlike syndromes that may develop due to other drugs, DRESS syndrome usually starts 2-8 weeks after the start of the drug, and symptoms continue to progress after discontinuation of the responsible drug [7, 8].

Symptomes such as fever, lymphadenopathy, hematological disorders, maculopapular rash and internal organ involvement are common in this syndrome [1, 9].

Diagnosis of DRESS is often difficult, as the clinical manifestations are varied and the latent period after the initiation of drug use can be up to 3 months [8].

Although the exact incidence of DRESS is unknown, it is estimated at 1.2-6 cases/1 million/year. However, for common causative drugs like anticonvulsants and sulfonamides, the incidence is estimated to be one in 1000-10.000 drug exposures [3, 10].

Diagnosis of DRESS syndrome is often difficult, as the clinical manifestations are varied and the latent period after the initiation of drug use can be up to 3 months.

As it shown below, diagnostic criteria were established by the RegiSCAR working group to identify potential cases of DRESS syndrome [3].

(The presence of 3 or more of the manifestations other than the first two criteria is required)

- Need for hospitalization

- Presence of suspected drug use that may cause a reaction

- Acute skin rash

- Fever above 38°C

- LAP in at least 2 areas

- At least one internal organ involvement

- Blood findings

*Less or more than normal lymphocyte count

*Eosinophil elevation (in number or percentage)

*Platelet count below normal values

DRESS syndrome is a condition with a high mortality of 10-20%, so early diagnosis and treatment are very consequential particularly in ED [2, 3, 11, 12].

Although more than 50 drugs have been reported as the cause of DRESS syndrome, the most common drugs are aromatic anticonvulsants, allopurinol, and sulfonamides [3]. It was reported that anticonvulsant drugs carbamazepine and phenytoin were responsible for 43.6% of all DRESS syndrome cases, whereas severe cutaneous drug reaction due to valproic acid and topiramate was not observed [13].

While the most common symptom of DRESS syndrome is fever (90%-100%), the second most common symptom (70%-97%) is skin manifestations and it usually occurs 1-8 weeks following the start of treatment (Figure 1) [2, 9, 14, 15].

Mucosal involvement is seen in 60% of cases, and the most common site is the oral mucosa (Figure 2) [14, 15]. The most common hematological disorder is Eosinophilia (>50%) [2, 14, 16, 17] and the most common systemic symptom is liver abnormalities (60%) [1, 3, 18].

It is recommended that patients presenting to the emergency department with signs and symptoms suggestive of hypersensitivity should be questioned whether they have been on medication within the last six months. Detailed physical examination, vital signs (especially temperature measurement) and laboratory tests should not be forgotten.

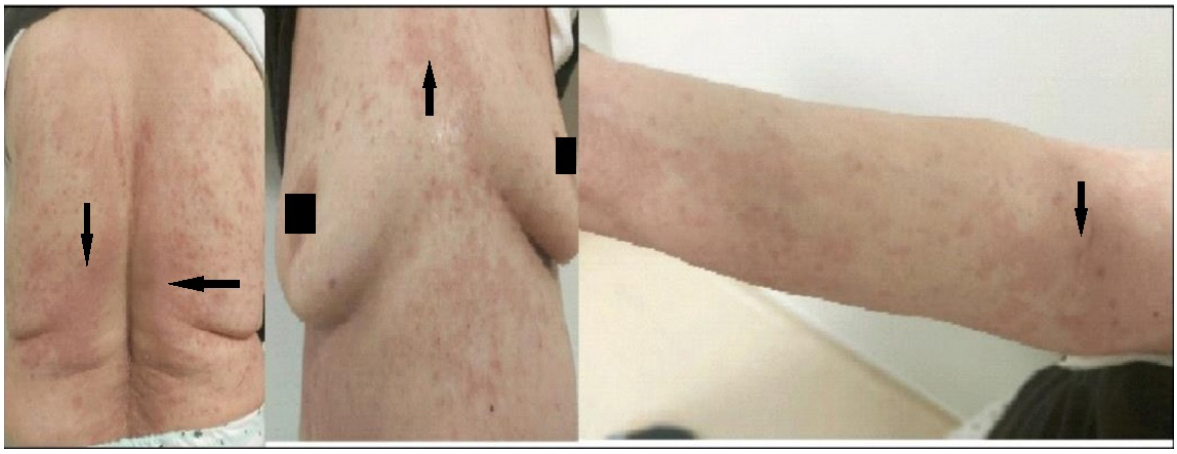

Figure 1. Diffuse maculopapular rash, more prominent on the back, chest, and arms

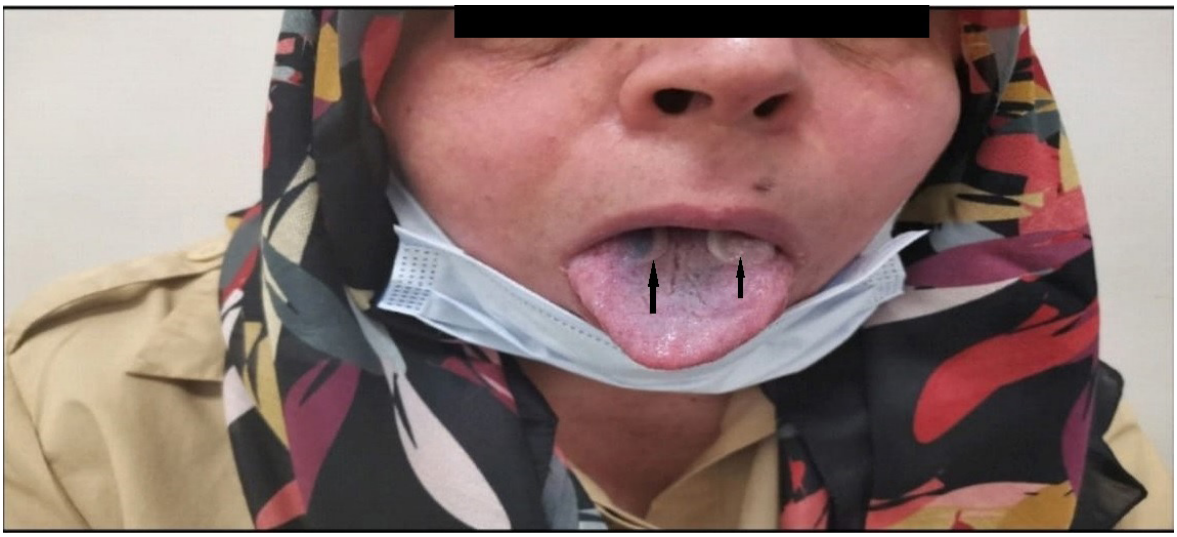

Figure 2. Oral mucosal erosion

Laboratory tests should include LFT, complete blood count (especially eosinophil) and KFT. Since the most important cause of mortality in these patients is liver failure, liver enzymes should be followed up [2, 14].

There are many expert opinions that glucocorticoids and intravenous immunoglobulin (IVIG) are beneficial, especially in the treatment of severe cases [19].

As a conclusion, When emergency physicians detect any new drug use, especially aromatic anticonvulsants, allopurinol, and sulfonamides, any rash or skin lesions accompanying systemic complaints (fever, hematological disorders, LFT disorder, etc.), DRESS syndrome should also be taken into account and dermatology consultation should be requested and it should not be forgotten that early diagnosis of the disease and discontinuation of the responsible drug in the early period will contribute to the reduction of mortality and morbidity in these cases.

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