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Evaluation of cough strength in bronchiectasis

Bronşektazide öksürme kuvvetinin değerlendirilmesi

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Abstract

Purpose: This study aimed to evaluate the cough strength in bronchiectasis patients. We also planned to examine the relationship between cough strength, exercise capacity and quality of life.

Materials and methods: The study included 24 bronchiectasis patients (bronchiectasis group) and 25 healthy individuals (healthy group). Exercise capacity was evaluated with the six minute walk test (6MWT). Cough strength (Peak cough flow (PCF)) was assessed using Mini-WrightTM peak flow meter (PFM) with a mouthpiece. The quality of life was evaluated with Leicester Cough Questionnaire (LCQ).

Results: A significant difference was found between the groups in terms of PCF, 6MWT, LCQ total score and subdimension scores showed significant differences in favor of the healthy group (p<0.05). A positive high correlation was observed between PCF and the following variables: 6MWT and LCQ total score (r=0.780, p<0.000 and r=0.885, p<0.000, respectively).

Conclusion: This study found that cough strength was worse in bronchiectasis patients compared with healthy individuals. In addition, cough strength could negatively affect exercise capacity and quality of life. Therefore, cough strength should be added to the evaluation parameters.

Keywords: Bronchiectasis, cough strength, peak cough flow, exercise capacity, quality of life.

Yilmaz A, Kilinc M, Telli Atalay O, Metin M, Ugurlu E, Senol H, Altınisik Ergur G. Evaluation of cough strength in bronchiectasis. Pam Med J 2023;16:528-535.

Öz

Amaç: Bu çalışmada bronşektazi hastalarında öksürme kuvvetinin değerlendirilmesi amaçlandı. Ayrıca öksürme kuvveti ile egzersiz kapasitesi ve yaşam kalitesi arasındaki ilişkiyi incelemeyi planladık.

Gereç ve yöntem: Çalışmaya 24 bronşektazi hastası (bronşektazi grubu) ve 25 sağlıklı birey (sağlıklı grup) dahil edildi. Egzersiz kapasitesi 6 dakika yürüme testi (6DYT) ile değerlendirildi. Öksürme kuvveti (Tepe öksürük akımı (TÖA)), Mini-WrightTM Pef cough metre (PCM) kullanılarak değerlendirildi. Yaşam kalitesi, Leicester Öksürük anketi (LÖA) ile değerlendirildi.

Bulgular: Gruplar karşılaştırıldığında TÖA, 6DYT, LÖA total puan ve alt boyutları arasında sağlıklı grup lehine anlamlı fark görüldü (p<0,05). TÖA ile 6DYT ve LÖA total puan arasında pozitif yönde yüksek düzeyde anlamlı ilişki saptandı (sırasıyla r=0,780, p<0,000 ve r=0,885, p<0,000).

Sonuç: Bronşektazi hastalarının öksürme kuvvetinin sağlıklı bireylere göre daha kötü olduğu görüldü. Ayrıca, öksürme kuvveti egzersiz kapasitesini ve yaşam kalitesini olumsuz etkilediği için değerlendirme parametrelerine öksürük kuvveti eklenmelidir.

Anahtar kelimeler: Bronşektazi, öksürme kuvveti, tepe öksürük akımı, egzersiz kapasitesi, yaşam kalitesi.

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Introduction

Bronchiectasis is characterized by enlargement of the airways and thickening of the bronchial wall; it occurs together with chronic cough and sputum complaint [1]. The cough-operated mucociliary clearance mechanism constitutes the normal defense mechanism of the lungs. Mucociliary clearance depends on the harmonious action of the cilia and its effective interaction with mucins, one of the proteins synthesized by epithelial cells that form the upper viscous mucus layer in the airways. The stickiness of mucins traps particles, and the lower aqueous layer allows the movement of the cilia [2]. A disrupted mucociliary clearance mechanism in patients makes the lungs vulnerable. A vicious cycle of bacterial infection and inflammation begins with secretion accumulation. Problems also occur in effective coughing due to intense inflammation, damage, and bronchial wall weakness. This leads to problems in clearing secretions and causes a decrease in flow [3]. As a result of increased perception of dyspnea and decreased expiratory airflow, exercise capacity may also be reduced in patients with bronchiectasis [4]. The decrease in exercise capacity is an important finding to evaluate the relationship between cough strength and exercise capacity.

Increased perception of dyspnea, symptoms associated with the disease, especially cough, and decreased exercise capacity negatively affect the quality of life. It is important to determine the relationship between cough and quality of life, including harmony and integrity of mental and physical health, because the quality of life was found to be more important than the deterioration in the lung function of the patient. In fact, the main purpose of rehabilitation programs is to improve the quality of life [5].

Cough is a very important symptom in patients with bronchiectasis and must be evaluated during the medical follow-up. Previous studies were conducted using questionnaires or by assessing the number or severity of coughing [6-8]. Studies evaluating the cough strength with PCF were generally conducted to determine the severity of neuromuscular diseases or to make extubation/decannulation decisions in intensive care [9, 10].

This study aimed to evaluate the cough strength in bronchiectasis patients. We also planned to examine the relationship between cough strength, exercise capacity and quality of life.

Materials and methods

A total of 24 patients with bronchiectasis aged more than 18 years, who were followed up by the Pamukkale University, Chest Diseases Polyclinic with the diagnosis of non-cystic fibrosis (CF) bronchiectasis, who did not have any other respiratory disease, who did not have acute and/or chronic respiratory failure, and who were cooperative and volunteered, besides 25 healthy volunteers of the same age and sex, who had no known comorbidities, were included in the study. The participants were divided into two groups: the bronchiectasis group and the healthy group.

The exclusion criteria for patients with bronchiectasis were as follows: cor pulmonale and/or heart failure, hemoptysis, acute myocardial infarction, vertebral injury, any health problems that prevented coughing, and any problem in the musculoskeletal system that prevented participation in the study and/or presence of mobility problems. The exclusion criteria for volunteers were as follows: Smoking, any health problems that prevented coughing, any problem in the musculoskeletal system that prevented participation in the study and/or presence of mobility problems, and any lung, heart, systemic, orthopedic, and/or neurological disease. Participants were informed about the purpose and scope of the study, and written consent was obtained from each participant. This study was approved by the Pamukkale University Ethics Committee, and the ethical principles stated in the Helsinki Declaration were followed during the study.

Study design

The participants' demographic data were recorded. Dyspnea perception was measured with the Modified Medical Research Council (MMRC) scale. Exercise capacity was evaluated with the six minute walk test (6MWT). Cough strength was assessed using a Mini-Wright™ peak flow meter (PFM) with a mouthpiece. The quality of life was measured with the Leicester Cough Questionnaire (LCQ) specific to cough. The participants who met the inclusion criteria

were questioned about their sociodemographic characteristics through face-to-face interviews.

Respiratory function parameters were measured and evaluated with the Jaeger brand MasterScope device that could also be used for body plethysmography to perform respiratory function test. The patients were seated in a comfortable position, after which they were put on a nose clip to perform a forced vital capacity (FVC) maneuver, for measuring respiratory function parameters. During this maneuver, the person first breathed calmly, and then he/she was asked to take a deep and strong breath and fill the lungs with air. Further, he/she was asked to exhale quickly and powerfully until all the air was out of the lungs. In evaluating the pulmonary function test, the FVC maneuver was repeated at least three times and the best values were accepted. PFT measurements were recorded in the evaluation form for both groups [11].

Cough strength (PCF), was evaluated with a portable PFM device (Mini-Wright™ peak flow meter) while the patients were in a sitting position. After deep inspiration (after waiting for at least 2 s), the peak expiratory flow (PEF) they were able to reach with a strong coughing maneuver was recorded. The PEF maneuver lasted approximately 1 s as opposed to FVC. Three measurements for cough strength were repeated, while the highest value was recorded; a 30-s pause occurred between each measurement. The measurements were both carried out with a mouthpiece [12, 13].

The patient's exercise capacity was measured with the 6MWT. The standard test protocol was applied in a continuous 30-m corridor or in an open flat-floor area. A marker was placed at every 3 m. The patients, who wore comfortable clothes and shoes, were given standard directions during the tests orally. The heart rate and blood pressure were measured before and after the test. In addition, the dyspnea level was measured with a Borg ruler and oxyhemoglobin saturation with pulse oximetry (Pulsemed Finger Type Pulse Oximeter Device). The walking distance was recorded with a measuring stick [14].

The LCQ was used to measure quality of life. The LCQ is a short, easy-to-administer, and cough-specific health-related quality-of-life questionnaire. The LCQ was self-directed and included a 7-point Likert response scale; it had 3 health areas (physical, psychological, and social) and consisted of 19 items. It was practical and short for clinical use. A high LCQ score indicated a good health status. Its validity and reliability were tested [15, 16].

The patient's shortness of breath was evaluated with the MMRC scale. The scale options were read to the patients, who were then asked to select the most appropriate grade that described his/her respiratory distress. The MMRC scored from 0 to 4. A high MMRC score indicated a more severe perception of shortness of breath [17].

The Bronchiectasis Severity Index (BSI) was used to determine the disease severity. The BSI evaluated age, body mass index (BMI), FEV% (expected%), hospitalization, frequency of exacerbation, number of lung lobes affected, mMRC, and colonization. Patients' results were categorized as mild (KSE≤4), medium (BSI 5-8), and severe (KSE≥9) according to the scoring system [18].

Statistical analysis

The effect size obtained in the reference study was strong (d=1.306). As a result of power analysis made considering that a lower effect size could be obtained, it was found that when at least 46 people (at least 23 for each group) were included in the study for the effect size value at a strong level (d=1), 95% power at a 95% confidence level could be obtained [19].

Statistical analyses were performed using SPSS 25.0. Categorical variables were defined by number and percentage. Continuous variables were defined by the minimum - maximum, median and mean±standard deviation. Shapiro Wilk test was used for determination of normal distribution. For independent group comparisons, we used Independent samples t test when parametric test conditions were satisfied and Mann-Whitney U test when parametric test conditions were not satisfied. Pearson and Spearman correlation analysis was used for analyzing the relationships between continuous variables. The difference between categorical variables were analyzed with Chi-square analysis. Statistical significance was determined as p<0.05.

Results

The study included 24 (11 women and 13 men) patients with bronchiectasis and 25 (15 women and 10 men) healthy controls. The comparison of the groups revealed no significant difference in terms of age, height, and BMI (p>0.05). A significant difference was found between the groups in terms of respiratory parameter results (p<0.05). The results are shown in Table 1. The mean disease duration of patients with bronchiectasis was found to be 25.39±17.12 years. The mean MMRC score was 2.45±1.06.

Underlying etiologies of non-CF bronchiectasis were idiopathic in 8 (33.3%), infection in 4 (16.7%), tuberculosis in 1 (4.2%), and childhood infections in 4 (16.7%) pneumonia in 4 (16.7%) tuberculosis 2 (8.2%) in and whooping cough in 1 (4.2%). There were 12 (50%) mild, 10 (41.7%) moderate, and 2(8.3%) severe patients according to the Bronchiectasis severity Index.

The examination of the groups' PCF, 6MWT, LCQ total score and subdimension scores showed significant differences in favor of the healthy group (p<0.05). The results are shown in Table 2.

The relationships between PCF, 6MWT, LCQ total score and subdimension scores, dyspnea scores and disease duration of bronchiectasis patients are shown in Table 3.

Table 1. Mean values (mean ± SD) and ranges of characteristics of spirometric and anthropometric values in the bronchiectasis and healthy groups

Variables	Bronchiectasis group (n=24)		Healthy group (n=25)		*p*
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
Age (year)	51.75±4.28	55 (22-70)	50.84±10.18	48 (30-67)	0.610‡
Height (cm)	165.75±8.4	166.5 (150-180)	165.32±9.11	169(150-180)	0.888§
Weight (kg)	71±12.69	70 (43-94)	69.28±11.03	68 (46-94)	0.624§
BMI (kg/m²)	25.94±4.83	25.73(15.99-34.11)	25.35±3.42	25.29(15.92-32.53)	0.603§
FEV1	1.71±0.88	1.35 (0.72-3.86)	2.78±0.67	2.75 (1.31-3.72)	**0.000**‡
FEV1%	58.03±23.71	55 (23-106)	87.76±9.29	89 (64-100)	**0.000**§
FVC	2.35±1.01	2.26 (0.80-4.81)	3.36±0.84	3.24 (1.64-4.92)	**0.001**§
FVC%	66.57±21.22	65 (23-107)	90.68±11.13	92 (69-111)	**0.000**§
FEV1/FVC	71.05±15.14	75 (37-91.42)	82.70±5.56	81 (74-97)	**0.002**§
PEF	4.07±2.03	3.30 (1.10-8.03)	5.97±1.40	5.56 (4.03-8.90)	**0.002**§
PEF%	54.77±23.62	56.5 (16-106)	79.04±9.82	79 (62-103)	**0.000**§
Sex	**n**	**%**	**n**	**%**	***p***
Female	11	45.8	15	60	
Male	13	54.2	10	40	0.321‖

*p<0.001, † p<0.05, ‡: Mann Whitney U test, §: Independent samples t test, ‖: Chi Square test. SD: Standart deviation, BMI: Body mass index %: Percentage, FEV1: Forced expiratory volume in first second, FEV1/FVC: Tiffeneau index,FVC: Forced vital capacity, PEF: Peak expiratory flow

Table 2. Comparison of mean values (±SD) of PCF, 6MWT, and LCQ total score and subcategories between the bronchiectasis and healthy groups

Variables	Bronchiectasis group (n=24)		Healthy group (n=25)		*p*
	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	
PCF (L/m)	323.12±142.46	300 (150-700)	493.6±103.51	500 (350-750)	**0.000**†
6MWT (m)	386.02±143.06	395.78 (20-608.92)	589.41±83.58	582 (450-770)	**0.000**‡
LCQ total score	11.16±5.12	10.35 (3.89-20.09)	–	–	–
LCQ Psychosocial	3.66±1.63	3.5 (1.14-6.71)	–	–	–
LCQ Social	3.54±1.78	3.25 (1-6.5)	–	–	–
LCQ Physical	35±1.9	3.5 (1.25-6.88)	–	–	–

*p<0.001, †: Mann Whitney U test, ‡: Independent samples t test, SD: Standart deviation, PCF: Peak cough flow, 6MWT: Six minute walk test LCQ: Leicester Cough Questionnaire

Table 3. Relationship between PCF, 6MWT, LCQ total score and subcategories, duration of illness, disease severity, and dyspnea in the bronchiectasis group

Variables	PCF	
	r	*p*
6MWT (m)	0.780	**0.000**§
LCQ total score	0.885	**0.000**‡
LCQ Psychosocial	0.886	**0.000**‡
LCQ Social	0.888	**0.000**§
LCQ Physical	0.832	**0.000**‡
BSI	-0.619	**0.001**§
MMRC	-0.794	**0.000**§
Duration of illness (year)	-0.209	0.326‡

˙$p<0.05$, † $p<0.001$; PCF: Peak cough flow, 6MWT: Six minute walk test; LCQ: Leicester cough.questionnaire
BSI: Bronchiectasis severity index, MMRC:.Modified.medical research council; §: Spearman correlation coefficient
‡: Pearson correlation coefficient

Discussion

Cough is a serious problem in patients with bronchiectasis. Studies showed that the cough strength could be measured with a portable PFM in evaluating respiratory muscle strength that provides the efficiency of coughing and mucus clearance in neuromuscular diseases. However, these studies were generally used to determine the termination of mechanical ventilation in intensive care units or for follow-up in neuromuscular diseases [9, 10, 19]. No previous study evaluated cough strength using a PFM in patients with bronchiectasis. Studies on patients with bronchiectasis and other respiratory diseases were mostly conducted with questionnaires to evaluate cough frequency, severity, and sensitivity of the underlying cough reflex [6-8].

One study reported that the orally applied PFM method was an easy and accurate method of measuring cough flow because the intubation tube passed the glottis space [9]. Although the measurements were made through a mouthpiece connected to the tracheal tube, no clear information was available about the position of the patient. The participants in the present study were cooperative and had no orthopedic problems. Therefore, the measurements were made in a sitting position with the spine kept vertical, where lung ventilation could be provided under the most ideal conditions. In addition, the patients placed the instrument in their mouth after deep inspiration, and the measurement was taken with the “Cough” command, which helped capture the measurement in the expressive phase of the cough. This way we were able to catch the glottis opening immediately after closing, which suggested that the glottis factor did not affect the cough flow rate measurement result.

In addition, a significant relationship was found between exercise capacity, quality of life, mMRC, and BSI in both measurements. The data obtained from this study supported the view that the PFM provided sufficient and consistent information about cough strength in patients with bronchiectasis by measuring the cough flow rate. A study comparing cough flow velocity in healthy individuals with that in patients with neuromuscular diseases measured once using the portable PFM and then by pneumotachograph reported no large difference between the measurement results of the two devices, and that the PFM could be easily used in the clinic [13].

An inverse relationship was observed between cough strength and dyspnea and disease severity in the present study. This indicated that the cough strength decreased as the severity of the disease increased. Likewise, the cough strength decreased as the severity of dyspnea increased. No relationship between the duration of disease and cough strength was found. The reason for the lack of relationship might be factors other than the duration of the disease on the severity of the disease [20].

Studies involving field intraoral pressure measurements were used for measuring

respiratory muscle strength. Cough strength, which reflected the role of respiratory muscles more functionally and whose importance was emphasized clinically in the prevention of pulmonary complications, was not evaluated much; also, its relationship with exercise capacity was not examined. Chronic cough, sputum production, recurrent infections, and airway obstruction are common symptoms in patients with bronchiectasis [1]. Shortness of breath and fatigue are important symptoms that limit the activity of a person in daily life, and exercise capacity is also lower than expected in these patients [21].

Respiratory muscles play an important role in observing functional limitations and symptoms related to chronic respiratory diseases. The disparity between workload and capacity of the muscle, which develops due to the weakness of inspiratory muscle strength, can result in dyspnea and a decrease in exercise capacity. In the case of decreased expiratory muscle strength, effective cough is eliminated and problems related to the release of secretions occur [22, 23]. This may reduce exercise capacity in patients with bronchiectasis with increased perception of dyspnea and expiratory flow limitation [4] Symptoms such as excessive sputum production, ineffective cough with inadequate sputum discharge, dyspnea, and decreased muscle strength in patients with bronchiectasis negatively affect exercise capacity [4, 24]. Exercise tests are a key approach to evaluating the effects of treatments on function in patients. The 6MWT, evaluating exercise capacity, is the most used test. The present study found that patients diagnosed with bronchiectasis had lower exercise capacity compared with healthy individuals, and a high correlation existed with cough strength. Measuring the patient's exercise capacity is also a key approach to evaluating the effects of treatment on function. In this context, we think that using a PFM is an appropriate method in the follow-up and treatment of patients.

Like reduced exercise capacity, shortness of breath has more than one cause; possible causes include varying pulmonary mechanics, insufficient gas exchange, decreased muscle mass, and accompanying psychological morbidity [3]. Decreased exercise capacity is closely related to increased dyspnea perception scores. The vicious cycle in disease pathogenesis also manifests itself in symptoms. Increasing dyspnea limits exercise capacity and negatively affects the quality of life, whereas decreased exercise tolerance leads to a decrease in the perception threshold of dyspnea. Dyspnea is a symptom observed in patients with bronchiectasis; some studies showed that it is one of the factors affecting exercise capacity [4]. The present study showed a strong negative relationship between cough strength and dyspnea.

Quality-of-life measures can be used to facilitate communication with patients and inform them about the problems affecting them. Questionnaires can be comprehensive and disease-specific. General quality-of-life questionnaires regarding the respiratory system, for example, St. George's Respiratory Questionnaire, identify various problems affecting patients but do not evaluate the effect of cough [15]. Cough-specific, health-related quality-of-life questionnaires assess aspects of cough severity that are important to patients. They should be short, easy to implement, and well verified. The LCQ was used to evaluate coughing in previous studies. It is a symptom-specific questionnaire aiming to evaluate the physical, psychological, and social effects of chronic cough, the main symptom of bronchiectasis; its validity and reliability testing was performed in patients with bronchiectasis. It was used to evaluate cough in studies conducted on patients with bronchiectasis [16]. Therefore, the LCQ was used in the present study specifically cough. A high correlation was found between PCF and LCQ scores. Insufficient cough negatively affected exercise capacity over time because of secretion accumulation and restriction of expiratory airflow. Quality of life and exercise capacity were affected in patients with bronchiectasis with increased perception of dyspnea and limitation of expiratory flow.

Taking the patient's perspective into account when assessing the quality of life is what can enable the patient and the physician to reach a consensus on the health impact of the disease and treatment choices. In addition, an objective and correct assessment of cough may be a guiding factor in the diagnosis and treatment. Predicting pharmacological responses to antitussive therapies can provide

useful guidance for treatment. Also, a study conducted on patients with COPD reported that an increase in cough strength was achieved at the end of a 4-week rehabilitation program [25]. When looking at the issue from this angle, it can be said that cough strength can be used for the follow-up of rehabilitation programs. We think that the use of a PFM together with cough-specific quality-of-life questionnaires may be very effective in the follow-up of the disease.

The strength of our work, our study is the first study that objectively evaluates coughing in patients with bronchiectasis. Studies were mostly evaluated with questionnaires or subjective methods. In our study, we evaluated both subjectively and objectively and looked at the relationship between them. We have shown that with the PFM, clinical evaluation can be made both quickly and objectively. The limitation of our study, although our power analysis was adequate, it would be better to evaluate more patients.

In conclusions, cough strength negatively affects quality of life and exercise capacity. In addition, since the cough strength is lower than in healthy individuals, it is very important to evaluate the cough strength in patients with bronchiectasis. PFM is an easy-to-use, portable, objective, and cheap device. We have shown in our study that this can be done with the PFM. We think that a PFM is a useful tool for both physicians and physiotherapists to follow up on the patient's clinical and rehabilitation programs.

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

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Author contributions

A.Y. was responsible for drafting the manuscript. A.Y. and M.K. was responsible for Data collection and Interpretation and for drafting the manuscript. G.A. was responsible for conceptualization, funding acquisition, desing of the study, supervision and for drafting the manuscript. E.U. was responsible for data collection and Interpretation. M.M. and O.T.A. was responsible for data collection and Interpretation. H.S. was responsible for data analysis and Interpretation. All authors reviewed the article critically for important intellectual content and approved the final version to be submitted.

Research Article

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How we protected ourselves as workers in operating rooms during the Covid-19 pandemic: operating room experience for 2 years

Covid-19 pandemisinde ameliyathane çalışanı olarak kendimizi nasıl koruduk: 2 yıllık ameliyathane deneyimi

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Abstract

Purpose: Covid-19 virus is a viral disease that is transmitted quickly between people through close contact and droplets. It spread from China to the rest of the world easily and within a few months. The limited information about Covid-19 and the fact that it has changed the life routine has inevitably affected hospitals and many operating room settings, as in all parts of the countries. The aim of this article is to discuss the use of personal protection methods in our hospital, to examine the virus exposure of our personnel working in the operating room with the current protection methods in the operating room during the pandemic period lasting more than two years, and to examine and evaluate the effects of vaccination on the severity of the disease.

Materials and methods: This study was based on prospective data obtained from Pamukkale University Faculty of Medicine operating room staff between March 2020 and 2022 after receiving the approval from the Ethics Committee. The use of personal protection equipment against Covid-19 virus, exposure to the virus, vaccination status, and hospitalization status of healthcare workers in operating rooms, which is an isolated part of the hospital, were evaluated from the first period of the Covid-19 pandemic. At the same time, the groups were divided into 2 different time periods: before and after vaccination. The use of personal protective equipment, status of having Covid-19 infection, hospitalizations due to the virus, symptoms in case of illness, vaccination status and the number of vaccine doses were examined. During this time, people who were dismissed from the hospital were excluded from the study.

Results: Data were collected at 2 different time points as before and after the vaccination of healthcare workers. Demographic data, personal protective equipment use, Covid-19 positivity and negativity and symptoms of 144 participants were analyzed at two different time points. It has been found in many different analyses that women are better protected than men, but also that the protection of anesthesiologists is higher than other groups. Hospitalizations were very rare in operating room staff and they did not have severe symptoms. Finally, there was a significant decrease in symptoms and their severity after vaccination.

Conclusion: In conclusion this study revealed the fact that operating rooms are the most important places where precautions should be taken during pandemics. This study aims to shed light on the protection of operating room staff during possible future outbreaks.

Keywords: Covid-19, operating room, personal protective equipment.

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Öz

Amaç: Covid-19 virüsü, insanlar arasında yakın temas ve damlacık yoluyla hızla bulaşan viral bir hastalıktır. Çin'den dünyanın geri kalanına kolayca ve birkaç ay içinde yayılmıştır. Covid-19 hakkındaki sınırlı bilgi ve hayatın rutinini değiştirmiş olması, ülkelerin her yerinde ve her bölümünde olduğu gibi ister istemez hastaneleri ve birçok ameliyathane ortamını da etkilemiştir. Bu makalenin amacı, hastanemizde kişisel korunma yöntemlerinin kullanımını ele almak, iki yılı aşkın süren pandemi döneminde ameliyathanede çalışan personelimizin güncel korunma yöntemleri ile ameliyathanede virüs maruziyetini ve aşılamanın hastalık şiddeti üzerindeki etkilerini incelemek ve değerlendirmektir.

Gereç ve yöntem: Bu çalışma, Etik Kurul onayı alındıktan sonra Mart 2020-2022 tarihleri arasında Pamukkale Üniversitesi Tıp Fakültesi ameliyathane personelinden elde edilen prospektif verilere dayalıdır. Hastanenin izole bir bölümü olan ameliyathanelerde sağlık çalışanlarının Covid-19 virüsüne karşı kişisel koruyucu ekipman kullanımı, virüse maruz kalma durumları, aşılanma durumları ve hastanede yatış durumları Covid-19'un ilk döneminden itibaren değerlendirildi. Aynı zamanda gruplar aşılama öncesi ve aşılama sonrası olmak üzere 2 farklı zaman dilimine ayrıldı. Kişisel koruyucu ekipman kullanımı, Covid-19 enfeksiyonu geçirme durumu, hastalık durumunda belirtileri, hastaneye yatışları, aşılanma durumu ve aşı doz sayısı incelendi. Bu süre içinde hastanede işine son verilen insanlar çalışma dışı bırakıldı.

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Bulgular: Veriler sağlık çalışanlarının aşılanması öncesi ve sonrası olmak üzere 2 farklı zaman noktasında toplanmıştır. 144 katılımcının demografik verileri, kişisel koruyucu ekipman kullanımı, Covid-19 pozitifliği/negatifliği ve semptomları iki farklı zaman aralığında analiz edildi. Kadınların erkeklere göre anestezistlerin de diğer gruplara göre daha fazla korunduğu bulundu. Ameliyathane personelinde hastaneye yatışlar çok nadirdi ve ciddi semptomlar yoktu. Son olarak, aşılamadan sonra semptomlarda ve şiddetinde önemli bir azalma oldu.
Sonuç: Bu çalışma, pandemi döneminde önlem alınması gereken önemli yerlerin başında ameliyathanelerin de olduğunu ortaya koymuştur. Bu çalışma olası salgınlar sırasında ameliyathanede çalışan personelin korunmasına yönelik fikir verebilir.

Anahtar kelimeler: Covid-19, ameliyathanelerde korunma, kişisel korunma ekipmanları.

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Introduction

The new Coronavirus disease (Covid-19) emerged in Wuhan, China in December 2019 and a pandemic was declared by the World Health Organization in January 2020. Covid-19 virus causes a viral disease that spreads rapidly between individuals through close contact and droplets. The rapid spread of the virus from China to the whole world had occurred easily within a few months [1]. The scarcity of knowledge about Covid- 19 and its impact on daily life eventually impacted every location and subdivision of government, particularly hospitals and many operating room setups. The priorities of the transactions and the way they are performed have been necessarily changed. The priority was to protect healthcare workers and to heal patients diagnosed with Covid-19 both in the service and intensive care units. During this chaotic time, the order of the operating rooms had to be altered and all priorities changed. Managing employees and work environments during emergencies such as disasters or epidemics is challenging and expensive. Many details that need to be considered have entered our lives with the Covid-19 epidemic and “the new normal” expression has been added to our literature [2]. Again, the order of resource use in epidemic management has been a challenging condition for medical personnel health and structure, as well as freshly acquired principles and details [3]. To cope with the expected increasing number of Covid-19 patients, the entire world has turned to limiting the number of elective surgeries [4]. Among healthcare employees, operating room workers, particularly anesthesiologists, face substantial risks. Airway manipulation and close contact with the patient, and the fact that emergencies often occur in operating theaters, put operating room employees at a greater risk than other healthcare professionals [5]. The importance of personal protective equipment is also essential for those working in this field. Personal protection equipment (PPE) used to prevent contact includes gloves, gowns, a N95 or higher grade respirator, and a full face shield or goggles. Face masks are recognized worldwide as an acceptable alternative when respirators are not available [6]. The importance of vaccination in the Covid-19 pandemic process, which has been going on for about 3 years, has been stated by many authors [7]. In our country, vaccination of healthcare workers started on January 14, 2021. Exposure to corona virus after vaccination reduced the severity of the disease. The purpose of this article is to talk about the use of personal protection methods in our hospital and to examine the virus exposure of our healthcare personnel working in the current prevention and operating room during the pandemic period. Another aim was to evaluate the effects of the vaccination status of the employees on the severity of the disease.

Material and methods

This study was conducted with Pamukkale University Faculty of Medicine operating room staff between 16 March 2020 and 16 March 2022. The study, which was started after the approval of Pamukkale University Non-Interventional Clinical Research Ethics Committee, was based on the data obtained prospectively. The use of personal protection equipment against the Covid-19 virus, exposure to the virus, vaccination status, and hospitalization status of the healthcare workers in the operating rooms, which is an isolated part of the hospital, were assessed beginning with the first phase of the pandemic. In the study, the employees were divided into 4 groups: Group 1

consists of anesthesiologists, Group 2 consists of anesthesia technicians, Group 3 consists of operating room nurses and Group 4 consists of operating room assistants. Simultaneously, the timeline between groups was split into two distinct time periods: before and after vaccination. The use of personal protective equipment, status of Covid-19 infection, hospitalizations due to the virus, symptoms in case of illness, vaccination status and doses were examined. Those who stopped working at the hospital during this period were excluded from the study.

Statistical method

Within the scope of the research, first of all, demographic findings and frequency analyzes of the participants were shared. Then, independent samples T-test, one-way analysis of variance (ANOVA) and correlation analyzes were performed, respectively. The findings of the relevant analyzes are also shared respectively.

Results

The findings of the study were obtained by analyzes at 2 different times. Data were collected at 2 different times, before and after the vaccination of healthcare workers in our country. Demographic findings in the first time period are shown in Table 1. According to Table 1, it is seen that the 144 participants participating in the research show an almost equal distribution in terms of gender and title. 23.6% of the participants were identified as Covid-19 positive cases. The average age of the participants is 34. The level of protection was 2.77, slightly above the average in the 5-point Likert type. The frequency analyzes of the demographic characteristics of the study participants who are positive for Covid-19 and their symptoms are presented in Table 2. 34 of the 144 participants in the study were Covid positive. The majority of the positive individuals were anesthesiologists and operating room personnel. The average age is 32 and 7.6% of those who tested positive for Covid-19 were hospitalized. The level of protection was 2.73 in the 5-point Likert type. When the symptoms of these 34 participants were examined, it was seen that the most common complaints were fever, cough, loss of taste, headache and muscle pain, respectively. The least complaints were determined as chest pain, diarrhea, shortness of breath and nausea, respectively. Independent Samples T-Test was applied to examine whether the protection levels differ according to the categorical variables within the scope of the research. Table 3 and Table 4 include the T-test findings performed to examine the differences in terms of hospitalization variable. Table 3 shows the average values of the protection levels of the participants according to gender. Accordingly, while the average value of women is 3.09, the average value of men is 2.42. When Table 4 is examined, it is concluded that the level of protection of women is statistically significantly different than that of men (p<0.05). Accordingly, women are more protected than men. However, if p>0.05 as a result of Levine's equality of variance test, the variance is considered to be equally distributed. Accordingly, it was concluded that the variance in the examined variable was not evenly distributed. When Table 5 is examined, it is concluded that the level of protection of the patients does not differ statistically according to the status of hospitalization (p<0.05). If the p value is greater than 0.05 as a result of the Levine equality of variance test, the variance is considered to be equally distributed. Accordingly, it was concluded that the variance in the examined variable was equally distributed. Table 6 demonstrates the average values of the protection levels of individuals with and without Covid-19. Accordingly, the average of those with and without Covid-19 is 2.73 and 2.78, respectively. In the study, the protection levels of the participants differed according to the title (Anesthesiologist, Technician, nurse, staff). The Sheff Test was used to determine from which categories this differentiation was originated. The results of the Scheffe Analysis show that anesthesiologists are significantly different from nurses and staff. Accordingly, anesthesiologists have a higher level of protection than nurses and staff.

Technicians and nurses are more protected than operating room personnel. Correlation analysis was performed to examine the relationship between age and the level of protection. A negative and weak correlation was found between the age variable and the level of protection. This means that as age increases, the level of protection decreases. Table 7 summarizes the results in the procedure following the delivery of vaccines to healthcare personnel. According to this information, the 154 individuals

have a nearly equal distribution based on their title. 38.3% of the participants were identified as Covid-19 positive cases. The hospitalization rate of the participants was very low, at 0.6. When the vaccination status of the participants is examined, it is seen that the majority of them received 4 vaccinations consisting of 2 Sinovac and 2 Biontech vaccines. However, the majority of the participants preferred the surgical mask instead of N95. If we examine the frequency distribution of the symptoms of Covid-19 positive health personnel; the majority of the positive ones are anesthesiologists and nurses. The distribution is 23 (39%) anesthesiologists, 16 (27.1%) nurses, 13 (22%) operating room personnel, and 7 (11.9%) anesthesia technicians. When the vaccination status of the participants is examined, it is seen that the vast majority (96.6%) have 4 vaccines (2 Sinovac + 2 Biontech). It has been determined that patients with only 2 Biontech vaccines (3.4%) have Covid-19 infection more rarely than those who have 4 vaccines. This situation may also be related to the characteristics of the research sample. It was determined that the preferred type of mask for protection was the surgical mask (79.7%). The hospitalization rate for those who are positive after vaccination is 1.7%. When the symptoms of 59 participants were examined, the most common complaints were muscle pain (39%), headache (35.6%), cough (27.1%), fever (23.7%) and loss of taste (11.9%). The least common complaints were determined as chest pain, shortness of breath, nausea and diarrhea, respectively.

Table 1. Frequency distribution regarding the demographic characteristics of the participants

Variable	Category	Frequency	%
Gender	Woman	74	51.4
	Man	70	48.6
Title	Doctor	35	24.3
	Technician	23	16.0
	Nurse	43	29.9
	Operating Room Staff	43	29.9
Positive/Negative	Positive	34	23.6
	Negative	110	76.4
	n	**Mean**	**Standard deviation**
Age	144	34.26	7.174
Protection levels	144	2.7708	.74532

Table 2. Frequency distribution of the symptoms of Covid 19 positives

Variable	Category	Frequency	%
Gender	Woman	15	44.1
	Man	19	55.9
Title	Doctor	11	32.4
	Technician	4	11.8
	Nurse	8	23.5
	Operation Room Staff	11	32.4
Hospitalization	Yes	6	17.6
	No	28	82.4
Cough	Yes	32	94.1
	No	2	5.9
Headache	Yes	26	76.5
	No	8	23.5
Fever	Yes	33	97.1
	No	1	2.9
Shortness of breath	Yes	6	17.6
	No	28	82.4
Muscle Pain	Yes	25	73.5
	No	9	26.5
Nausea	Yes	7	20.6
	No	27	79.4
Diarrhea	Yes	4	11.8
	No	30	88.2
Loss of Taste	Yes	32	94.1
	No	2	5.9
Chest Pain	Yes	3	8.8
	No	31	91.2
	n	**Mean**	**Standard deviation**
Age	34	32.56	5.333
Protection levels	34	2.7353	.86371

Table 3. Group statistics for gender

Variables	Gender	N	Mean	Standard deviation
Protection levels	Woman	74	3.0946	.60066
	Man	70	2.4286	.73369

Table 4. Independent samples T-test results for gender variable

Variables	Variance distribution	Levene's Equation of Variance Test		T-test			
		F	*p*	t	df	*p*	o.difference
Protection Level	Assuming equal variance	10.983	.001	5.974	142	.000	.66602
	When Variance Is Not Assumed Equal			5.942	133.505	.000	.66602

Table 5. Independent samples T-test findings for hospitalization or not

Variables	Variance distribution	Levene's Equation of Variance Test		T-test			
		F	*p*	t	df	*p*	o.difference
Protection Level	Assuming equal variance	.980	.324	-.349	142	.728	-.10870
	When Variance Is Not Assumed Equal			-.255	5,223	.808	

Table 6. Group statistics for Covid-19 positive and negative variable

Variables	Covid 19	N	Mean	Standard deviation
Protection Level	Positive	34	2.7353	.86371
	Negative	110	2.7818	.70881

Table 7. Frequency distribution of the participants' demographic characteristics in the post-vaccination timeframe

Variable	Category	Frequency	%
Title	Doctor	45	29.2
	Technician	23	14.9
	Nurse	43	27.9
	Operation Room Staff	43	27.9
Positive/Negative	Positive	59	38.3
	Negative	95	61.7
Hospitalization	Yes	1	0.6
	No	153	99.4
Vaccination Status	2 Sinovac+2 Biontech	129	83.8
	2 Biontech	25	16.2
Mask Usage Status	N95 mask	18	11.7
	Surgical mask	136	88.3

Discussion

Pandemics have required innovations in work environments. With the Covid-19 pandemic, working procedures in operating rooms, as in many other areas, have altered, and awareness of employees have been concentrated on protection [8]. In a study in which the level of personal protection was assessed with a survey for health workers during the Covid-19 pandemic, more than 60% of the 358 participants stated that they dreaded of being exposed in hospitals [9]. In the studies in which many precautions were emphasized with the Covid-19 epidemic in operating rooms, the priority was to protect healthcare workers, however, the initiation times of elective surgeries were prolonged [10, 11]. From the beginning of the epidemic, the first priority in this study was the supply and use of personal protection equipment of operating room personnel. Anesthesiologists battled at the front lines both in operating rooms and in intensive care units during the pandemic [12]. As seen in the results of this study, personal protection rates are high among anesthesiologists. However, due to the frequency of dealing with the airway, anesthesiologists were among those who were most vulnerable to the Corona virus. Many studies on the subject have recommended the use of personal safety devices, particularly for operating room personnel [8-11]. In the analyzes performed in this study, the rates of protection were found to be high in our operating room. If we consider the first phase of the study as the period when vaccines are not yet in use, 34% of the operating room workers were Covid positive in the first period and 17.6% of the workers were hospitalized. Although there are not many publications in the literature on this subject, virus exposure is not only related to working in the operating room. Because the majority of the workers were believed to have been in the same rooms as the patients in various locations throughout the hospital, and they may have encountered individuals who had the virus in their social activities. Many symptoms mentioned in the Covid-19 studies in the literature [13] were also seen in many employees in this study. The most prevalent symptoms in Covid positive employees in this research were fever, cough, loss of flavor, headache, and muscle pain. In the United States, it was decided on January 1, 2021 that healthcare personnel should be vaccinated first and put on paid administrative leave in case of adverse effects [14]. In our country, Covid-19 vaccination was started on January 14, 2021 and priority was given to healthcare workers [15]. Vaccines were administered to all operating room staff as of the vaccination date in this study, and Covid-19 positivity rates were assessed after this time. In the study group, the highest rate of positivity was found in anesthesiologists. The studies have also stated the importance of having the necessary number of personnel to reduce the virus circulation in the operating room, the importance of the airway and the importance of an anesthesiologist in critical situations, and the fact that the majority of the exposure to the virus is to anesthesiologists during the Covid pandemic [16]. However, many studies emphasize that hospitalization rates are reduced in patients after vaccination [17, 18]. Similar results were also found in this research, and hospitalization rates were found to be significantly lower compared to first phase.

In conclusion, the fact that operating rooms are at the top of the list of locations where precautions must be taken during epidemics has come to light. It has been stated in the literature that operating rooms and the anesthesiologists in charge of these positions should be protected, and that employees with a poor level of education should be trained in terms of personal protection [19]. With this research, we expect that the methods used in operating rooms during the pandemic time will serve as a model for future studies. We believe that it can also shed light on the approaches in unexpected epidemic situations that may be experienced in the future.

Among the limitations of this study, variability due to sample difference can be counted. However, since it is a long-term study, the change in the number of staff in the operating room is not thought to change the results, but it can still be a limitation.

Conflict of interest: There was no conflict of interest among the authors in this study.

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Authors' contributions to the article

A.M.Y. constructed the main idea and hypothesis of the study. A.M.Y. and I.H.A. developed the theory and arranged/edited the material and method section. A.M.Y., I.H.A., S.K. and H.S. have done the evaluation of the data in the Results section. Discussion section of the article written by A.M.Y., I.H.A., S.K. and H.S. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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Relationship between CONUT score and mortality in patients with pulmonary arterial hypertension

Pulmoner arteriyel hipertansiyonlu hastalarda nütrisyonel durum kontrolü (CONUT) skorunun mortalite ile ilişkisi

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Abstract

Purpose: Data about the association of malnutrition with prognosis in pulmonary arterial hypertension (PAH) is limited. This study aims to evaluate the relationship of Controlling Nutritional Status (CONUT) score with long-term mortality in PAH.

Materials and methods: All consecutive patients newly diagnosed with PAH between 2013 and 2020 were evaluated. CONUT score at diagnosis was calculated through total lymphocyte, albumin and total cholesterol levels. Primary outcome was long-term all-cause mortality. Patients were followed up for 62 (31.3-91.5) months.

Results: 92 patients (mean age=43.9±15.7 years, 65.2% women) were included. 37% of the patients had any degree of malnutrition according to CONUT score (≥2). Patients without malnutrition were significantly more in the low-risk categories of risk stratification tools (44.8% vs 17.6% according to ESC/ERS guideline, *p*=0.03; 70.7% vs 35.3% and 70.7% vs 32.4% according to REVEAL 2.0 and REVEAL Lite 2, *p*<0.01 for both). In multivariate analysis, CONUT score predicted all-cause mortality (HR:1.51, 95% CI:1.01-1.52, *p*=0.03) independently after adjustment with ESC/ERS guideline risk score.

Conclusion: CONUT score is independently associated with worse outcome in PAH patients and may indicate severe disease in this patient group.

Keywords: Pulmonary arterial hypertension, malnutrition, controlling nutritional status score, mortality.

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Öz

Amaç: Birçok kronik hastalıkta olumsuz sonuçlarla ilişkili olduğu gösterilen malnütrisyonun, pulmoner arteriyel hipertansiyonda (PAH) prognoz ile ilişkisi net değildir. Bu çalışmada, PAH hastalığında Nütrisyonel Durum Kontrolü (CONUT) skoru ile uzun dönem mortalite arasındaki ilişkiyi değerlendirmeyi amaçladık.

Gereç ve yöntem: 2013 ve 2020 tarihleri arasında PAH tanısı alan tüm ardışık hastalar retrospektif olarak incelendi. Tanı anındaki CONUT skoru; toplam lenfosit sayısı, albümin ve total kolesterol düzeyleri ile hesaplandı. Birincil sonlanım uzun dönem tüm nedenlere bağlı mortalite olarak belirlendi. Hastalar 62 (31,3-91,5) ay takip edildi.

Bulgular: Çalışmaya 92 hasta dahil edildi. Ortalama yaşı 43,9±15,7 olan hasta grubunun %65,2'si kadındı. Hastaların %37'sinde CONUT skoruna göre herhangi bir derecede malnütrisyon mevcuttu (CONUT skoru ≥2). Malnütrisyon tespit edilmeyen hastalar, risk değerlendirme skorlarına göre düşük risk kategorisinde anlamlı olarak daha fazla yer almaktaydı (ESC/ERS kılavuzu risk skorlama sistemine göre %44,8'e karşı %17,6, *p*=0,03; REVEAL 2.0 risk sınıflamasına göre %70,7'ye karşı %35,3, *p*<0,01; REVEAL Lite 2 risk sınıflamasına göre %70,7'ye karşı %32,4, *p*<0,01). Çok değişkenli analizde, ESC/ERS kılavuzu risk skoru ile düzeltme yapıldıktan sonra, CONUT skoru (HR:1,51, 95% CI:1,01-1,52, *p*=0,03) uzun dönem tüm nedenlere bağlı mortaliteyi bağımsız olarak öngördürmekteydi.

Sonuç: CONUT skoru, PAH'lı hastalarda kötü prognoz ile ilişkilidir ve bu hasta grubunda hastalığın şiddetini gösterebilir.

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Anahtar kelimeler: Pulmoner arteriyel hipertansiyon, malnütrisyon, nütrisyonel durum kontrolü skoru, mortalite.

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Introduction

Progressive remodelling of the pulmonary vasculature and increased pulmonary vascular resistance that eventually leads to right heart dysfunction and death characterize pulmonary arterial hypertension (PAH) [1]. Despite advances in medical therapy, PAH still carries a high morbidity and mortality burden.

Malnutrition is associated with poor prognosis in many chronic diseases. PAH patients are prone to malnutrition due to various disease-related factors [2, 3]. Despite this, role of nutritional status in PAH is unclear since there are few studies on this subject [4-6]. The Controlling Nutritional Status (CONUT) score was developed to assess nutritional status of hospitalized patients by Ignacio de Ulíbarri et al. [7]. It is calculated through serum albumin concentration (as an indicator of protein reserve and inflammation), total cholesterol (TC) level (as a parameter of caloric depletion and inflammation) and total lymphocyte count (TLC, as a parameter reflecting immune system). Since then malnutrition defined by CONUT score was evaluated in various diseases and shown to be associated with prognosis. To our knowledge, there are no studies about CONUT score in patients with PAH in the literature. Therefore, we aimed to evaluate the relationship of CONUT score with prognosis in PAH patients.

Materials and methods

Study design and participants

We retrospectively evaluated all consecutive incident patients with PAH in our hospital between 01.2013 and 01.2020. PAH was diagnosed in patients with mean pulmonary artery pressure ≥25 mm Hg, pulmonary arterial wedge pressure ≤15 mm Hg and pulmonary vascular resistance >3 Wood unit measured during right heart catheterization at rest based on the valid guidelines at the time of diagnosis [1]. Patients <18 years of age; pulmonary hypertension patients other than group 1; patients with estimated glomerular filtration rate <60 ml/min/1.73 m^2, hepatic diseases, hematological or other malignancies; patients that were on antilipidemic drug therapy and patients without essential laboratory data for the assessment of CONUT score at diagnosis were excluded from the study. Permission was obtained from the local ethics committee and the study conformed to the principles in the Declaration of Helsinki.

Demographical, clinical, biochemical, echocardiographic and invasive hemodynamic data at the time of diagnosis were collected from medical records of the patients.

CONUT score

CONUT score was evaluated from TLC, serum albumin and TC levels of the patients. Each parameter was categorized into four groups and scores were assigned according to the levels of the patients' test results (Figure 1). Then CONUT score was calculated as the sum of scores taken from three parameters. Scores of 0 and 1 reflected normal patients. Scores of 2 to 4 and ≥5 indicated mild and moderate-severe malnutrition, respectively [7]. Patients were grouped into two according to presence of any degree of malnutrition (CONUT score <2=Normal patients, CONUT score ≥2=Patients with Malnutrition).

Parameters	Degree of Malnutrition			
	Normal	Mild	Moderate	Severe
Serum albumin (g/dL)	≥3.5	3-3.49	2.5-2.99	<2.5
Score	0	2	4	6
Total lymphocyte count (x10^9/L)	≥1.6	1.2-1.59	0.8-1.19	<0.8
Score	0	1	2	3
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3

Figure 1. Calculation of the Controlling Nutritional Status (CONUT) score

PAH risk assessment

Disease severity at the time of diagnosis was defined using several PAH risk assessment tools: Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) Lite 2, REVEAL 2.0 and 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline.

REVEAL Lite 2 score was evaluated using World Health Organization-functional class (WHO-FC), N-terminal pro-brain natriuretic peptide (NT-proBNP), six-minute walking distance (6MWD), estimated glomerular filtration rate, systolic blood pressure and heart rate. REVEAL 2.0 score was assessed using REVEAL Lite 2 variables, etiology, demographics, pericardial effusion, right atrial pressure and pulmonary vascular resistance [8, 9].

ESC/ERS PAH guideline risk score was calculated using available variables; WHO-FC, NT-proBNP, 6MWD, right atrial area, pericardial effusion, right atrial pressure and cardiac index [1].

Then according to calculated risk scores, patients were categorized into low-, intermediate- or high-risk categories.

Outcome and follow-up

The primary outcome was all-cause mortality. Patients were followed up since the diagnosis of PAH. After diagnosis, all patients received guideline-directed optimal PAH-specific drug therapy. None of the patients received lung or lung-heart transplant during follow-up. Dates of death were obtained from medical records.

Statistical analysis

Distribution of the data was determined by Shapiro-Wilk test. Continuous data were presented as mean±standard deviation or median (interquartile range) and categorical data were presented as numbers (percentages). Student's *t*-test or Mann-Whitney *U* test was used to compare continuous data, as appropriate. Categorical data was compared using x^2 or Fisher's exact test, as appropriate. Correlates of CONUT score was defined by Pearson's correlation coefficient (r). Predictors of long-term all-cause mortality was identified with multivariate Cox regression analysis. The results were presented as hazard ratios (HR) and 95% confidence intervals (CI). Survival probabilities of the groups with and without malnutrition were graphically presented with Kaplan-Meier survival curves and compared with log-rank test. Two-tailed *p*-values <0.05 were considered statistically significant. All analyses were performed using R 4.02 software (R Foundation for Statistical Computing, Vienna, Austria) with ''ggplot'' and ''rms'' packages.

Results

A total of 92 patients were included in the study. 65.2% of the patients were women and the mean age of the participants was 43.9±15.7 years. 34 patients had idiopathic PAH (37%), 14 patients had connective tissue disease-associated PAH (15.2%) and 44 patients had congenital heart disease-associated PAH (47.8%). Characteristics of the study group are represented in Table 1 and 2.

Table 1. Baseline clinical characteristics of the study population according to CONUT score

Variables		All (n=92)	Normal (CONUT score <2) (n=58)	Malnutrition (CONUT score ≥2) (n=34)	*p* value
Age (years)		43.9±15.7	42.8±16	45.9±15.1	0.36
Female		60 (65.2)	36 (62.1)	24 (70.6)	0.41
Etiology					
Idiopathic PAH		34 (37)	25 (43.1)	9 (26.5)	0.28
CTD-APAH		14 (15.2)	8 (13.8)	6 (17.6)	
CHD-APAH		44 (47.8)	25 (43.1)	19 (55.9)	
Comorbidities					
Hypertension		21 (22.8)	13 (22.4)	8 (23.5)	0.90
Diabetes Mellitus		12 (13)	7 (12.1)	5 (14.7)	0.72
Atrial Fibrillation		18 (19.6)	8 (13.8)	10 (29.4)	0.07
Body Mass Index (kg/m^2)		24.6±5.8	24.8±5.4	24.7±6.5	0.99
Systolic Blood Pressure (mmHg)		131±29	133±25	136±33	0.66
Diastolic Blood Pressure (mmHg)		75±11.5	78±12	75±13	0.18
Heart rate (beats/min)		86±14	86±13	86±17	0.94
WHO functional class	II	52 (56.5)	39 (67.2)	13 (38.2)	**0.007**
	III-IV	40 (43.5)	19 (32.8)	21 (61.8)	
6MWD (meters)		366±128	402±105	299±142	**<0.001**
ESC/ERS guideline risk assessment tool	low	32 (34.8)	26 (44.8)	6 (17.6)	**0.03**
	intermediate	56 (60.9)	30 (51.7)	26 (76.5)	
	high	4 (4.3)	2 (3.4)	2 (5.9)	
REVEAL 2.0 risk assessment tool	low	53 (57.6)	41 (70.7)	12 (35.3)	**0.003**
	intermediate	16 (17.4)	6 (10.3)	10 (29.4)	
	high	23 (25)	11 (19)	12 (35.3)	
REVEAL Lite 2 risk assessment tool	low	52 (56.5)	41 (70.7)	11 (32.4)	**0.002**
	intermediate	15 (16.3)	6 (10.3)	9 (26.5)	
	high	25 (27.2)	11 (19)	14 (41.2)	
PAH-specific treatment					
Combination treatment		61 (66.3)	37 (63.8)	24 (70.6)	0.50
Long-term mortality		24 (26.1)	13 (22.4)	11 (32.4)	0.29

Categorical data are presented as numbers (percentages) and continuous data are presented as mean ± standart deviation and median (interquartile range), as appropriate, CHD-APAH= Congenital heart disease-associated pulmonary arterial hypertension
CONUT= Controlling nutritional status, CTD-APAH= Connective tissue disease-associated pulmonary arterial hypertension
ESC/ERS= European Society of Cardiology/European Respiratory Society, PAH= pulmonary arterial hypertension
REVEAL= Registry to Evaluate Early and Long-Term PAH Disease Management, 6MWD= 6-minute walking distance
WHO= World Heart Organization. Bold *p* values indicate statistical significance

Table 2. Baseline laboratory, echocardiographic and hemodynamic parameters of the study group according to CONUT score

Variables	All (n=92)	Normal (CONUT score <2) (n=58)	Malnutrition (CONUT score ≥2) (n=34)	*p* value
Laboratory parameters				
Neutrophil (x10^9/L)	4.8±1.6	4.6±1.6	5±1.5	0.29
Lymphocyte (x10^9/L)	2.1±0.8	2.4±0.7	1.6±0.8	***<0.001***
Monocyte (x10^9/L)	0.5±0.2	0.6±0.2	0.5±0.2	0.43
Hemoglobin (g/dL)	14.1±2.4	14.3±2.4	13.4±2.2	0.10
Glucose (mg/dL)	97.3±26.3	92.1±16.3	105.9±36	***0.01***
Creatinine (mg/dL)	0.8±0.2	0.8±0.2	0.8±0.2	0.73
Estimated GFR (ml/min/1.73m^2)	99.8±21.9	101.2±19.6	97.9±25.2	0.48
Total cholesterol (mg/dL)	169±34	184±29	145±29	***<0.001***
Aspartate transaminase (IU/L)	25.1±11.6	24±8.4	26.9±14.9	0.24
Alanine transaminase (IU/L)	22.3±13.6	22.1±12.6	23.1±14.5	0.70
Albumin (g/dL)	4.2±0.5	4.3±0.3	3.9±0.6	***<0.001***
NT-proBNP (pg/mL)	179 (80-480)	119 (48-342)	313 (99-1106)	***0.02***
C-reactive protein (mg/dL)	0.6 (0.2-1.6)	0.4 (0.1-1.1)	1.2 (0.3-2.8)	***0.01***
Echocardiographic parameters				
Right atrial area (cm^2)	21.1±7.2	20.7±8.1	22±5.9	0.43
RV basal diameter (mm)	43.9±9.4	41.7±12.4	45.1±6.4	0.15
TAPSE (mm)	18.4±4.8	18.7±4.3	17.8±4.9	0.34
RV S' velocity (cm/s)	10.7±2.6	11±2.5	9.6±2.6	***0.01***
sPAP (mm Hg)	80±26.7	80.3±27	79.2±26.8	0.84
Inferior vena cava (mm)	19.4±5.3	19.1±5.8	20.4±5.1	0.26
Pericardial effusion	14 (15.2)	5 (8.6)	9 (26.5)	***0.02***
Hemodynamic parameters				
RAP (mm Hg)	10 (7-17)	10 (7-15)	12 (6.8-17.3)	0.64
mPAP (mm Hg)	52±17.5	47±17.3	54.7±17.2	0.23
PAWP (mm Hg)	10 (8-12)	10 (7.5-14)	10 (8.8-12)	0.74
PVR (Wood units)	11 (4.8-19)	8 (5-15.2)	13 (4.3-20)	0.15
Cardiac index (L/min/m^2)	2.2 (1.6-2.7)	2.5 (1.7-3.2)	2.1 (1.6-2.6)	0.11

Categorical data are presented as numbers (percentages) and continuous data are presented as mean ± standart deviation and median (interquartile range), as appropriate, CONUT= Controlling nutritional status, GFR= Glomerular filtration rate
mPAP= mean pulmonary artery pressure, NT-proBNP= N-terminal pro-brain natriuretic peptide, PAWP= pulmonary arterial wedge pressure PVR= pulmonary vascular resistance, RAP= right atrial pressure, RV= Right ventricular
RV S' velocity= Tissue Doppler-derived tricuspid lateral annular systolic velocity
sPAP= systolic pulmonary artery pressure, TAPSE= Tricuspid annular plane systolic excursion
TR= Tricuspid regurgitation, Bold *p* values indicate statistical significance

The prevalence of patients with any degree of malnutrition (CONUT score ≥2) was 37% (n=34). Moderate-to-severe malnutrition (CONUT score ≥5) was encountered in 5.4% (n=5). Demographical variables, PAH etiologies and comorbidities did not differ in patients with and without malnutrition. Body mass indexes of the groups were also similar. Presentation with WHO-FC III-IV was observed more in patients with malnutrition (61.8% vs 32.8%, p<0.01). Significantly shorter 6MWD was found in malnutrition (+) group (299±142 vs 402±105 meters, p<0.001). Patients without malnutrition were significantly more in the low-risk categories of the risk stratification tools at the time of diagnosis (44.8% vs 17.6%, p=0.03 according to ESC/ERS guideline; 70.7% vs 35.3%, p<0.01 according to REVEAL 2.0 and 70.7% vs 32.4%, p<0.01 according to REVEAL Lite 2).

Regarding laboratory parameters, patients with malnutrition had significantly lower levels of the parameters used to calculate CONUT score (TLC, TC and albumin levels). Besides that, they had significantly higher levels of fasting blood glucose, NT-proBNP and C-reactive protein levels.

In echocardiographic examination, pericardial effusion was encountered more in malnutrition (+) group and they had significantly lower tricuspid lateral annular peak systolic velocity than patients without malnutrition. Other echocardiographic parameters and invasive hemodynamic parameters at diagnosis were similar among groups.

CONUT score was negatively correlated with 6MWD (r=-0.398, p<0.001), tricuspid lateral annular peak systolic velocity (r=-0.237, p=0.024) and positively correlated with ESC/ERS (r=0.247, p=0.018), REVEAL 2.0 (r=0.312, p=0.002) and REVEAL Lite 2 risk scores (r=0.369, p<0.001), NT-proBNP (r=0.279, p=0.007) and C-reactive protein (r=0.494, p<0.001).

Mortality occured in 24 (26.1%) patients in the follow-up period of 62 (31.3-91.5) months. Survival rate were 67.6% and 77.6% in malnourished and normal patients, respectively. Kaplan-Meier curves demonstrated a trend towards lower survival among patients with malnutrition without reaching statistical significance (Figure 2). Multivariate analysis (Table 3) revealed that CONUT score, as a continuous variable, is an independent predictor of all-cause mortality (HR:1.51, 95% CI:1.01-1.52, p=0.03) after adjustment with ESC/ERS risk score (HR:6.9, 95% CI:2.4-19.9, p<0.001).

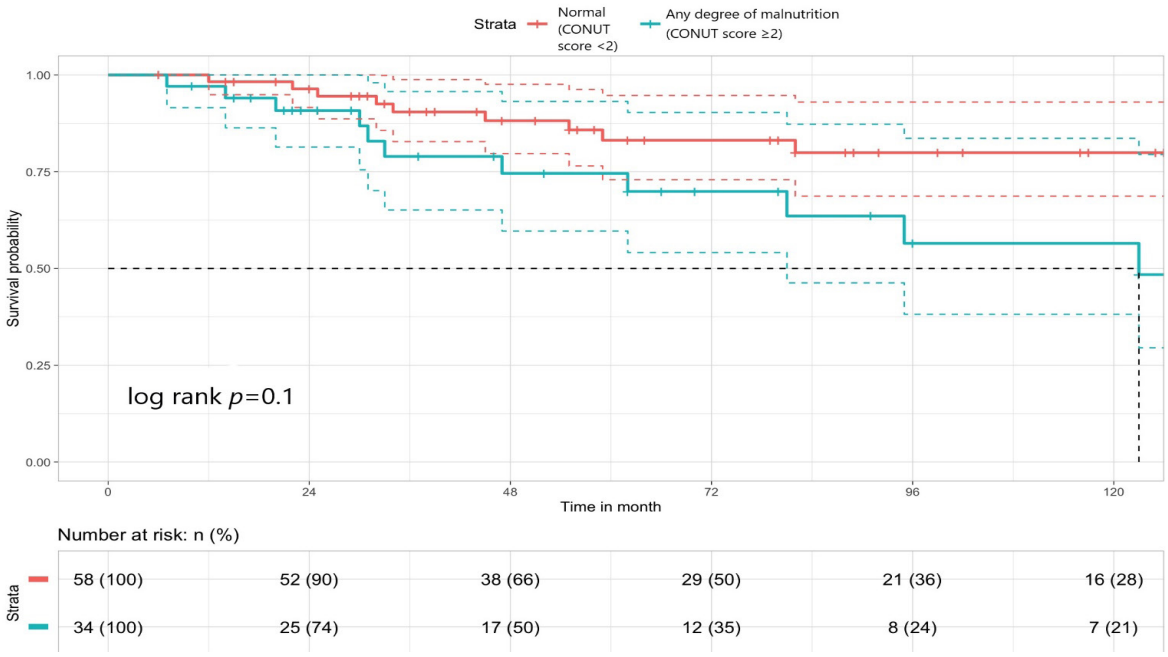

Figure 2. Kaplan-Meier curves for all-cause mortality by the Controlling Nutritional Status (CONUT) score

Table 3. Multivariable Cox regression analysis to predict all-cause mortality

Variables	Hazard Ratio	95% CI	*p* value
ESC/ERS risk score	6.95	2.4-19.9	<0.001
*CONUT, continuous (increase from 0 to 2)	1.51	1.01-1.52	0.03
*Age (increase from 32 to 56)	1.79	0.90-3.53	0.09
*eGFR (increase from 91 to 114)	1.08	0.66-1.78	0.76

*Adjusted with European Society of Cardiology/European Respiratory Society (ESC/ERS) risk score; CI= Confidence interval
CONUT= Controlling nutritional status; eGFR= estimated glomerular filtration rate; Bold *p* values indicate statistical significance

Discussion

Our main findings were: (1) Any degree of malnutrition assessed with CONUT score was observed in 37% of PAH patients, (2) CONUT score predicts long-term all-cause mortality in PAH, (3) CONUT score was related with parameters and risk scores indicating more severe disease.

Malnutrition is common in chronic diseases including heart failure and indicates increased morbidity and mortality [10]. Patients with PAH are at risk of malnutrition due to various reasons. Right heart failure with low cardiac output and venous congestion causing intestinal edema, alterations in gut microbiome, chronic inflammatory status and altered immune function, dysfunctional mitochondrial energy metabolism due to chronic hypoxia, higher prevalence of insulin resistance, changes in gut-derived satiety hormones and side effects of the drugs used in the treatment of the disease can be counted as some of these factors [2, 3]. There are studies reporting vitamin and micronutrient deficiences in patients with PAH more than general population like vitamin D and iron [11, 12]. Guidelines recommend supplemental iron treatment in PAH patients with iron deficiency but other than that, there are no recommendations in the guidelines except general measures like restriction of fluid and salt intake to relieve symptoms of heart failure [1].

Serum albumin concentration, TC level and TLC are commonly used in the assessment of malnutrition. Serum albumin level is frequently used as an indicator of nutritional status but in PAH besides malnutrition decreased serum albumin levels may result from liver dysfunction, systemic inflammatory state or vascular leakage [13, 14]. Snipelisky et al. [6] reported that prevalence of hypoalbuminemia was 25.2% and lower albumin levels were associated with increased mortality in PAH. Low cholesterol levels were defined in chronic illnesses and thought to result from malnutrition and chronic inflammation [15, 16]. Also lower TC level was shown to associate with higher death or lung transplantation risk in PAH together with higher NT-proBNP and lower von Willebrand factor [17]. Nutritional status affects immune cells in terms of number, metabolism and function. In states of malnutrition, lymphocytes, especially T cells, decrease in number due to reduced survival and proliferation [18, 19]. Therefore, TLC, is often incorporated in nutritional scores as a simple measure of the effect of nutrition on immune system. CONUT score, based on serum albumin concentration, TC level and TLC, reflects patients' nutritional, inflammatory and immune status.

Literature about the general nutritional status of PAH patients is limited. We found that 37% of the patients with PAH had any degree of malnutrition based on CONUT score. Luo et al. [4] recently reported 39.7% malnutrition, assessed with prognostic nutritional index (PNI) calculated through serum albumin level and TLC, in patients with idiopathic PAH similar to our findings. As a common finding, clinicians should be aware of malnutrition in patients with PAH and utilize screening tools like CONUT score that are simple to calculate and shown to be related to disease severity and prognosis in our study to identify patients at risk.

We demonstrated that CONUT score was an independent predictor of long-term all-cause mortality in PAH patients after adjustment with ESC/ERS guideline risk score. This is consistent with the findings from Kubota et al. [5] (studied geriatric nutritional risk index in PAH and chronic thromboembolic pulmonary

hypertension) and Luo et al. [4] (assessed PNI in patients with idiopathic PAH) although different nutritional screening tools were employed in different study groups. Low geriatric nutritional risk index, evaluated at diagnosis using serum albumin level and body mass index, was related to mortality and hospitalization in group 1 and 4 pulmonary hypertension [5]. Luo et al. [4] reported a 4% decrease in mortality risk with a one-point increase in PNI in idiopathic PAH. When they categorized patients as normal and malnourished (PNI cut-off 44.8), malnutrition was associated with mortality with borderline statistical significance after adjustment (HR:1.88, 95% CI:1.00-3.52, *p*=0.05). In the present study, when we grouped patients as normal and malnourished based on their CONUT scores and performed survival analysis although the difference between survival curves increased over time, statistical significance was not observed which might be due to small sample size.

To our knowledge, association of nutritional status with disease severity assessed by commonly used and validated PAH prognostic risk scores was not studied before. Patients with any degree of malnutrition according to CONUT score (≥2) had higher WHO-FC, NT-proBNP, lower 6MWD and more frequent pericardial effusion at presentation. And patients with normal CONUT scores at diagnosis presented more with low-risk according to commonly used risk scores in everday practice evaluated in this study. In a small study with 8 stable PAH patients, Kawamoto et al. [20] reported correlation between markers of nutritional status (body mass index, blood urea nitrogen and serum prealbumin) and markers of congestion (estimated pulmonary arterial pressure, inferior vena cava diameter). Contrary to their findings, we observed no significant difference in right ventricular diamaters, inferior vena cava diameter, systolic pulmonary arterial pressure and invasively measured mean pulmonary arterial pressure among groups. In another study, hypoalbuminemia was not found to be associated with parameters like WHO-FC and 6MWD in PAH patients. Only pericardial effusion was more frequent in patients with hypoalbuminemia similar to our results [6]. Important parameters like 6MWD and NT-proBNP were not evaluated in the study of Luo et al. [4] but they observed similar New York Heart Association functional class across PNI quartiles. Unlike our findings, Kubota et al. [5] reported that the severity of pulmonary hypertension was not associated with geriatric nutritional risk index in terms of WHO-FC and NT-proBNP. Invasive hemodynamic parameters were not found to be related with PNI, geriatric nutritional risk index or hypoalbuminemia in these studies, supporting our findings. Although more comprehensive studies are needed on the subject, in the light of the present literature, CONUT score may outperform PNI and geriatric nutritional index in predicting disease severity in patients with PAH.

There are some limitations to our study. Inherit disadvantages secondary to study design exist and casuality can not be determined. Sample size was small which also prevented us from further statistical analysis in this complex disease with different etiologies. CONUT score was not compared with more comprehensive nutritional assessment methods. Changes in nutritional status during follow-up and its relation with mortality were not evaluated.

To conclude, this study showed that malnutrition was common among PAH patients based on CONUT score and CONUT score, an easy to calculate screening tool of nutritional status through routinely taken laboratory parameters, predicts long-term mortality and associated with higher risk in this patient group. Randomized controlled trials are needed to determine how nutrition affects PAH patients' prognosis and whether nutritional intervention can improve the outcome.

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

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Authors' contributions to the article

M.A.S., A.S. and O.Y. constructed the main idea and hypothesis of the study. M.A.S., A.S., F.C., A.E.Z., B.G. and O.Y. developed the theory and arranged the material and method section. M.A.S., F.C., A.E.Z. and B.G. have done the evaluation of the data in the Results section. Discussion section of the article was written by M.A.S. and A.S.

M.A.S., A.S., F.C., A.E.Z., B.G. and O.Y. have reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Association between vascular calcification, atherosclerosis and inflammatory markers in end-stage renal disease patient and simple method for detecting vascular calcification (direct radiography)

Son dönem böbrek yetmezlikli hastalarda vasküler kalsifikasyon, ateroskleroz ve inflamatuar belirteçler arasındaki ilişki ve vasküler kalsifikasyonun saptanmasında basit bir yöntem (direkt radyografi)

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Abstract

Purpose: In our study, we planned to investigate the relationship of malnutrition with inflammation, atherosclerosis and calcification in dialysis patients.

Materials and methods: 140 Chronic kidney disease (CKD) patients and 44 healthy controls were included in the study. Carotid artery intima-media thickness (CIMT) was measured by doppler ultrasonography. Valvular calcification was assessed by echocardiography and vascular calcification scores (VCS) were done based on the radiograms. Biochemical parameters were assessed using routine laboratory methods. Subjective global assessment (SGA) was used to evaluate malnutrition.

Results: In the study, VCS showed no differences between hemodialysis (HD) and peritoneal dialysis (PD) patients (1.84±2.35 for HD, 1.77±1.64 for PD; *p*=0.83). CIMT, Osteopontin (OPN), interleukin-6 (IL-6) and homocysteine were significantly different in both dialysis groups compared to healthy controls. The Mean carotid intima-media thickness (m-CIMT) was higher in HD patients compared to PD group. CIMT, vascular calcification and SGA scores showed positive correlation with age, dialysis duration and valvular calcification grades, and negative correlation with albumin levels. A positive correlation between SGA scores and high-sensitive C-reactive protein (hs-CRP) levels was also noted. On multiple regression analysis, m-CIMT was independently associated with age, VCS and albumin levels. VCS was found to be independently associated with only albumin levels.

Conclusion: Vascular and valvular calcification, an indicator of cardiovascular mortality and morbidity in dialysis patients, was found to be significantly associated with malnutrition. We found higher rates of valvular calcification in patients with vascular calcification. Malnutrition was more prominent in these patients.

Keywords: Atherosclerosis, calcification, chronic renal failure, inflammation, malnutrition.

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Öz

Amaç: Çalışmamızda diyaliz hastalarında malnütrisyonun; inflamasyon, ateroskleroz ve kalsifikasyonla olan ilişkisini araştırmayı planladık.

Gereç ve yöntem: Çalışmaya 140 kronik böbrek yetmezlikli (KBH) hasta ve 44 sağlıklı kontrol dahil edildi. Karotis intima-media kalınlığı (KİMK) doppler ultrasonografi ile ölçüldü. Kapak kalsifikasyonu ekokardiyografi ile değerlendirildi ve direkt grafi ile vasküler kalsifikasyon skorları (VKS) hesaplandı. Biyokimyasal parametreler rutin laboratuvar yöntemleri kullanılarak değerlendirildi. Malnütrisyonun değerlendirilmesinde subjektif global değerlendirme skorlaması (SGA) kullanıldı.

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Bulgular: Çalışmada hemodiyaliz (HD) ve periton diyalizi (PD) hastaları arasında VKS açısından fark bulunmadı (HD için 1,84±2,35, PD için 1,77±1,64; *p*=0,83). KİMK, Osteopontin (OPN), interlökin-6 (IL-6) ve homosistein her iki diyaliz grubunda sağlıklı kontrollerle karşılaştırıldığında anlamlı olarak farklıydı. Ortalama karotis intima media kalınlığı (m-KİMK) HD hastalarında PD grubuna göre daha yüksekti. KİMK, vasküler kalsifikasyon ve SGA skorları yaş, diyaliz süresi ve kapak kalsifikasyon dereceleri ile pozitif, albümin seviyesi ile negatif korelasyon göstermekteydi. SGA skorları ile yüksek duyarlı C-reaktif protein (hs-CRP) seviyeleri arasında da pozitif yönde korelasyon kaydedildi. Çoklu regresyon analizinde m-KİMK bağımsız olarak yaş, VCS ve albümin seviyesi ile ilişkili bulunurken; VCS'nun bağımsız olarak sadece albümin seviyesi ile ilişkili olduğu bulundu.
Tartışma: Çalışmamızda diyaliz hastalarında kardiyovasküler mortalite ve morbiditenin önemli bir göstergesi olan vasküler-valvüler kalsifikasyonla malnütrisyonun önemli ilişkisinin olduğunu gördük. Vasküler kalsifikasyonu olan hastalarda valvüler kalsifikasyon belirgindi. Bu grup hastada malnütrisyon da belirgindi.
Sonuç: Diyaliz hastalarında kardiyovasküler mortalite ve morbiditenin bir göstergesi olan vasküler ve kapak kalsifikasyonunun malnütrisyon ile anlamlı ilişkisi bulundu. Vasküler kalsifikasyonu olan hastalarda daha yüksek oranda kapak kalsifikasyonu bulduk. Bu hastalarda malnütrisyon daha belirgindi.

Anahtar kelimeler: Ateroskleroz, kalsifikasyon, kronik böbrek yetmezliği, inflamasyon, malnütrisyon.

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Introduction

Accelerated cardiovascular calcification is one of the most important causes of morbidity and mortality in chronic kidney disease (CKD) [1]. Besides, increased levels of calcification stimulators such as hyperphosphatemia, hypercalcemia, increased levels of oxidized low-density lipoprotein (LDL)-cholesterol and hyperleptinemia, decreasing levels of calcification inhibitors like matrix G1a protein, fetuin-A, osteoprotegerin and osteopontin (OPN) play fundamental role in vascular calcification [2, 3].

The presence of plaques and increased intima-media thickness in the carotid arteries are strong predictors for cardiovascular events in general population [4]. Carotid artery intima-media thickness (CIMT) is a simple, reliable and non-invasive method, widely used in clinical trials for detecting asymptomatic atherosclerosis [5]. CIMT is increased in patients with renal failure and may help to predict patients that are at a higher risk of future cardiovascular events [5, 6].

In patients with end-stage renal disease (ESRD), malnutrition is a multifactorial condition with significantly poor clinical outcome [7, 8]. Malnutrition and cardiovascular diseases, especially atherosclerosis and related complications are linked to each other [8]. CKD is characterized by chronic inflammation which is responsible for the manifestation of malnutrition [9-11]. Malnutrition and conditions leading to excessive weight loss can cause inflammation [10]. Oxidative stress might be the main underlying cause in both conditions [12]. Inflammation in stage 5 CKD is multifactorial; impaired renal cytokine clearance, the presence of persistent infections such as oral cavity and gingival infections, vascular access infections, peritonitis, exogenous factors such as usage of bioincompatible dialysate, dialysis membranes and endotoxin exposure from contaminated dialysate especially in ESRD patients on renal replacement therapy (RRT) are the potential causes of inflammation [12]. Increased mortality and morbidity caused by this pathological condition is called malnutrition-inflammation-atherosclerosis (MIA) syndrome [8]. Pro-inflammatory cytokines play an important role in the pathogenesis of MIA syndrome [12]. Studies have shown that proinflammatory cytokines are 8 to 10 times higher in HD patients when compared to healthy controls [10-12].

OPN is produced by cells involved in bone morphogenesis and one major physiological role of OPN is to be in the control of biomineralization and calcification [13-15]. In addition, significant increase of OPN expression has been shown in smooth muscle cells of renal failure patients with vascular calcification [16, 17].

Prospective cohort studies conducted in stage 5 CKD patients have revealed the relationship between high levels of high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6) and all cause-and cardiovascular cause-deaths [18-22].

Cohen et al. [21] stated that homocysteine elevation in renal insufficiency was first reported in 1977. Results of the studies on the role of hyperhomocysteinemia in dialysis patients and increased atherosclerosis vary. Two studies have shown that hyperhomocysteinemia was associated with increased cardiovascular morbidity in dialysis patients [23, 24]; while another study showed no correlation between increased homocysteine levels and cardiovascular events [25].

The aims of our study were: 1) to point out the importance of calcification (vascular and valvular), atherosclerosis, malnutrition and inflammation cascade on CKD 2) to identify markers that might affect atherosclerosis and vascular calcification 3) to figure out whether inflammatory markers and CIMT are different or not in dialysis groups compared to healthy controls of the same age group 4) to evaluate whether direct radiography, accessible and inexpensive method in routine practice, can be used in routine for vascular calcification scoring in these patients.

Materials and methods

In this cross-sectional single center study, after informed consent was obtained, stage 5 CKD patients treated with maintanence dialysis for at least 2 years period and healthy individuals were included. The patients were admitted from the department of Nephrology of Gazi University Medical Faculty, Ankara, Türkiye, from January to December 2007.

A total of 140 patients [78 under haemodialysis (HD); 62 under peritoneal dialysis (PD)], diagnosed with chronic renal failure and under renal replacement therapy for at least two years, and 44 healthy controls were included in the study. Firstly, we planned to include more healthy controls at least as much as the number of the patients in our study. However, we couldn't reach our goal finding that much healthy participants, given our strict conditions on these individuals which must not have any comorbidities (diabetes, thyroid diseases, hypertension, renal and cardiac diseases) and must be drug free. An other reason was the fact that as the CIMT measurements are made two times with one week intervals, it caused difficulty for some of the participants continue to the study. Subjects aged <18 or >70 years, those with underlying malignancy, chronic liver disease, autoimmune disease, current or recent (<1month) active infection, a catheter or graft as vascular access (for HD group) and those with history or symptoms of cardiovascular disease and cardiovascular instability (myocardial infarction, congestive heart failure, arrhythmia, peripheral vascular disease, transient ischemic attacks or cerebrovascular accidents) were excluded from the study. All patients were informed about the study and their written informed consent was obtained.

Measurement of the thickness of the carotid intima media

Patients were placed in a supine position, and their heads were positioned in extension. The right and left carotid arteries were imaged with a 7 MHz linear probe of an ultrasonic device ATL (HDI 5000, Philips Bothell WA). Intima media thickness was measured after identification of a 1 cm-segment without atherosclerotic plaque at the 2 cm proximal of the main carotid artery bulb. The measurement was done on the echogenic line formed by the lumen and media layer. Mean carotid intima-media thickness (m-CIMT) was calculated by arithmetic averages of the right and left CIMT values. The CIMT measurements were performed (without knowing real identity of the participitants) twice with one week intervals by the radiology specialist Serap Gültekin, MD. The value of CIMT was calculated by taking the average of the two measurements.

Vascular calcification scoring

Adragao et al. [22] stated that this scoring was based on the publications. Pelvic X-ray image was evaluated in four areas by dividing the image by the upper horizontal line passing between the apex of the two femur bones, and a median vertical line passing on the vertebral column. Similarly, hand X-rays were examined in two sections, divided by a horizontal line passing on the metacarpal bones. In each section, the presence of linear calcification was scored as 1 and non-presence as 0, and the total score was presented between 0-8. Linear calcifications along the iliac and femoral arteries in pelvic X-rays, and those along radial and digital arteries in hand X-rays were included in the scoring.

Patch calcifications, phleboliths, and extra-vascular calcifications were excluded. Vascular calcification scorings were calculated according to the references by a Nephrologist and a Radiologist, seperately. Without sharing their data with each other, the averages of the two calculations were taken.

Evaluation of valvular calcification

Echocardiographic examination was performed in the left lateral decubitus position using Vingmed System Five (GEVingmed Sound; Horten, Norway) echocardiography device and a 1.5-3.6 mHzultrasound probe. Parasternal long-, short-axis, and apical views were recorded. The valvular calcification evaluation was carried out by a Cardiologist, without knowing the real idendities of the patients. All echocardiographic examinations were performed according to the recommendations of the American Society of Echocardiography [26, 27]. Valvular calcifications were assessed as >1 mm-spot brightness on the valves. Calcification grades were as follows: mild (point calcification <3 mm), moderate (multiple calcium dots of >3 mm), severe (wide calcification area in valvular annulus, semilunar cusps or both) [28].

Blood analyses

Blood samples of PD patients and controls were taken between 08.00-10.00 in the morning, and at the same hours but before the HD session in HD patients following at least an 8 h-fasting period. Serum/plasma were separated, and stored at -80°C until analysed (not longer than 3 months). Blood cells counts, levels of urea, creatinine, uric acid, calcium, phosphorus, albumin, total cholesterol, triglyceride, high-density lipoprotein (HDL), low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) cholesterol, and fasting blood glucose were measured using standard laboratory techniques. Serum intact parathyroid hormone (iPTH) levels were measured by immunoradiometric assay (IRMA) with a commercially available kit (BioSource, Nivelles, Belgium).

The hs-CRP levels were measured by the nephelometric method. Serum IL-6 Levels were measured by enzyme-linked immunosorbent assay (ELISA) using Human IL-6 kit (BIOSOURCE Immunoassay Kit, USA), and the results were expressed in pg/mL. Plasma OPN levels were measured by enzyme immunometric assay using Human OPN Enzyme Immunoassay kit (TiterZyme EIA, Kit-IBL [ImmunoBiological Laboratories] Co., Ltd., Japan), and results were expressed in ng/mL. Plasma homocysteine levels were measured by enzymatic assay using Homocysteine Enzymatic Assay kit (DIAZYME, USA), and results were given in micromol/L.

Nutrition status assessment

Kalantar Zadeh et al. [29] stated that malnutrition was assessed using the modified quantitative subjective global assessment (SGA) method defined. Scores up to 7 were considered as normal nutrition or mild malnutrition, while scores higher than 35 were defined as severe malnutrition [29]. Body mass indexes (BMI) of all patients and healthy controls were calculated by the formula, body weight (kg)/height(cm)^2.

Statistical analyses

The results were expressed as mean ± SD. In all cases, comparisons were two-tailed and *p*-value of <0.05 was considered statistically significant. Parametric variables (age, BMI, m-CIMT, OPN, IL-6, homocysteine, hs-CRP, haemoglobin, BUN, creatinine, uric acid, calcium, phosphorus, albumin, total, HDL and LDL-cholesterol) were evaluated by ANOVA and Tukey HSD tests. Non-parametric variables were examined by Chi-square test. For the binary group comparisons of the parametric variables, t-test; for OPN, IL-6, and hs-CRP values, due to large standard deviation, Mann-Whitney U test; and for correlation analyses Pearson and Spearman correlation tests were performed. Backward multiple linear regression analyses were performed to test the associations between several possible associated factors and CIMT and VCS evaluation scoring separately. The SPSS version 10.0 package program was used for all the baseline descriptive statistics, hypothesis tests and other analyses (SPSS, Inc., Chicago, IL, USA).

Results

The study group consisted of 78 HD (26 female, 52 male), 62 PD patients (32 female, 30 male) and 44 healthy controls (21 female, 23 male). Mean ages were 47.8±16.8 in the HD group, 45.9±13.2 in the PD group, and 45.1±12.3

years in the control group. Age distribution of the three groups were similar. As compared with PD group, HD group had higher smoking rate (32% vs 64%, respectively) (p=0.000). The dialysis pasts of HD patients were longer than of the PD patients (p=0.05). Demographic characteristics of patients and controls are given in Table 1. Significant differences were found in BUN, serum uric acid, triglyceride, serum albumin levels and BMI values when HD patients were compared with PD group (Table 2).

At the comparison of dialysis patients in terms of vascular calcification rates, the proportion of patients without calcification were higher in HD patiens than PD patients. Those with a calcification score above 5 were significantly higher in the HD group than PD group (p=0.001). More than the half of PD patients had a moderate VCS. The incidence of valvular calcification for both valves was higher in HD group compared to PD group (Table 3).

While the mean OPN (p=0.06), IL-6 (p=0.23) and homocysteine (p=0.17) levels of HD and PD patients did not show statistically significant difference, m-CIMT (p=0.000) values were significantly different in both groups (Table 2). When HD patients were compared with healthy controls, values of OPN (p=0.000), IL-6 (p=0.01), homocysteine (p=0.000) and m-CIMT(p=0.000) were significantly different. Similarly, when PD patients were compared with healthy controls, the values of OPN (p=0.000), IL-6 (p=0.01), homocysteine (p=0.000) and m-CIMT(p=0.000) were significantly different (Table 4).

Based on the modified SGA scoring method; on the HD group, 5 of the patients (6%) were normal, 71 of the patients (91%) were moderate and 2 of them (2.6%) were severely malnourished. On the PD group, 9 of the patients (14.5%) were normal and 53 of the group patients (85.5%) were moderately malnourished (p=0.05). When compared the two dialysis groups, the SGA score below 15 was 88% in PD group and 82% in HD group. In the current study, HD patients were found to be prone to malnutrition compared to PD patients.

Positive correlation was found between m-CIMT and age (p=0.000, r=0.35), dialysis period (p=0.04, r=0.14), VCS (p=0.004, r=0.23), SGA score (p=0.000, r=0.29), mitral valve calcification grade (p=0.002, r=0.26) and aortic valve calcification grade (p=0.008, r=0.22). Negative correlation was found between m-CIMT and between albumin (p=0.01, r=-0.18), calcium (p=0.05, r=-0.14) and phosphorus (p=0.04, r=-0.16) (Table 5). m-CIMT was independently associated with age (p=0.01, Beta:0.26), VCS (p=0.03, Beta:0.19) and albumin levels (p=0.01, Beta:-0.26) on multiple regression analysis (Table 6).

Positive correlation was found between VCS and age (p=0.01, r=0.20), dialysis period (p=0.001, r=0.27), m-CIMT (p=0.004, r=0.23), SGA score (p=0.001, r=0.27), mitral valve calcification grade (p=0.000, r=0.47) and aortic valve calcification grade (p=0.000, r=0.38). There was a negative correlation between VCS and albumin level (p=0.002, r=-0.25) (Table 5). VCS was independently associated with only albumin levels (p=0.02, Beta:-2.23) on multiple regression analysis (Table 6).

Patients' SGA scores showed positive correlation with age (p=0.000, r=0.45), duration of dialysis (p=0.000, r=0.34), m-CIMT (p=0.000, r=0.29), VCS (p=0.001, r=0.27), mitral valve calcification grade (p=0.000, r=.30), aortic valve calcification grade (p=0.003, r=0.24), hs-CRP (p=0.000, r=0.31); and negative correlation with albumin (p=0.004, r=-0.24), calcium (p=0.06, r=-0.13) and phosphorus (p=0.01, r=-0.21) (Table 5).

Duration of dialysis (p=0.01, r=0.2), phosphorus (p=0.001, r=0.27) and parathormone (p=0.000, r=0.35) showed positive correlation with OPN. Homocysteine levels showed positive correlation with uric acid (p=0.03, r=0.17), hs-CRP (p=0.009, r=0.22) and IL-6 (p=0.000, r=0.59). IL-6 levels had positive correlation with homocysteine (p=0.000, r=0.59), age (p=0.02, r=0.19) and hs-CRP (p=0.001, r=0.29).

Table 1. General characteristics of haemodialysis and peritoneal dialysis patients and controls

	HD group (n=78)	PD group (n=62)	Control group (n=44)
Male	52 [a,b]	30 [a,b]	23 [a]
Age (years)	47.8±16.8[c,d]	45.9±13.2[c,d]	45.1±12.3[c]
Dialysis duration (month)	69.76±41.10[e]	57.09±39.41[e]	-
Body mass index (kg/m²)	23.38±4.76[f,g]	25.21±5.67[f,g]	25.03±4.72[f]
Smokers (%)	50 (64.1%)[h,ı]	20 (32.3%)[h,ı]	15 (34.1%)[h]
Comorbidities			
Hypertension (%)	23 (29.5%)	20 (32.3%)	
Diabetes Mellitus (%)	14 (17.9%)	10 (16.1%)	
Glomerulonephritis (%)	15 (19.2%)	8 (12.9%)	
Nephrolithiasis (%)	2 (2.6%)	5 (8.1%)	
Amyloid (%)	3 (3.8%)	2 (3.2%)	
Polycystic renal disease (%)	1 (1.3%)	3 (4.8%)	
Pyelonephritis (%)	6 (7.7%)	1 (1.6%)	
Malignity (%)	1 (1.3%)	0	
Unknown (%)	13 (16.7%)	13 (21%)	

Data are presented as n (%) or mean±SD, HD, haemodialysis; PD, peritoneal dialysis, [a]*p*=0.07 (for all groups)
[b]*p*=0.02 (HD compared to PD group), [c]*p*=0.56 (for all groups), [d]*p*=0.46 (HD compared to PD group), [e]*p*=0.05 (HD compared to PD group)
[f]*p*=0.06 (for all groups), [g]*p*=0.04 (HD compared to PD group), [h]*p*=0.04 (for all groups), [ı] *p*=0.000 (HD compared to PD group)

Table 2. Laboratory findings of haemodialysis and peritoneal dialysis patients

	HD group (n=78)	PD group (n=62)	*p*
BUN (mg/dl)	67.16±16.19	55.38±16.33	0.000
Creatinine (mg/dl)	8.76±2.62	9.15±3.01	0.41
Kt/V	1.28±0.28	1.68±0.94	0.001
Calcium (mg/dl)	8.82±0.81	8.95±0.70	0.33
Phosphate (mg/dl)	5.30±1.32	5.07±1.45	0.32
PTH (pg/ml)	433.38±412.61	468.08±419.75	0.62
Uric acid (mg/dl)	6.07±0.80	5.55±0.88	0.000
Fasting blood glucose (mg/dl)	112.12±53.96	109.61±52.62	0.78
Haemoglobin (g/dl)	10.71±1.35	10.97±1.75	0.31
Total cholesterol (mg/dl)	173.75±42.92	185.01±34.83	0.09
HDL-cholesterol (mg/dl)	41.46±12.80	46.38±18.41	0.06
LDL-cholesterol (mg/dl)	96.28±34.75	105.29±28.85	0.10
Triglyceride (mg/dl)	203.80±137.27	161.41±59.45	0.02
Total protein (g/dl)	6.93±0.58	6.85±0.47	0.41
Albumin (g/dl)	4.13±0.46	3.98±0.37	0.03
hs-CRP(mg/dl)	0.77±1.13	0.85±0.86	0.14
Osteopontin (ng/ml)	33.42±18.44	28.26±20.65	0.06
IL-6 (pg/ml)	10.42±23.80	6.02±11.60	0.23
Homocysteine (µmol/L)	29.57±11.78	26.88±11.30	0.17
m-CIMT (mm)	1.01±0.30	0.82±0.29	0.000
VCS	1.84±2.35	1.77±1.64	0.83
SGA	11.79±5.43	10.93±3.16	0.27
BMI (kg/m²)	23.38±4.76	25.21±5.67	0.04

Data are mean values±SD, BMI: Body Mass Index, BUN: Blood Urea Nitrogen, hs-CRP: high sensitive C reactive protein
HD: haemodialysis, Kt/V: fractional urea clearance, m-CIMT: mean carotid intima-media thickness
PD: peritoneal dialysis, SGA: subjective global evaluation score, VCS: vascular calcification score

Table 3. Vascular and valvular calcification values in haemodialysis and peritoneal dialysis patients

	HD Group n (%)	PD Group n (%)
Vascular calcification[a]		
None	39 (50%)	18 (29%)
Score between 1-4	27 (34.6%)	41 (66.1%)
Score ≥5	12 (15.4%)	3 (4.8%)
Mitral valve calcification present[b]	48 (61.5%)	26 (41.9%)
Atrioventricular valve calcification present[c]	28 (35.9%)	12 (19.4%)

HD: haemodialysis, PD: peritoneal dialysis, [a]p=0.001 HD compared to PD group, [b]p=0.02 HD compared PD group, [c]p=0.03 HD compared to PD group

Table 4. Osteopontin, interleukin-6, and homocysteine levels, and mean carotid artery intima-media thickness of haemodialysis and peritoneal dialysis patients and controls

	HD group (n=78)	PD group (n=62)	Control group (n=44)
Osteopontin (ng/ml)	33.42±18.44[a,x]	28.26±20.65[a]	9.58±8.88
IL-6 (pg/ml)	10.42±23.80[b,y]	6.02±11.60[b]	0.69±2.63
Homocysteine (µmol/L)	29.57±11.78[a,z]	26.88±11.30[a]	9.61±3.25
m-CIMT (mm)	1.01±0.30[a,c]	0.82±0.29[a]	0.184±0.25

Data are mean values ± SD, [a]p=0.000 compared to controls, [b]p=0.01 compared to controls [c]p=0.000 compared to PD group
[x]p=0.06 HD compared to PD group, [y]p=0.23 HD compared to PD group, [z]p=0.17 HD compared to PD group
m-CIMT: mean carotid artery intima-media thickness, IL-6: interleukin-6, HD: haemodialysis, PD: peritoneal dialysis

Table 5. Correlations of m-CIMT, VCS and SGA values with study parameters

	m-CIMT		VCS		SGA	
Variables	**r**	***p***	**r**	***p***	**r**	***p***
Age	0.35	0.000	0.20	0.01	0.45	0.000
Dialysis period	0.14	0.04	0.27	0.001	0.34	0.000
m-CIMT			0.23	0.004	0.29	0.000
VCS	0.23	0.004			0.27	0.001
SGA	0.29	0.000	0.27	0.001		
MV calcification	0.26	0.002	0.47	0.000	0.30	0.000
AV calcification	0.22	0.008	0.38	0.000	0.24	0.003
Albumin	-0.18	0.01	-0.25	0.002	-0.24	0.004
Calcium	-0.14	0.05	-0.01	0.82	-0.13	0.06
Phosphorus	-0.16	0.04	0.06	0.46	-0.21	0.01
Uric acid	0.07	0.41	0.12	0.06	0.17	0.03
Osteopontin	-0.06	0.47	-0.11	0.17	0.03	0.72
IL-6	0.14	0.09	0.12	0.08	0.09	0.27
Homocysteine	0.14	0.09	0.07	0.40	0.04	0.96
hs-CRP	0.14	0.08	0.13	0.16	0.31	0.000

AV: atrioventricular valve, m-CIMT: mean carotid artery intima-media thickness, hs-CRP: high sensitive C reactive protein, IL-6: interleukin-6
MV: mitral valve, SGA: Subjective global evaluation score, VCS: vascular calcification score

Table 6. Multiple regression analyses of factors affecting m-CIMT and VCS

Dependent	Independent	Beta	*p*
m-CIMT	Age	0.26	0.01
	VCS	0.19	0.03
	Albumin	-0.26	0.01
VCS	Albumin	-2.23	0.02

VCS: vascular calcification score, m-CIMT: mean carotid artery intima-media thickness

Discussion

In our study, m-CIMT levels were found significantly higher in HD patients compared to PD patients and healthy controls. Levels of m-CIMT were also higher in PD patients than healthy controls. Recent studies have shown that m-CIMT is an independent marker of cardiovascular mortality in HD patients [30, 31]. One of the reasons of the higher levels of m-CIMT in HD patients might be the better protection of PD patients for their residual renal function (RRF). This claim would become more important if RRF of PD patients could have been evaluated in our study. Rroji et al. [32] stated that RRF is an independent predictor for atherosclerosis proposed. Dialysis duration of HD patients were longer than those of PD patients. That could be explanation of the increased atherosclerosis in the HD group. The high smoking rate of HD patients may also play a role for this difference. Smoking is a well-documented cardiovascular risk factor [33, 34].

There is also a positive link between age and atherosclerosis. Preston et al. [35] stated that m-CIMT increases with age and LDL-cholesterol, and decreases with HDL-cholesterol. In our study, CIMT values significantly increased with increasing age. Majority of studies showed negative correlation between m-CIMT and albumin, and positive correlation between m-CIMT and CRP [29-31]. In the present study, a considerable negative correlation was established between the m-CIMT and albumin, as cited at previous studies. Though there are studies in the literature reporting the correlation between higher inflammatory levels and m-CIMT, we could not confirm this in our study. We found that m-CIMT values were associated with age, VCS and albumin levels in dialysis patients. There may be many reasons why we did not find a direct relationship between m-CIMT, and inflammatory parameters; atherosclerosis is a chronic pathology and aging and long dialysis time may be more predictive factors for atherosclerosis. Perhaps malnutrition plays a more important role in atherogenesis than inflammation. Inflammation may trigger malnutrition, leading to atherosclerosis.

Although the relationship between calcification and inflammation has been shown in many studies [36, 37], we could not present significant association between calcification scores and the two inflammation markers, IL-6 and hs-CRP. In contrast, there was a significant linear relationship between vascular calcification grades and clinical (i.e. SGA), and laboratory findings (*i.e.* albumin) of malnutrition. SGA and m-CIMT were significantly associated in patients with vascular calcification. Therefore, it can be assumed that the effect of inflammation on vascular calcification may be via indirect pathways. As in our patient groups, inflammation might lead to vascular calcification by triggering malnutrition.

In our study, higher SGA scores were associated with positively correlated m-CIMT and vascular calcification. We also observed that malnutrition was more pronounced and severe in elderly long-duration dialysis patients. We found that malnutrition was associated with higher hs-CRP, however, we could not confirm that with IL-6 levels. While no significant association was found between SGA scores and IL-6, the observation of a positive association with hs-CRP contradicts the knowledge that IL-6 is a more sensitive cytokine than other cytokines [36]. At the previous studies, high levels of hs-CRP and IL-6 were proposed to be the best predictors of malnutrition in end stage renal failure patients, even IL-6 was proposed to be a better predictor particularly on cardiovascular events and mortality [19, 20]. At present, proinflammatory cytokines, which can be used for different diagnostic purposes, are influenced by many factors, and are not sufficient to distinguish the relationship between vascular

calcification, atherosclerosis and malnutrition. Moreover, since this study is not a prospective mortality and morbidity study, it is impossible to anticipate which cytokine is more closely related to malnutrition, and what could be its future consequences. However, the close association between the inflammation indicator hs-CRP and malnutrition score reminds once again the tight link between inflammation and malnutrition. Many publications reported a linear relationship between inflammation and malnutrition [7-9, 36-42]. We have also achieved similar results.

OPN levels were significantly higher in dialysis groups compared to healthy controls. The expression of OPN increases in case of hyperphosphatemic, parathyroid hormone-elevated, and calciphylaxed vascular bed [43]. The role of OPN on the development of atherosclerosis is unclear. Because of its role in the pathogenesis of vascular calcification, the relationship between plasma OPN levels and m-CIMT was investigated in patients with essential hypertension, and it was found that there was a positive correlation between the two [44]. We did not find a significant relationship between m-CIMT and OPN. Duration of dialysis, higher phosphorus and parathormone levels showed positive correlation with OPN. Nitta et al. [45] stated that in a study in 2001, reported a relation between high levels of OPN and presence of vascular calcification in HD patients but we could not confirm this relation in our study.

In our study, we found increased levels of homocysteine in CKD patients. Renal failure is a well-known cause of hyperhomocysteinemia [46]. Yet, it is not clear whether hyperhomocysteinemia is an independent risk factor for atherosclerosis. IL-6 and hs-CRP, predictors of inflammation, were positively corralated with homocysteine levels. Similar to our results, previous studies confirmed that elevated inflammation is associated with hyperhomocysteinemia [47]. We did not find significant relation between m-CIMT, vascular calcification and homocysteine levels in our study. The results of studies emphasizing the relationship between m-CIMT and homocysteine levels are also contradictory. Similar findings to our results could be found in the literature [48].

IL-6 levels were also significantly higher in dialysis patients than in healthy controls. We did not find significant association between m-CIMT, VCS, and SGA and IL-6 levels. It has been shown that IL-6 is a good predictor of mortality in dialysis patients [10, 20], and that there is positive correlation between m-CIMT and IL-6 [49]. IL-6 and CRP levels are 8 to 10 times higher in dialysis patients [41]. In our patient group, IL-6 levels were 6 to 10 times higher than the healthy population, supporting the literature. In our study, there was a strong association between IL-6 and hs-CRP. Elevated hs-CRP levels significantly predicted malnutrition in dialysis groups. However, we could not show positive correlation between malnutrion and calcification. No significant correlation between m-CIMT and IL-6 might suggest a weak relationship between inflammation and atherosclerosis for our patient group. As mentioned previously, although the relationship between m-CIMT and IL-6 has not been fully clarified, IL-6 is a strong predictor of mortality for dialysis patients. Prospective follow-up of our dialysis population would be needed to test the accuracy of this information.

In our study, we did not see the relationship between osteopontin and vascular calcification, which has been shown in some other studies. Again, although IL-6 and homocysteine levels were higher in our dialysis patients than in healthy controls, we did not find a significant relationship between them and CIMT and calcification. We observed that hs-CRP, which we frequently use in daily practice, is higher especially in dialysis patients with significant malnutrition.

Study limitations: RRF has a major influence upon the efficacy of m-CIMT. If we knew the RRF of PD patients, we could have more detailed explanations about the different m-CIMT measurements between PD and HD patients. Of course, it would have been more valuable if the number of our patients was more and we could reach a conclusion by making repetitive measurements of these patients over the years. Demonstrating vascular calcification and atherogenesis with more detailed methods would also strengthen our study.

In conclusion, inflammation is an important factor triggering malnutrition in dialysis patients.

Moderate to severely malnourished dialysis patients have vascular/valvular calcification and atherosclerosis is more common. Direct radiography, which is an easy and inexpensive method in routine practice, can be used to predict vascular calcification in these patients. Moreover, there is a strong association between vascular and cardiac valve calcification. Both atherosclerosis and calcification are more common in dialysis patients with low serum albumin levels. Comprehensive nutritional treatment protocols should be established and implemented for these patients.

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

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Authors' contributions to the article

R.M. and U.D. conceived the idea, R.M., E.I.S. and C.K.D. collected the data. C.M. and N.T. performed the calculations, data analysis and created tables. S.G. evaluated direct radiographs. G.T. evaluated echocardiograms. S.G. made and evaluated laboratory measurements. R.M. 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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Evaluation of traumatic dental injuries in patients attending the pediatric dentistry clinic: a retrospective study

Çocuk diş hekimliği kliniğine travmatik diş yaralanmaları nedeniyle başvuran hastaların değerlendirilmesi: retrospektif bir çalışma

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Abstract

Purpose: The purpose of this study was to evaluate the prevalence of traumatic dental injuries (TDIs), as well as to evaluate different factors associated with TDIs among children and adolescents referred over three-year period to the Pamukkale University, Faculty of Dentistry, Department of Pediatric Dentistry, Denizli.

Materials and methods: Dental trauma records of patients were reviewed regarding demographic data, affected teeth, type and etiology of TDIs, location and season of TDIs, time elapsed following TDIs and initial treatment, and treatment of TDIs.

Results: Data associated with 258 patients, 471 traumatized teeth (primary teeth:152, permanent teeth:319) were analyzed. Both the primary and permanent maxillary central incisors were the most common affected teeth by TDIs. Primary teeth showed a higher frequency of periodontal tissue injuries (75.00%) and lower frequency of dental hard tissue injuries (21.05%) compared with permanent teeth (49.84% and 58.62%, respectively). Falls were the main etiological factor of TDIs both in the primary (73.68%) and permanent (58.31%) teeth. Only 27 patients (5.49%) were referred to the clinic within one hour following TDIs.

Conclusion: Early management of TDIs is important to improve the prognosis of traumatized teeth and prevent post-traumatic complications. The low rate of early referral indicates the need for educational and preventive programs regarding TDIs among the patients, parents/legal guardians, and teachers.

Keywords: Dental trauma, epidemiology, permanent tooth, primary tooth.

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Öz

Amaç: Bu çalışmanın amacı, Denizli Pamukkale Üniversitesi Diş Hekimliği Fakültesi Çocuk Diş Hekimliği Anabilim Dalı'na üç yıllık bir süre boyunca başvuran çocuk ve ergenler arasında travmatik diş yaralanmalarının (TDY) prevalansını ve ayrıca TDY ile ilişkili farklı faktörleri değerlendirmektir.

Gereç ve yöntem: Hastaların diş travma kayıtları; demografik veriler, etkilenen dişler, TDY'lerin tipi ve etiyolojisi, TDY'lerin yeri ve mevsimi, TDY'ler ve ilk tedavi arasında geçen süre ve TDY'lerin tedavisi açısından incelenmiştir.

Bulgular: Toplam 258 hasta, 471 travmatize diş (süt dişi:152, daimi diş:319) ile ilgili veriler analiz edildi. Hem süt hem de daimi üst orta kesici dişler, TDY'lerden en sık etkilenen dişlerdi. Süt dişleri, daimi dişler ile karşılaştırıldığında (sırasıyla %49,84 ve %58,62) daha yüksek oranda periodontal doku yaralanması sıklığı (%75,00) ve daha düşük diş sert doku yaralanması sıklığı (%21,05) gösterdi. Düşmeler, hem süt (%73,68) hem de daimi (%58,31) dişlerde TDY'lerin ana etiyolojik faktörüydü. Sadece 27 hasta (%5,49) TDY sonrası bir saat içerisinde kliniğe başvurdu.

Sonuç: TDY'lerin erken müdahalesi, travmatize dişlerin prognozunu iyileştirmek ve travma sonrası komplikasyonları önlemek için önemlidir. Düşük erken başvuru oranı hastalar, ebeveynler/yasal temsilciler ve öğretmenler arasında TDY'ler ile ilgili eğitici ve önleyici programlara ihtiyaç duyulduğunu göstermektedir.

Anahtar kelimeler: Diş travması, epidemiyoloji, daimi diş, süt dişi.

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Introduction

Traumatic dental injury (TDI) is an injury type involving the hard and soft tissues surrounding the teeth, which usually develops suddenly and unexpectedly and requires immediate medical attention [1]. TDIs are common in children and young adults, representing 5% of all injuries [2]. It has been reported that one-third of all children experience TDIs in the primary dentition, one-fourth of all school-age children and one-third of all adults experience TDIs in the permanent dentition [3]. TDIs can affect both primary teeth and their successors, may lead to physical, emotional, psychological problems, and have a negative impact on the quality of life of both children and parents [4, 5]. Also TDIs are more complex problems in children and adolescents than in adults, due to immature teeth and continued facial growth [6].

The prevalence of TDIs has been reported vary between 6% and 58.6% [1]. This results might have derived from differences in study type, regional and behavioral variability, age of the study population, and differences in TDI classification [1, 7]. The course of treatment may depend on the attention, knowledge and intervention of the parents and surrounding adults, especially in severe luxation injuries and dental fractures [8, 9]. The lack of parental knowledge regarding TDIs and their consequences has highlighted the need for educating them about TDIs and the benefits of early management [10]. It is essential to know how and where TDIs occur, as well as the types and etiology of TDIs in order to inform parents and take preventive measures against dental traumas [10, 11]. For this reason, epidemiological studies are required to increase public awareness concerning TDIs and the necessary precautions [12].

Although there are several epidemiological studies on TDIs in Türkiye [7, 10-21], studies involving south-west region of Türkiye are limited [7, 15, 16, 21]. Therefore, the aim of this study was to evaluate TDIs profiles of children and adolescents who referred to Pamukkale University, Faculty of Dentistry, in Denizli, south-west region of Türkiye.

Materials and methods

This retrospective study was approved by the Ethics Committee of the Faculty of Medicine, Pamukkale University. The dental trauma records of 290 patients aged between 0-15 years old who referred Pamukkale University, Faculty of Dentistry, Department of Pediatric Dentistry with a complaint of traumatic dental injuries between June 2019 to December 2022 were evaluated. During the recording of the dental trauma forms, parents or legal guardians were informed about research study, and written consent was obtained. Among 290 dental trauma records, 32 were excluded because of incomplete data of records. A total of 471 traumatized teeth in 258 patients (female:119, male:139) were included in the study.

The data regarding gender, age, affected teeth, type of TDIs, location (home, school, street, park, hospital) and seasonal variations, etiology of TDIs (falls, impact against an object, bicycle/traffic accident, fight, intubation), time elapsed following TDIs, and treatment were obtained from patients' dental trauma records. TDIs types were classified according to Andreasen's classification system [22].

Statistical analyses were performed using SPSS 24.0 software (SPSS Inc, Chicago, IL, USA). Descriptive statistics were calculated, and chi-square test was used to compare categorical variables. The results were presented as the number of cases and frequencies (percentages). Statistical significance was set at $p<0.05$.

Results

A total of 258 patients, including 119 females (46.12%) and 139 males (53.88%) with a total of 471 traumatized teeth (primary teeth:152, permanent teeth:319) were evaluated. Patients' age ranged between 1-15 years old (mean ages, for primary teeth:3.55±1.90 and permanent teeth:10.07±2.18 years). Regarding age, the most common TDIs occured at the age of 8 years (n:35), followed by 9 (n:29), and 11 (n:27) years (Figure 1). Both the primary and permanent maxillary central incisors were the most common affected teeth by TDIs (Figure 2).

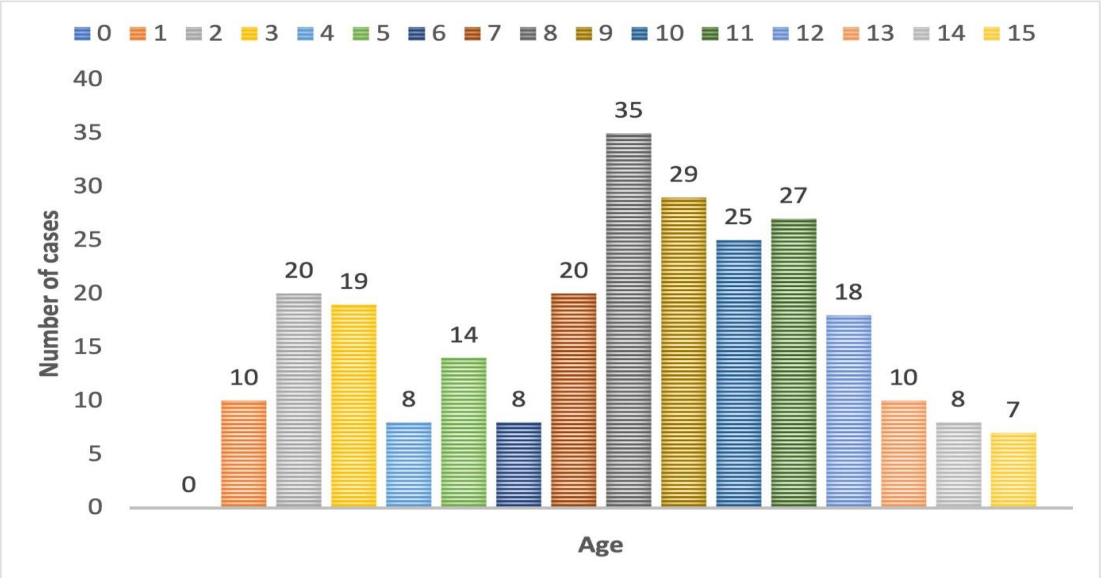

Figure 1. Distribution of TDIs by age

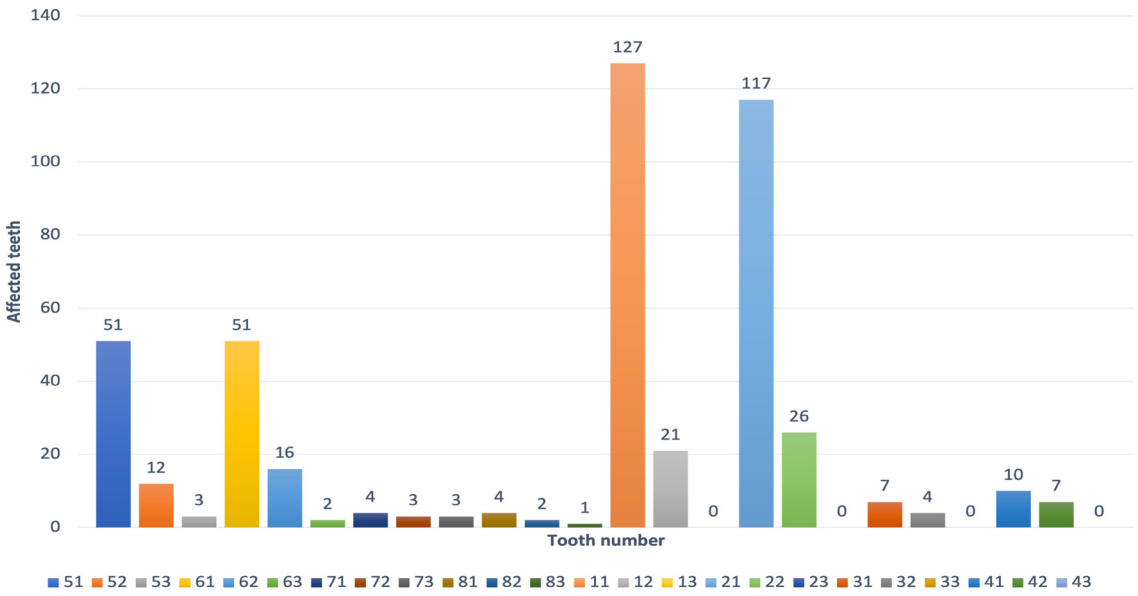

Figure 2. Distribution of TDIs by affected teeth

The distribution of the TDIs types is shown in Table 1. A statistically significant difference was observed between the primary and permanent teeth according to TDIs types. Dental hard tissue injuries occured more frequently in the permanent teeth, whereas periodontal tissue injuries were frequently observed in the primary teeth ($p<0.05$). It was observed that the most frequent TDIs type was enamel-dentin fracture in the permanent teeth (71.66%), and lateral luxations (36.84%) in the primary teeth (Table 1).

Regarding the location of TDIs, home (55.26%) was the most common location of occurrence in the primary teeth, and street (40.75%) was the most common location of occurrence in the permanent teeth. Patients' dental trauma records showed that the greatest number of TDIs were occured in the summer with regard to both primary (32.89%) and permanent (33.23%) teeth. In terms of location and seasonal variations, no statistically significant difference was observed between females and males ($p>0.05$) (Table 2).

Table 1. Distribution of the TDIs types in primary and permanent teeth

Type of TDIs	Primary teeth	Permanent teeth	Total	
	n (%)	n (%)	n (%)	*p*+
Dental hard tissue injuries	32 (21.05)	187 (58.62)	219 (46.50)	**0.0001**
Enamel infraction	-	2 (1.07)	2 (0.91)	0.999
Enamel fracture	1 (3.13)	6 (3.21)	7 (3.20)	0.999
Enamel-dentin fracture	5 (15.63)	134 (71.66)	139 (63.47)	**0.0001**
Enamel-dentin-pulp fracture	12 (37.50)	38 (20.32)	50 (22.83)	0.056
Crown-root fracture	9 (28.13)	2 (1.07)	11 (5.02)	**0.0001**
Root fracture	5 (15.63)	5 (2.67)	10 (4.57)	**0.005**
	Primary teeth	**Permanent teeth**	**Total**	
	n (%)	**n (%)**	**n (%)**	***p*+**
Periodontal tissue injuries	114 (75.00)	159 (49.84)	273 (57.96)	**0.0001**
Concussion	-	-	-	-
Subluxation	21 (18.42)	54 (33.96)	75 (27.47)	**0.007**
Lateral luxation	42 (36.84)	28 (17.61)	70 (25.64)	**0.0001**
Extrusion	6 (5.26)	9 (5.66)	15 (5.49)	0.887
Intrusion	28 (24.56)	9 (5.66)	37 (13.55)	**0.0001**
Avulsion	5 (4.39)	41 (25.79)	46 (16.85)	**0.0001**
Alveolar fracture	12 (10.53)	18 (11.32)	30 (10.99)	0.991

+, chi-square test; n, number; %, percent; TDIs, traumatic dental injuries

Table 2. Distribution of the location and season of TDIs according to gender and affected teeth

	Female	Male	Total	
Primary teeth - Location of TDIs	**n (%)**	**n (%)**	**n (%)**	***p*+**
Home	43 (58.90)	41 (51.90)	84 (55.26)	0.481
School	9 (12.33)	5 (6.33)	14 (9.21)	0.319
Street	17 (23.29)	20 (25.32)	37 (24.34)	0.919
Playground	4 (5.48)	13 (16.46)	17 (11.18)	0.059
Hospital	-	-	-	-
Primary teeth - Season of TDIs				
Winter (December/January/February)	16 (22.54)	18 (22.22)	34 (22.37)	0.963
Spring (March/April/May)	18 (25.35)	14 (17.28)	32 (21.05)	0.309
Summer (June/July/August)	21 (29.58)	29 (35.80)	50 (32.89)	0.521
Autumn (September/October/November)	16 (22.54)	20 (24.69)	36 (23.68)	0.904
Permanent teeth - Location of TDIs	**n (%)**	**n (%)**	**n (%)**	***p*+**
Home	21 (14.79)	20 (11.30)	41 (12.85)	0.449
School	46 (32.39)	68 (38.42)	114 (35.74)	0.318
Street	58 (40.85)	72 (40.68)	130 (40.75)	0.976
Playground	15 (10.56)	14 (7.91)	29 (9.09)	0.533
Hospital	2 (1.44)	3 (1.69)	5 (1.57)	0.837
Permanent teeth - Season of TDIs				
Winter (December/January/February)	24 (16.67)	23 (13.14)	47 (14.73)	0.468
Spring (March/April/May)	39 (27.08)	52 (29.71)	91 (28.53)	0.694
Summer (June/July/August)	49 (34.03)	57 (32.57)	106 (33.23)	0.875
Autumn (September/October/November)	32 (22.22)	43 (24.57)	75 (23.51)	0.761

+, chi-square test; n, number; %, percent; TDIs, traumatic dental injuries

The distribution of TDIs' etiology by gender and affected teeth is presented in Table 3. Falls were the main etiological factor of TDIs both in the primary (73.68%) and permanent (58.31%) teeth, followed by impact against an object (primary teeth:15.13%, permanent teeth:17.24%) (Table 3).

According to the time elapsed between TDIs and treatment, it was observed that the percentages of patients who referred to the clinic following TDIs within 1 hour was (5.49%), 1-6 hours (25.81%), 6-24 hours (33.33%), 1-7 days (23.37%), 1 week-6 months (8.74%), 6-12 months (1.63%), >1 year (1.63%). The distribution of the TDIs type with regard to the time elapsed between TDIs and treatment is presented in Table 4. Regarding the treatment of TDIs, the most common treatment choices were follow-up (46.05%) and extraction (39.47%) for primary teeth, and composite restorations (39.59%) for the permanent teeth (Table 5).

Table 3. Distribution of TDIs' etiology by gender and affected teeth

Etiology	**Female**	**Male**	**Total**	
Primary teeth	**n (%)**	**n (%)**	**n (%)**	***p*+**
Falls	47 (64.38)	65 (82.28)	112 (73.68)	**0.02**
Impact against an object	13 (17.81)	10 (12.66)	23 (15.13)	0.511
Bicycle accident	-	4 (5.06)	4 (2.63)	0.121
Traffic accident	13 (17.81)	-	13 (8.55)	**0.0001**
Fight	-	-	-	-
Intubation	-	-	-	-
Total	73 (100)	79 (100)	152 (100)	
Permanent teeth	**n (%)**	**n (%)**	**n (%)**	***p*+**
Falls	90 (62.94)	96 (54.55)	186 (58.31)	0.162
Impact against an object	24 (16.78)	31 (17.61)	55 (17.24)	0.963
Bicycle accident	21 (14.69)	31 (17.61)	52 (16.30)	0.581
Traffic accident	8 (5.59)	14 (7.95)	22 (6.90)	0.545
Fight	-	3 (1.70)	3 (0.94)	0.256
Intubation	-	1 (0.57)	1 (0.31)	0.999
Total	143 (100)	176 (100)	319 (100)	

+, chi-square test; n, number; %, percent; TDIs, traumatic dental injuries

Table 4. Time elapsed following TDIs and initial treatment

Type of TDIs	1 h n (%)	1-6 h n (%)	6-24 h n (%)	1-7 d n (%)	1 w-6 m n (%)	6-12 m n (%)	>1 y n (%)	Total n (%)
Enamel infraction	-	1 (0.79)	-	-	-	1 (12.50)	-	2 (0.41)
Enamel fracture	-	2 (1.57)	1 (0.61)	2 (1.74)	2 (4.65)	-	-	7 (1.42)
Enamel-dentin fracture	9 (33.33)	36 (28.35)	30 (18.29)	26 (22.61)	24 (55.81)	6 (75.00)	8 (100.00)	139 (28.25)
Enamel-dentin-pulp fracture	4 (14.81)	12 (9.45)	14 (8.54)	15 (13.04)	5 (11.63)	-	-	50 (10.16)
Crown-root fracture	-	2 (1.57)	4 (2.44)	4 (3.48)	1 (2.33)	-	-	11 (2.24)
Root fracture	1 (3.70)	2 (1.57)	3 (1.83)	3 (2.61)	-	1 (12.50)	-	10 (2.03)
Concussion	-	-	-	-	-	-	-	-
Subluxation	-	20 (15.75)	35 (21.34)	16 (13.91)	4 (9.30)	-	-	75 (15.24)
Lateral luxation	7 (25.93)	18 (14.17)	28 (17.07)	16 (13.91)	1 (2.33)	-	-	70 (14.23)
Extrusion	2 (7.41)	5 (3.94)	2 (1.22)	6 (5.22)	-	-	-	15 (3.05)
Intrusion	2 (7.41)	7 (5.51)	23 (14.02)	5 (4.35)	-	-	-	37 (7.52)
Avulsion	2 (7.41)	14 (11.02)	12 (7.32)	12 (10.43)	6 (13.95)	-	-	46 (9.35)
Alveolar fracture	-	8 (6.30)	12 (7.32)	10 (8.70)	-	-	-	30 (6.10)
Total	27 (5.49)	127 (25.81)	164 (33.33)	115 (23.37)	43 (8.74)	8 (1.63)	8 (1.63)	492 (100.00)

d: day, h: hour, m: month, n: number, %: percent, TDIs: traumatic dental injuries, w: week, y: year

Table 5. Treatment of TDIs according to type of teeth

Treatment	Primary teeth n (%)	Permanent teeth n (%)
Follow-up	70 (46.05)	31 (9.72)
Composite restoration	1 (0.66)	126 (39.50)
Reattachment of fractured tooth fragment	-	9 (2.82)
Cvek pulpotomy/Pulpotomy	3 (1.97)	21 (6.58)
Pulpectomy	6 (3.95)	24 (7.52)
Semi-rigid splint	4 (2.63)	42 (13.17)
Reposition+semi-rigid splint	8 (5.26)	34 (10.66)
Reimplantation+semi-rigid splint	-	20 (6.27)
Pediatric prosthesis	-	12 (3.76)
Extraction	60 (39.47)	-
Total	152 (100.00)	319 (100.00)

n, number; %, percent; TDIs, traumatic dental injuries

Discussion

During infancy, childhood and adolescence, children are susceptible to experiencing TDIs. TDIs represent a significant public health concern because of its high prevelance among children and adolescents, the negative psychosocial effects, and the costs of treatment [23]. Epidemiological studies provide useful information with regard to prevalence and related factors of TDIs. Therefore, retrospective studies are important to evaluate the prevalence and the different etiologies associated with TDIs, as well as development of preventive measures to reduce of TDIs [15, 16].

Results of this study showed that TDIs were more common in males (53.88%) than in females (46.12%). This result was in agreement with the previous studies [10, 11, 13-21, 24]. This can be explained by the fact that males being more energetic and participating more aggressive games and contact sports than females [11, 16, 17, 20].

Ritwik et al. [25] reported that most of TDIs occured in primary teeth at 2-4 years of age and in permanent teeth at 8-10 years of age. In the present study, the most affected age group was 2-3 year olds for primary teeth, and 8-9 year olds for permanent teeth (Figure 1). This results were in agreement with the previous studies [7, 13, 25, 26], and this can be related to the fact that children aged 2-3 years have insufficient motor coordination; hence, they are more prone to TDIs [18, 27], and in the 7-10 years old group, school-age children actively participate in social and sport activities which increase the risk of TDIs [27, 28]. The maxillary central incisors are more susceptible to TDIs due to their prominent position in the dental arch [13, 17, 26]. In agreement with the previous studies [7, 10-13, 16, 17, 26], the present study showed that the maxillary central incisors were the most common affected teeth by TDIs in both primary and permanent dentition.

Regarding the type of TDIs, there were significant differences among primary and permanent teeth. Dental hard tissue injury occured more frequently in the permanent teeth, whereas periodontal tissue injury was more frequently observed in the primary teeth (Table 1). It was found that enamel-dentin fractures were the most frequent type of TDIs in the permanent teeth, and lateral luxations were the most frequent type of TDIs in the primary teeth, which were in agreement with the previous studies conducted by Karabulut et al. [14], Eyupoglu et al. [29] and Cully et al. [30]. This may be associated with the resilience of supporting structure and short roots of the primary teeth [27, 31, 32]. Furthermore, the permanent teeth are firmly attached to the alveolar bone and thus more prone to fracture [33].

There were no statistically significant differences between females and males with regard to the distribution of the location and season of TDIs in both primary and permanent dentition. TDIs most frequently occured at home (55.26%) in the primary teeth, and at street (40.75%) in the permanent teeth. Similar to the previous studies [10-13, 19], TDIs most commonly occured during the summer season for both primary and permanent teeth. This result may be related to increased outside activities throughout the summer months. Children's physical activities can lead to increased TDIs when they play outside. Additionally, parents may find difficult to control their children's behaviour when they are allowed to run freely in large parks and/or playgrounds [10-12]. Consistent with the result of the previous studies [7, 10, 11, 13, 15-18, 29], the main etiological factor of TDIs in both primary and permanent teeth was falls (Table 3).

The time elapsed between TDIs and treatment has a significant impact on treatment choice and the prognosis of the injured teeth [34]. Unfortunately, in the present study, only 5.49% of the patients referred to the clinic within 1 h, 25.81% within 1-6 h, and 33.33% within 6-24 h following TDIs (Table 4). The low rate of early referral indicates that in our society, parents and/or guardians underestimate the importance of TDIs due to lack of knowledge about early management and possible complications, and they tend to delay in initial referral until acute symptoms of inflammation and esthetic problems appear [11, 16, 34]. Therefore, it is of great importance in order to increase awareness of parents/guardians about TDIs to improve the prognosis of traumatized teeth and prevent post-traumatic complications.

Similar to previous studies [10, 13, 29, 33], present study found that the most common treatment choice were follow-up (46.05%) and extraction (39.47%) in primary teeth, and composite restoration (39.50%) in permanent teeth (Table 5). Trauma records also showed that only twenty of forty-one avulsed permanent teeth were reimplanted because late referral of patients and lost of avulsed teeth. The significance of immediate reimplantation and necessity of storage media following avulsion injuries are often not well recognized not only by parents/guardians and teachers, but also by general dentists and physicians. Therefore, the public should be educated about the possibility of reimplanting the avulsed permanent teeth, and the preferred storage media, which are fresh milk or Hanks' Balanced Salt Solution (if available) [35].

Limitations of this study included the small sample size and relatively short study period. However, this is the first conducted study which evaluated the epidemiologic data related to TDIs in Denizli, south-west region of Türkiye. Based on the results of present study, further studies on long-term survival and complications of TDIs could be conducted.

In conclusion, the results of this study are in agreement with previous studies with regard to the distribution of factors associated with TDIs. The low rate of early referral to the clinic following TDIs highlights the need for education to the patients, parents/guardians, teachers about preventive program and the importance of emergency treatment against TDIs.

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Authors' contributions to the article

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

Research Article

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Social media addiction in medical faculty students; the relationship with dissociation, social anxiety, and alexithymia

Tıp fakültesi öğrencilerinde sosyal medya bağımlılığı; dissosiyasyon, sosyal anksiyete ve aleksitimi ile ilişkisi

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Abstract

Purpose: The aim of this study was to evaluate social media addiction in medical faculty students and the relationships with dissociation and social anxiety experienced in social media use and the level of alexithymia.

Materials and methods: 329 students who agreed to participate in the research completed the following scales; Bergen Social Media Addiction Scale (BSMAS), Toronto Alexithymia Scale (TAS-20), Van Online Dissociative Experiences Scale (VODES), Social Anxiety Scale for Social Media Users (SAS-SMU). The 4 sub-scales of the SAS-SMU, the 3 sub-scales of the TAS, and the VODES were analyzed as independent variables and the BSMAS was evaluated as a dependent variable.

Results: Social media addiction was affected by the shared content anxiety and self-assessment anxiety sub-scale points of the SAS-SMU, and by the VODES points. Shared content anxiety was determined to predict social media addiction positively and significantly (β=0.264, t (320)=3.16, *p*=0.002). Self-assessment anxiety was determined to predict social media addiction positively and significantly (β=0.169, t (320)=2.23, *p*=0.026). Online dissociative experiences was determined to predict social media addiction positively and significantly (β=0.217, t (320)=4.15, *p*<0.001).

Conclusion: It has been shown that the risk of social media addiction is predicted in young people who are prone to dissociation, have difficulties in social relations, and have social anxiety, but alexithymia does not predict social media addiction. There is a need for further experimental and longitudinal studies to establish the potential causative link between social anxiety, dissociation, and social media addiction.

Keywords: Social media addiction, social anxiety, dissociation, alexithymia, psychiatry.

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Öz

Amaç: Tıp fakültesi öğrencilerinde sosyal medya bağımlılığı ve sosyal medya kullanımında yaşanan dissosiyasyon ve sosyal kaygı ve aleksitimi düzeyi arasındaki ilişkiyi değerlendirmektir.

Gereç ve yöntem: Çalışmaya katılmayı kabul eden 329 öğrenci Bergen Sosyal Medya Bağımlılığı Ölçeği (BSMBÖ), Toronto Aleksitimi Ölçeği (TAS-20), Van Çevrimiçi Disosiyatif Yaşantılar Ölçeği (VÇDYÖ), Sosyal Medya Kullanıcıları için Sosyal Anksiyete Ölçeği (SMKSKÖ) ve sosyodemografik veri formunu eksiksiz doldurmuştur. SMKSKÖ'nin 4 alt ölçeği, TAS-20'nin 3 alt ölçeği ve VÇDYÖ bağımsız değişken olarak, BSMBÖ bağımlı değişken olarak değerlendirildi.

Bulgular: Sosyal medya bağımlılığı, SMKSKÖ'nin paylaşılan içerik kaygısı ve kendini değerlendirme kaygısı alt ölçek puanlarından ve VÇDYÖ puanlarından etkilenmektedir. Paylaşılan içerik kaygısı sosyal medya bağımlılığını olumlu ve anlamlı olarak yordamaktadır (β=0,264, t (320)=3,16, *p*=0,002). Kendini değerlendirme kaygısı sosyal medya bağımlılığını olumlu ve anlamlı olarak yordamaktadır (β=0,169, t (320)=2,23, *p*=0,026). Çevrimiçi disosiyatif yaşantılar da sosyal medya bağımlılığını olumlu ve anlamlı olarak yordamaktadır (β=0,217, t (320)=4,15, *p*<0,001).

Sonuç: Disosiyasyona yatkın, sosyal ilişkilerde zorluk yaşayan, sosyal kaygıları bulunan gençlerin sosyal medya bağımlılığı riskinin arttığı ancak aleksitiminin ise sosyal medya bağımlılığını predikte etmediği gösterilmiştir. Sosyal anksiyete ve dissosiyasyon ile sosyal medya bağımlılığı arasında potansiyel bir nedensel bağlantı kurmak için daha fazla araştırma deneysel ve boylamsal çalışmalar yapılması gerekmektedir.

Anahtar kelimeler: Sosyal medya bağımlılığı, sosyal anksiyete, dissosiyasyon, aleksitimi, psikiyatri.

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Introduction

Social media has become the currently most used communication tool of adolescents and young adults, with communication through social media preferred to almost all face-to-face communication [1]. Social media addiction associated with increased use and symptoms of addiction has become conceptualised as a series of disorders originating from social media such as social media disorder and excessive social media use [2, 3]. In the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) of the American Psychiatry Association, there is as yet no place for social media addiction although it is felt to be a problem [4].

As there is no common definition for problematic social media use, it is difficult to estimate the extent [5]. There may be several reasons why social media use is so high among young people. It is important for young people to want to show themselves and be noticed, and social media can be used anonymously or using different names. By making adjustments to both the image and surroundings of images used on social media, photographs and videos with idealised properties can be uploaded. These images or written texts can reach a very large mass. If accepted by peer groups, this plays a role in structuring the social identity in terms of popularity [6]. Therefore, it is both important and necessary for mental health professionals dealing with adolescents and young adults to have knowledge of social media and its use.

Normative dissociation is thought to be related to people's experience of excessive technology use. Loss of control and awareness described by users, and the question of "what just happened?" after scrolling through social media are characteristic of normative dissociation. Every stimulus outside the area of attention with narrow and deep focus is discounted [7, 8]. Previous studies have reported that social media users experience "internet blackout" and go into a trance of social media use [9, 10]. Although not only stated as social media, previous studies have determined a high-level positive correlation between the time spent on the internet and dissociation [11-13]. Similarly, Olson et al. [14] reported a positive relationship between smartphone addiction and being able to be hypnotised. Hypnosis is accepted as a dissociative status [8].

Social anxiety generally starts in adolescence when acceptance by friendship groups and peers, and the impressions made on others become more important, and in most cases continues through the university period. Although it is thought that social anxiety will be seen less in social media use for reasons such as not being in the same physical environment and the opportunity to remain anonymous, as the boundaries in social media relationships have not been clearly drawn, this lack of boundaries leads to anxiety in some individuals. Therefore, it is thought that communication established on social media can increase social anxiety [15].

Alexithymia is defined as difficulty in describing and expressing emotions [16]. Those with high-level alexithymia try to regulate emotional states behaviourally. There are many studies proving that alexithymia plays an important role in the etiology of behavioral addictions [13, 17, 18]. As technology facilitates interpersonal relationships, this can lead to abuse and addiction in individuals with high-level alexithymia [19-21]. In addition, alexithymia is accepted as a predictor of dissociative experiences. There has been shown to be a strong relationship between alexithymia and disassociation in addiction [16, 22].

In the light of this information, the hypothesis of this study was that individuals with social media addiction would be predisposed to dissociation, and have high levels of social anxiety and alexithymia.

The aim of this study was to evaluate social media addiction in medical faculty students and the relationships with dissociation and social anxiety experienced in social media use and the level of alexithymia. Our study investigated social media addiction in three dimensions: social anxiety experienced in social media use, dissociation and alexithymia.

Materials and methods

Study design

The study is a cross-sectional epidemiological study. The population consisted of all students (n=1514) enrolled in the 2022-2023 academic year of a medical school located in Denizli. An online questionnaire was sent to medical faculty students (1st -6th grade students) via WhatsApp between 15 December 2022 and 1 January

2023. Students who agreed to participate in the research completed the questionnaire and the following scales; Bergen Social Media Addiction Scale (BSMAS), Toronto Alexithymia Scale (TAS-20), Van Online Dissociative Experiences Scale (VODES), Social Anxiety Scale for Social Media Users (SAS-SMU), and a Sociodemographic Form prepared by the researchers.

To avoid repeat submissions, the online questionnaire system used accepted only one form from an IP address. The questionnaire did not allow the respondent to pass to another question without completing the previous one. The forms of all the participants who completed all the items were included for analysis. The questionnaire was distributed to a total of 1514 students, of which 503 opened the questionnaire attachment and consented to participate in the study. Of these 503, all the questionnaire items were fully completed by 329, so the responses of a total of 329 medical students were analyzed and evaluated.

Sociodemographic data form

This form was designed by the researchers to obtain the information of age, gender, year of study, social media applications used, and the time spent on the internet.

Bergen Social Media Addiction Scale (BSMAS)

The BSMAS was developed by Andreassen et al. [23], and validity and reliability studies for the Turkish version were conducted by Demirci [24]. Each of the 6 items of the scale corresponds to the 6 basic measurements of addiction; mental distraction, mood change, tolerance, deprivation, conflict, and failure to quit. The items are answered on a 5-point likert-type scale graded from 1=very rarely to 5=very often, to give a total score in the range of 6-30 points [24].

Van Online Dissociative Experiences Scale (VODES)

The VODES was designed by Boysan et al. [25] to evluate the degree to which an individual tends to experience various dissociative symptoms during online activities. The 62 items of the scale are scored with likert-type scoring from 0=never to 10=always, with higher points indicating a greater intensity of dissociative experiences.

Social Anxiety Scale for Social Media Users (SAS-SMU)

Although various scales have been developed to measure certain levels of social anxiety of students, none of those studies addressed the measurement of social anxiety in social media. SAS-SMU developed by Alkis et al. [26] can be used to measure the social anxieties of university students. The scale is formed of 21 items in 4 sub-scales of shared content anxiety, privacy anxiety, interaction anxiety, and self-assessment anxiety. With alpha coefficients for these dimensions ranging between 0.80 and 0.92, satisfactory reliability has been determined. Each item in the scale is scored with a 5-point likert-type scale from 1 to 5 points, with higher points indicating a higher level of anxiety.

Toronto Alexithymia Scale (TAS-20)

The 20-item TAS was developed by Bagby et al. [27], and the Turkish adaptation validity and reliability studies were conducted by Güleç et al. [28]. It is a likert-type self-assessment scale. Item numbers 4, 5, 10, 18, and 19 are reverse scored. The sub-scale of difficulty in describing emotions includes 7 items (#1, 3, 6, 7, 9, 13, 14) defined as difficulty in identifying emotions and distinguishing them from the physical sensations that accompany emotional stimulation. The difficulty in verbalizing emotions sub-scale consists of 5 items (items 2, 4, 11, 12, 17), defined as difficulty in transferring emotions to others. The externally-oriented thinking sub-scale consists of 8 items (items 5, 8, 10, 15, 16, 18, 19, 20), defined as the presence of an extroverted cognitive structure and the weakness of the power of introspective thinking and imagination. The subject is instructed to mark each item with the most appropriate response; never, occasionally, sometimes, often, always. Higher points indicate a higher level of alexithymia.

Statistical analysis

Data obtained in the study were analyzed statistically using SPSS vn. 22.0 software. Conformity of the data to normal distribution was assessed with the Kolmogorov-Smirnov test and Skewness-Kurtosis coefficients. The difference

in measured variables between independent groups was evaluated using the Student's t-test. Correlations between variables were examined with the Pearson correlation test. Multiple linear regression analysis was performed to evaluate the risk of independent variables. Results were given in a 95% confidence interval and statistical significance was accepted as $p<0.05$ in all tests.

Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University Medical Faculty (decision no:18, dated:13.12.2022), and permission to conduct the study was received from the Dean's Office of Pamukkale University Medical Faculty.

Results

Sociodemographic data

The distribution of the sociodemographic data of the 329 medical students included in the study is shown in Table 1. The students comprised 215 (65.3%) females and 114 (34.7%) males. The grades of study of the students were determined as grade 1 for 58 (17.6%), grade 2 for 53 (16.1%) grade 3 for 56 (17%), grade 4 for 60 (18.2%), grade 5 for 49 (14.9%) and grade 6 for 53 (16.1%). It was stated by 255 (77.5%) students that they did not live on campus.

Characteristics associated with social media use

When the rates of social media use were examined, 148 (45%) students reported that they generally used Instagram, and 110 (33.4%) stated that they never used Twitter, 269 (80.5%) Facebook, 161 (48.9%) Snapchat, 270 (82.1%) Tiktok, 284 (86.3%) LinkedIn, and 263 (79.9%) Twitch. Other than these social media sites, 219 (66.6%) students stated that they did not use any other program, and 80 (24.3%) reported that they used YouTube. The time spent per day on social media was determined to be mean 1-3 hours by 147 (44.7%) students, and 3-5 hours by 111 (33.7%). The distribution of the characteristics related to social media use of the students is shown in Table 2.

Table 1. The distribution of the sociodemographic data

		n	%
Gender	Female	215	65.3
	Male	114	34.7
Grade	Grade 1	58	17.6
	Grade 2	53	16.1
	Grade 3	56	17.0
	Grade 4	60	18.2
	Grade 5	49	14.9
	Grade 6	53	16.1
Place of residence	Live on campus	74	22.5
	Did not live on campus	255	77.5

Table 2. Characteristics associated with Social Media Use

		n	%
Average time spent on social media per day	<1 hour	37	11.2
	1-3 hour	147	44.7
	3-5 hour	111	33.7
	5-7 hour	33	10.0
	>7 hour	1	0.3

Table 2. Characteristics associated with Social Media Use (continued)

Average time spent on the Internet excluding social media per day	<1 hour	110	33.4
	1-3 hour	123	37.4
	3-5 hour	62	18.8
	5-7 hour	27	8.2
	>7 hour	7	2.1
Frequency of Instagram usage	None	29	8.8
	Rarely	13	4.0
	Sometimes	48	14.6
	Generally	148	45.0
	Always	91	27.7
Twitter usage frequency	None	110	33.4
	Rarely	69	21.0
	Sometimes	59	17.9
	Generally	42	12.8
	Always	49	14.9
Facebook usage frequency	None	265	80.5
	Rarely	44	13.4
	Sometimes	15	4.6
	Generally	4	1.2
	Always	1	0.3
Snapchat usage frequency	None	161	48.9
	Rarely	38	11.6
	Sometimes	42	12.8
	Generally	46	14.0
	Always	42	12.8
TikTok usage frequency	None	270	82.1
	Rarely	24	7.3
	Sometimes	15	4.6
	Generally	12	3.6
	Always	8	2.4
LinkedIn usage frequency	None	284	86.3
	Rarely	35	10.6
	Sometimes	7	2.1
	Generally	3	0.9
	Always	0	0
Twitch usage frequency	None	263	79.9
	Rarely	30	9.1
	Sometimes	20	6.1
	Generally	10	3.0
	Always	6	1.8
Other social media platforms used	None	219	66.6
	Pinterest	7	2.1
	Youtube	80	24.3
	Other	23	7.0

Scale evaluations

The total scale and sub-scale points of the students are shown in Table 3. The total scale points for all the students were determined to be mean 6.67±5.15 (6-30) for the BSMAS, 76.63±70.84 (0-423) for the VODES, 54.55±17.10 (21-105) for the SAS-SMU, and 51.64±10.92 (30-87) for the TAS.

In the comparisons of the scale points according to gender, the mean points were found to be similar for both genders for the TAS (p=0.850), the difficulty in describing emotions sub-scale (p=0.156), difficulty in verbalizing emotions sub-scale (p=0.600), and the VODES (p=0.106). The TAS externally-oriented thinking sub-scale points were determined to be statistically significantly higher in males than females (p=0.002). The total and sub-scale points of the BSMAS and the SAS-SMU were determined to be statistically significantly higher in females than males (p<0.05). The comparisons of the scales and sub-scales according to gender are shown in Table 4.

A moderate level positive correlation was determined between the BSMAS points and the SAS-SMU points (r=0.489, p<0.001). As social media addiction increased, there was determined to be a statistically significant increase in social anxiety. When the sub-scale correlations were examined, all the correlations were positive at a strong level with shared context anxiety (r=0.524, p<0.001), at a weak level with privacy anxiety (r=0.235, p<0.001), and at a moderate level with interaction anxiety (r=0.342, p<0.001) and self-assessment anxiety (r=0.488, p<0.001). A moderate level positive correlation was determined between the TAS scale and the difficulty in describing emotions and difficulty in verbalizing emotions sub-scales (r=0.293, r=0.313, r=0.274, respectively) (p<0.001). No correlation was determined with the TAS externally-oriented thinking sub-scale (p>0.05). A moderate level positive correlation was determined between the BSMAS and the VODES (r=0.488, p>0.001). All the correlations are shown in Table 5.

Table 3. The total scale and sub-scale points of the students

Scales	Mean±SD	min-max
BSMAS	16.67±5.15	6-30
VODES	76.63±70.84	0-423
SAS-SMU Total	54.55±17.10	21-105
SAS-SMU Shared content anxiety	16.14±6.90	7-35
SAS-SMU Privacy anxiety	16.79±5.39	5-25
SAS-SMU Interaction anxiety	15.15±6.18	6-30
SAS-SMU Self-assessment anxiety	6.49±2.78	3-15
TAS-20 Total	51.64±10.92	30-87
TAS-20 Difficulty identifying feelings	17.23±6.17	7-35
TAS-20 Difficulty describing feelings	13.72±3.72	5-25
TAS-20 Externally-oriented thinking	20.69±3.84	12-32

SD: Standart Deviation, **Min-max:** minimum-maximum, **BSMAS:** Bergen Social Media Addiction Scale
VODES: Van Online Dissociative Experiences Scale, **SAS-SMU:** Social Anxiety Scale for Social Media Users
TAS-20: Toronto Alexithymia Scale

Table 4. The comparisons of the scales and sub-scales according to gender

Scales	Female	Male	t	*p**
BSMAS	17.52±4.91	15.08±5.23	4.183	**<0.001**
VODES	71.73±65.22	85.87±79.86	-1.625	0.106
SAS-SMU Total	57.89±16.57	48.25±16.36	5.043	**<0.001**
SAS-SMU Shared content anxiety	17.08±6.94	14.38±6.48	3.435	**0.001**
SAS-SMU Privacy anxiety	17.61±4.99	15.25±5.80	3.694	**<0.001**
SAS-SMU Interaction anxiety	16.51±6.14	12.58±5.42	5.975	**<0.001**
SAS-SMU Self-assessment anxiety	6.68±2.80	6.04±2.71	1.992	**0.047**
TAS-20 Total	51.56±11.02	51.80±10.78	-0.189	0.850
TAS-20 Difficulty identifying feelings	17.59±6.23	16.57±6.00	1.423	0.156
TAS-20 Difficulty describing feelings	13.80±3.91	13.58±3.35	0.525	0.600
TAS-20 Externally-oriented thinking	20.18±3.51	21.65±4.24	-3.172	**0.002**

***p<0.05** statistically significant, *T test, **BSMAS:** Bergen Social Media Addiction Scale, **VODES:** Van Online Dissociative Experiences Scale **SAS-SMU:** Social Anxiety Scale for Social Media Users, **TAS-20:** Toronto Alexithymia Scale

Table 5. Distribution of the relationship between BSMAS and other scale points

		BSMAS
VODES	r	0.380
	p	**<0.001**
SAS-SMU Total	r	0.489
	p	**<0.001**
SAS-SMU Shared content anxiety	r	0.524
	p	**<0.001**
SAS-SMU Privacy anxiety	r	0.235
	p	**<0.001**
SAS-SMU Interaction anxiety	r	0.342
	p	**<0.001**
SAS-SMU Self-assessment anxiety	r	0.488
	p	**<0.001**
TAS-20 Total	r	0.293
	p	**<0.001**
TAS-20 Difficulty identifying feelings	r	0.313
	p	**<0.001**
TAS-20 Difficulty describing feelings	r	0.274
	p	**<0.001**
TAS-20 Externally-oriented thinking	r	0.064
	p	0.250

p*<0.05 statistically significant, **r: Pearson Correlation, **BSMAS:** Bergen Social Media Addiction Scale
VODES: Van Online Dissociative Experiences Scale, **SAS-SMU:** Social Anxiety Scale for Social Media Users
TAS-20: Toronto Alexithymia Scale

Multiple linear regression model

The 4 sub-scales of the SAS-SMU, the 3 sub-scales of the TAS, and the VODES were analyzed as independent variables and the BSMAS was evaluated as a dependent variable. As a result of the analysis, a significant regression model, F (8, 320)=21.38, p<0.001 and 33% of the variance in dependent variable ($R^2_{adjusted}$=0.33) was explained by independent variables. According to this, social media addiction was affected by the shared content anxiety and self-assessment anxiety sub-scale points of the SAS-SMU, and by the VODES points. Shared content anxiety was determined to predict social media addiction positively and significantly (β=0.264, t (320)=3.16, p=0.002). Self-assessment anxiety was determined to predict social media addiction positively and significantly (β=0.169, t (320)=2.23, p=0.026). Online dissociative experiences were determined to predict social media addiction positively and significantly (β=0.217, t (320)=4.15, p<0.001). Alexithymia had no effect on the model. The results of the linear regression analysis are shown in Table 6.

Table 6. Results of multiple linear regression analysis regarding the prediction of social media addiction by social anxiety, alxiethymia and dissociative experiences scale points

Scales	BSMAS				
	B	**SE**	***β***	**95% CI**	***p***
SAS-SMU Shared content anxiety	0.197	0.062	0.264	0.075-0.319	**0.002**
SAS-SMU Privacy anxiety	-0.023	0.052	-0.024	-0.125-0.79	0.655
SAS-SMU Interaction anxiety	0.072	0.050	0.087	-0.027-0.171	0.151
SAS-SMU Self-assessment anxiety	0.313	0.140	0.169	0.037-0.589	**0.026**
TAS-20 Difficulty identifying feelings	0.051	0.056	0.061	-0.059-0.160	0.364
TAS-20 Difficulty describing feelings	0.019	0.091	0.013	-0.160-0.198	0.838
TAS-20 Externally-oriented thinking	-0.033	0.064	-0.025	-0.160-0.093	0.604
VODES	0.016	0.004	0.217	0.008-0.023	**<0.001**

F (8, 320)=21.38, p<0,001- ($R^2_{adjusted}$=.33), *p<0.05 statistically significant; 95% **C.I:** Confidence Interval, **SE:** Standard Error, **BSMAS:** Bergen Social Media Addiction Scale, **VODES:** Van Online Dissociative Experiences Scale, **SAS-SMU:** Social Anxiety Scale for Social Media Users **TAS-20:** Toronto Alexithymia Scale

Discussion

In this study, the social media addiction of medical faculty students was evaluated together with the dissociation and social anxiety experienced in social media use, and the alexithymic personal characteristics of the students, and the relationships between these.

The hypothesis of the study was that social anxiety, alexithymia, and online dissociative experiences would be factors increasing social media addiction. In the advanced statistical analysis, in the model which examined the effect of dissociation, social anxiety, and alexithymia on social media addiction, it was determined that dissociation and social anxiety predicted the risk of social media addiction, and alexithymia had no effect.

Social media addiction has been found to be statistically significantly higher in females. Studies in literature have reported higher use of social media at the level of addiction by females and females have been reported to be more prone to developing addiction behaviours in activities involving social interaction [2, 29].

Female social media users were determined to have statistically significantly higher social anxiety total and all sub-scale points than male social media users. In a previous review that investigated gender differences in social anxiety, it was reported that social anxiety was seen more often and at a greater level in females [30].

Results of previous studies have shown no difference between the genders in respect of dissociation. Similarly in the current study of university students in Türkiye, no statistically significant difference was determined between the genders in respect of dissociation [31].

No significant difference was observed between the genders in respect of alexithymia in the current study. Similarly, Pasini et al. [32] observed no difference in alexithymia between

the genders, and that study in Italy was also conducted on healthy volunteers. Another community-based study in Finland reported that although the frequency of alexithymia was higher in females, the difference between the genders was not statistically significant [33, 34]. These different findings in literature related to gender can be attributed to different samples and methods used, sample size, and time differences.

The current study results showed that dissociation predicted social media addiction. In literature, a connection has been indicated between normative separation and social media use [7]. There are studies in literature that have shown a positive correlation between inernet addiction and dissociation [11-13]. It has also been reported that hypnosis is a dissociative state and there is a positive relationship between smartphone addiction and the ability to be hypnotised [7, 8, 14]. Tran et al. [35] reported that the study subjects described a feeling of disgust when they realized how long they spent and did not realize how time passed when they went on to their phone briefly to check social media. The current study results were consistent with the findings in literature. The few studies in literature that have examined the relationship between dissociation and social media addiction have been discussed above. There are also studies in the literature that have examined dissociation and internet addiction without differentiation as social media addiction. Studies which have been conducted in university students in Türkiye to examine the relationship between dissociation and internet addiction have determined a positive correlation [11]. In a study of adults which examined dissociative symptoms and accompanying psychological disorders, dissociative symptoms were reported to show a positive correlation with the severity of internet addiction [12]. In another study of young adults aged 18-21 years, dissociation was shown to play a role in internet addiction [13]. The results of the current study showed that dissociative processes predicted social media addiction. This showed that an individual with dissociative processes while scrolling social media can be more easily removed from external stimuli, can pass into a trance, may experience blackout, and these processes can increase social media addiction.

In the study, a scale was used which was developed to evaluate social anxiety in social media users and this scale is formed of 4 sub-scales [26]. The content sharing anxiety sub-scale which determines social anxiety originating from sharing their own content or content shared by others related to themselves on social media platforms predicted social media addiction, and the self-assessment anxiety sub-scale, which evaluates social anxiety originating from how the individual evaluates themself and how they think they are seen by others on social media platforms predicted social media addiction.There has been shown to be a relationship between anxiety level and the behaviour patterns of individuals in the social media environment [26]. Studies have reported a relationship between depression and social anxiety and aimless use such as surfing the internet [36], and it has been shown that intense inactive computer use leads to depression and anxiety disorders [37]. It has been shown that individuals with social anxiety can feel more comfortable in online interaction rather than face-to-face interaction as they can preserve their anonymity and think that they are less exposed to negative evaluations [38]. Various studies have stated that the internet can meet the social needs of some people, especially those who have difficulty in establishing social relationships, thereby helping social cohesion and providing a feeling of belonging [39, 40]. In this context it has been suggested that the internet can be used as a means of improving low self-esteem, depression, anxiety, and loneliness by individuals with social anxiety [38, 41, 42]. It has been reported that individuals who feel uncomfortable in face-to-face interaction use the internet more for social interaction, and those who feel more comfortable in offline interaction use the internet more to obtain information [43]. In a recent study of adults aged 18-35 years, social anxiety was shown to be a predictor of social media addiction [44]. The reason that sharing content anxiety and self-assessment anxiety increase social media addiction could be that these individuals prefer online communication because of difficulties in face-to-face communication, fear of being rejected or disliked, and self-confidence problems. The current study results and literature findings support the hypothesis that social media may be used intensely by individuals with social anxiety

to regulate their emotions and reduce social anxieties. However, the ruminative thoughts and anxieties related to what they have shared on social media platforms, what has been shared by others related to them, and what others think of them as a result of this shared material, can trigger social media addiction in these individuals.

The total points of the alexithymia scale used in the study were found to be positively correlated with social media addiction, dissociation and the social anxiety scale points. In the advanced statistical analysis when the factors affecting social media addiction were evaluated, alexithymia was not seen to have a predictive effect. In literature, alexithymia has been reported to be associated with overuse or problematic internet use and internet addiction [13, 17, 19, 20].

However, in contrast to several studies showing a relationship between alexithymia and internet addiction, two different studies of adults aged 18-35 years, have shown that alexithymia does not predict social media addiction [44, 45]. Individuals with a high level of alexithymia have difficulties in personal relationships and do not like or avoid close relationships [46, 47], and this therefore seems compatible with the absence of a positive relationship between alexithymia and social media use [44, 45].

In the study, there was determined to be a positive correlation between the total points of the TAS-20 and the 3 sub-scales and dissociation, and similarly in literature a positive correlation has been shown between alexithymia and dissociation [22, 48, 49]. The difficulty in describing emotions and difficulty in verbalising emotions sub-scales of the TAS-20 were found to be positively correlated with the SAS-SMU points. Consistent with these findings, Panayiotou et al. [50] showed that alexithymia predicted social anxiety and there was a positive relationship between them.

Due to the cross-sectional design of the study, the sample size, that the majority of the participants were female, and that a specific group were studied, the sample of this study cannot represent the general population. The study was conducted by filling out an online form, and participants were not subjected to a psychiatric evaluation or asked about their psychiatric history. Despite these limitations, our study is the first to investigate social media addiction in three dimensions: social anxiety experienced in social media use, dissociation and alexithymia.

Consequently, in the study has been shown that the risk of social media addiction is predicted in young people who are prone to dissociation, have difficulties in social relations, and have social anxiety, but alexithymia does not predict social media addiction. Young people with social anxiety who experience difficulty in social relationships are at great risk because of their intense social media use in an effort to be active in social areas and to control social relationships. The results obtained in this study showed that individuals with social anxiety tend to prefer online interaction to face-to-face interaction and are at risk of social media addiction. Therefore, it is thought that recognizing social anxiety in young people by both educators and health professionals working with young people and making appropriate referrals for treatment may be protective in the development of social media addiction. In the study, a strong relationship was determined between dissociation and social media addiction. Young people who are prone to dissociation can easily get out of the moment and get away from stimuli while browsing social media, which increases social media addiction. If we want to address social media addiction, we need to keep in mind the susceptibility to dissociation and investigate whether the young person has symptoms of dissociation. Although one of the hypotheses of our study was that alexithymia could predict social media addiction, it was found that alexithymia was not a predictor of social media addiction. The size and characteristics of the sample may have influenced the results; therefore, further experimental and longitudinal studies with much larger samples and diverse study groups are needed to establish the potential causal relationship between social anxiety, dissociation, alexithymia and social media addiction.

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

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Ethical aspect of the study

Approval for the study was granted by the Non-Interventional Clinical Research Ethics Committee of Pamukkale University Medical Faculty (decision no:18, dated:13.12.2022), and permission to conduct the study was received from the Dean's Office of Pamukkale University Medical Faculty.

Authors' contributions to the article

M.A.T. constructed the main idea and hypothesis of the study. M.A.T. and T.T.U. developed the theory and arranged/edited the material and method section. M.A.T. and T.T.U. have done the evaluation of the data in the Results section. Discussion section of the article written by M.A.T. and T.T.U.

M.A.T. and T.T.U. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Decreased *GADD45A* gene expression level in MGUS

MGUS'ta azalmış GADD45A gen ekspresyonu seviyesi

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Abstract

Purpose: Monoclonal gammopathy of undetermined significance (MGUS) is a plasma cell dyscrasia. It is known that MGUS has an increased risk of progression to multiple myeloma (MM), and prepares the ground for diseases such as Waldenstrom macroglobulinemia (WM), non-Hodgkin lymphoma, and chronic lymphocytic leukemia (CLL). Our study aimed to evaluate whether some important p53 pathway genes differ in terms of expression between MGUS and healthy individuals.

Materials and methods: Bone marrow was collected from eight healthy individuals and eight individuals diagnosed with MGUS, and RNA samples were isolated. The expression levels of various genes involved in the p53 pathway were compared using an RT2-profiler PCR array. *β-Actin* housekeeping gene expression level was used for normalization. Pearson's Correlation and Receiver Operating Characteristic (ROC) analyses were conducted.

Results: Among the genes whose expression levels were examined in this study, it was determined that the expression level of only the *GADD45A* gene decreased significantly in the MGUS group compared to the control group (p=0.027). Pearson's correlation data showed that *GADD45A* gene expression was highly correlated with 12 of the other genes (*APAF1, CDK4, PCNA, BAX, CDKN2A, CASP9, CHEK2, MDM2, RB1, P53, BCL2, CHEK1*) examined in the p53 pathway (r>0.7). In addition, according to the ROC analysis, *GADD45A* was detected to have strong discrimination power between MGUS and healthy individuals (*AUC*=0.797 and p=0.015).

Conclusion: The decreased expression of the *GADD45A* gene in the MGUS group compared to the control group may be useful as a new biomarker to detect the development of MGUS.

Keywords: MGUS, p53 pathway, *GADD45A*.

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Öz

Amaç: Belirsiz öneme sahip monoklonal gamopati (MGUS), bir plazma hücre diskrazisidir. MGUS'un Multipl miyelom'a (MM) ilerleme riskini artırdığı, ayrıca Waldenstrom makroglobulinemi (WM), non-Hodgkin lenfoma ve kronik lenfositik lösemi (KLL) gibi hastalıklara zemin hazırladığı bilinmektedir. Çalışmamızda bazı önemli p53 yolağı genlerinin MGUS ve sağlıklı bireylerde ekspresyon açısından farklılık gösterip göstermediğini değerlendirmeyi amaçladık.

Gereç ve yöntem: Çalışma için 8 sağlıklı ve 8 MGUS tanılı bireyden kemik iliği toplandı ve RNA örnekleri izole edildi. p53 yolağında yer alan çeşitli genlerin (*BAX, CDKN2A, APAF1, ATM, ATR, CASP9, CDK4, CDKN1A, CHEK2, E2F1, E2F3, MCL1, MDM2, MDM4, PTEN, RB1, P53, BCL2, CHEK1, GADD45A, PCNA, PTX3*) ekspresyon seviyeleri, RT2-profiler PCR array yöntemiyle karşılaştırıldı. Normalizasyon için *β-Aktin* gen ekspresyon seviyesi kullanıldı. Pearson Korelasyon ve Receiver Operating Characteristic (ROC) analizleri yapıldı.

Bulgular: Bu çalışmada ekspresyon seviyeleri incelenen genlerden sadece *GADD45A* geninin ekspresyon seviyesinin kontrol grubuna göre MGUS'ta anlamlı olarak azaldığı belirlendi (p=0,027). Pearson korelasyon verileri, *GADD45A* gen ekspresyonunun, p53 yolağında incelenen diğer 12 gen (*APAF1, CDK4, PCNA, BAX, CDKN2A, CASP9, CHEK2, MDM2, RB1, P53, BCL2, CHEK1*) ile yüksek oranda ilişkili olduğunu gösterdi (r>0,7). Ayrıca ROC analizine göre *GADD45A*'nın MGUS ile sağlıklı bireyler arasında güçlü bir ayrım gücüne sahip olduğu saptandı (*AUC*=0,797 ve p=0,015).

Sonuç: *GADD45A* geninin MGUS grubunda kontrol grubuna göre azalmış ekspresyonu, MGUS gelişimini saptamak için yeni bir biyobelirteç olarak faydalı olabilir.

Anahtar kelimeler: MGUS, p53 yolağı, *GADD45A*.

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Introduction

Monoclonal gammopathy of undetermined significance (MGUS) is a clonal plasma cell proliferative disorder characterized by the presence of para(M) proteins in the peripheral blood or an abnormal free light chain (FLC) ratio, which progresses to multiple myeloma over time [1]. MGUS occurs as a result of acquired hyperdiploidy or a translocation [t(4;14), t(6;14), t(11;14)] involving the immunoglobulin heavy chain gene locus. Additional genetic changes, such as somatic mutations and copy number variations, are also present in subclonal populations, and the frequency of these additional mutations increases as the disease progresses to multiple myeloma [2]. The prevalence of pre-cancerous MGUS transforming into multiple myeloma is reported as approximately 1%. In a study by Akhtar et al. [3], it was suggested that myricetin is a protective supplement in cancer development from MGUS to myeloma by increasing p53 expression at both the mRNA and protein levels. *TP53* is one of the most important genes known to have a regulatory role in tumor suppression, and it achieves this by controlling genes involved in the cell cycle. Various changes that may occur in the *TP53* gene and genes related to the *TP53* pathway may be the source of various pathogeneses, especially cancers. For example, *TP53* deletion has been reported in up to 10% of MM cases [4, 5]. Therefore, the *TP53* pathway is indisputable for both MGUS and MM. Although *TP53* mutations have been associated with short survival in MM, there is limited literature on the association between the expression of this *TP53* gene and pathway-related genes in MGUS [6]. Thus, information in the literature regarding gene expressions in the *TP53* pathway needs to be enriched.

Materials and methods

Collection of samples

Bone marrow samples from eight MGUS and eight healthy controls were collected with written informed consent. Bone marrow samples collected in tubes with EDTA were obtained from İstanbul University Medicine Faculty, Department of Hematology. The healthy control group consisted of bone marrow samples obtained from transplantation donor candidates.

MGUS samples were taken in cases with plasma cell count less than 10%, abnormal protein less than 30 g/L, and without both hypercalcemia and lytic lesions. Samples of healthy controls were taken from individuals who were not relatives of MGUS patients. Healthy donors were screened for hematological diseases including MGUS. The study was approved by the İstanbul University Medical Faculty Clinical Research Ethics Committe, and was performed according to the Declaration of Helsinki.

RNA extraction and cDNA synthesis

RNA was isolated from bone marrow (BM) samples using the QiaAmp RNA Blood Mini Kit (Qiagen, USA). RNA quality and quantity were measured using a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, USA). cDNA was synthesized using the Qiagen RT2 HT First Strand Kit (Qiagen, USA) with 1000 ng of total RNA.

Expression pattern determination using qRT-PCR array

The RT2 Profiler PCR array (CAPH_133446F; cat no. 330131/12 plates) was used for expression pattern analysis on the LightCycler 480 II platform. The expressions of 22 genes (*BAX, CDKN2A, APAF1, ATM, ATR, CASP9, CDK4, CDKN1A, CHEK2, E2F1, E2F3, MCL1, MDM2, MDM4, PTEN, RB1, P53, BCL2, CHEK1, GADD45A, PCNA, PTX3*) involved in the p53 pathway and known to be involved in cellular processes that are important for cancer pathogenesis were evaluated by qRT-PCR. *SYBR* Green dye was used for the qRT-PCR analysis. β-*Actin* was used for normalization, and the study was designed in duplicate.

Statistical analysis

SPSS 21 was used for statistical analysis. The Kolmogorov-Smirnov test was performed to analyze whether the gene expression levels were distributed normally. Normally distributed ones were analyzed by Student's t-test, and non-normally distributed ones were analyzed by the Mann-Whitney U test. The expression correlation analysis of genes with statistically significant expression in the MGUS group was performed using Pearson's correlation analysis. In addition, Receiver Operating Characteristic (ROC) analysis was performed using MedCalc

to determine the power of statistically significant genes to distinguish between MGUS and healthy individuals. Statistical significance was set at $p<0.05$.

Results

Eight patients with MGUS and eight healthy individuals were included in this study. In MGUS, the male/female ratio was 4/4, and the male to female ratio was 1. In the control group, male/female ratio was 3/5 (the ratio of male to female was 0.6). The MGUS and control groups had mean ages of 63.12±12.40 and 40.5±13.27, respectively. The median, minimum, and maximum ages were respectively 63.12 (40-76) and 40.5 (18-56). The mean age of the MGUS group was higher than that of the control group (t=3.523, p=0.003).

In our study, the expression levels of 22 genes selected from the p53 pathway were examined in MGUS and healthy controls. The *BAX, CDKN2A, APAF1, ATM, ATR, CASP9, CDK4, CDKN1A, CHEK2, E2F1, E2F3, MCL1, MDM2, MDM4, PTEN, RB1, P53, BCL2, CHEK1, PCNA*, and *PTX3* gene expression levels were not statistically significant. Of these, only *GADD45A* expression was significantly decreased in the MGUS group compared to that in the control group (p=0.027) (Table 1).

Table 1. Comparison of relative expressions of genes in bone marrow samples of MGUS and healthy group

Gene	Groups MGUS group (n=8) Control group (n=8)	Relative Expression Unit (Mean±SD)	*p* value
BAX	MGUS group	0.0034±0.00067	**0.352**
	Control group	0.3273±0.91941	
CDKN2A	MGUS group	0.0001±0.00005	**0.377**
	Control group	0.0005±0.00138	
APAF1	MGUS group	0.0076±0.00109	**0.841**
	Control group	0.0084±0.01071	
ATM	MGUS group	0.0020±0.00109	**0.933**
	Control group	0.0021±0.00414	
ATR	MGUS group	0.0013±0.00055	**0.788**
	Control group	0.0016±0.00342	
CASP9	MGUS group	0.0014±0.00036	**0.510**
	Control group	0.0026±0.00513	
CDK4	MGUS group	0.0026±0.00104	**0.644**
	Control group	0.0036±0.00623	
CDKN1A	MGUS group	0.0044±0.00291	**0.134**
	Control group	0.0021±0.00273	
CHEK2	MGUS group	0.0007±0.00025	**0.406**
	Control group	0.0031±0.00763	
E2F1	MGUS group	0.0011±0.00064	**0.379**
	Control group	0.0007±0.00081	
E2F3	MGUS group	0.0020±0.00041	**0.811**
	Control group	0.0021±0.00126	

Table 1. Comparison of relative expressions of genes in bone marrow samples of MGUS and healthy group (continued)

MCL1	MGUS group	0.1128±0.03413	**0.138**
	Control group	0.0781±0.05242	
MDM2	MGUS group	0.0064±0.00220	**0.472**
	Control group	0.0165±0.03737	
MDM4	MGUS group	0.0010±0.00052	**0.714**
	Control group	0.0013±0.00183	
PTEN	MGUS group	0.0178±0.00717	**0.813**
	Control group	0.0196±0.01991	
RB1	MGUS group	0.0043±0.00119	**0.385**
	Control group	0.0281±0.07244	
P53	MGUS group	0.0044±0.00182	**0.371**
	Control group	0.0482±0.12947	
BCL2	MGUS group	0.0019±0.00071	**0.352**
	Control group	0.3217±0.90720	
CHEK1	MGUS group	0.0018±0.00077	**0.409**
	Control group	0.0091±0.02359	
GADD45A	MGUS group	0.0005±0.00027	**0.027***
	Control group	0.0011±0.00063	
PCNA	MGUS group	0.0140±0.00592	**0.481**
	Control group	0.0263±0.04768	
PTX3	MGUS group	0.0035±0.00197	**0.991**

$2^{-\Delta\Delta Ct}$ analysis, $p<0.05$, ΔCt: Delta cycle threshold, MGUS: Monoclonal gammopathy of undetermined significance

Changes in gene expression in MGUS and healthy control samples were determined using a bar graph (Figure 1). A heat map plot for the MGUS and healthy control group samples was created to show the mean fold change (Figure 2). All participants included in the study had no other known diseases and were not relatives of each other. Almost all genes in control 7 were observed to have increased gene expression, clearly different from MGUS and other healthy individuals. The reason for this may be associated with genetic variants of unknown underlying causes that may affect the expression of genes in this control sample (Figure 2).

Pearson's correlation data showed that *GADD45A* expression was highly correlated with the expression of *APAF1**, *CDK4**, *PCNA**, *BAX***, *CDKN2A***, *CASP9***, *CHEK2***, *MDM2***, *RB1***, *P53***, *BCL2*** and *CHEK1*** ($r>0.7$; *$p=0.001$ and **$p=0.002$). According to the ROC analysis result, *GADD45A* had a strong discrimination power between MGUS and healthy individuals (*AUC*=0.797 and $p=0.015$) (Figure 3).

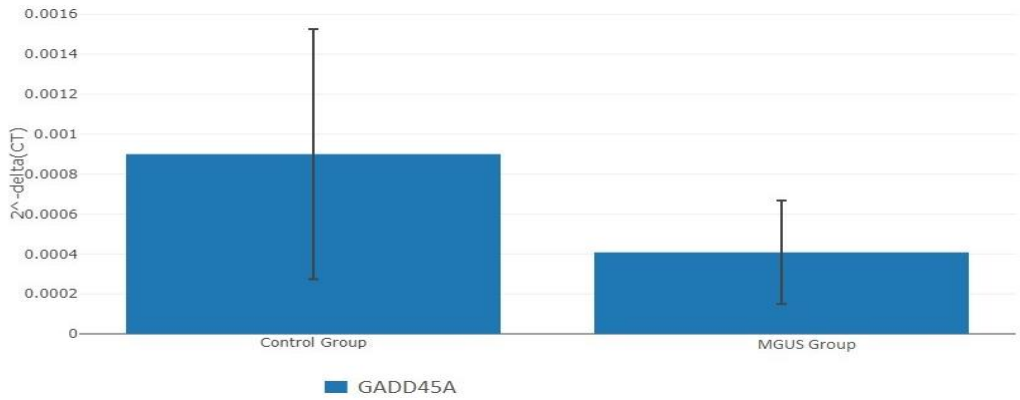

Figure 1. Boxplot representation of MGUS and control expression according to the $2^{-\Delta\Delta Ct}$ values of the *GADD45A* gene

The fold-change ($2^{-\Delta\Delta CT}$) is the normalized gene expression ($2^{-\Delta CT}$) in the MGUS sample divided by the normalized gene expression ($2^{-\Delta CT}$) in the control sample

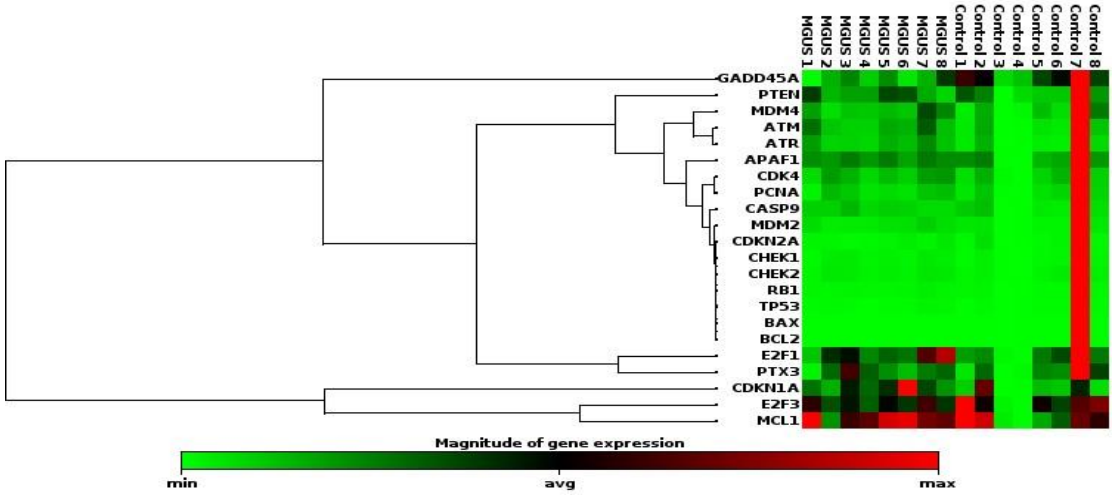

Figure 2. Evaluation of RT2 profiler PCR array data using clustergram analysis

Gene expression data are shown in a one-dimensional format (heatmap plot or clustergram) using color codes (genes). A heatmap plot (clustergram) displaying gene expression levels and grouping of genes according to their expression patterns. The RT2-PCR array expression data were compared between the two groups (MGUS and control), and the heat map displays the results in terms of up- or downregulation. The intensity of the color change represents the level of variation in gene expression. Low gene expression (ratio <1) is shown by green squares in the MGUS samples. Genes with a ratio close to one are shown as black squares. The presence of red squares indicates gene expression levels that were significantly greater than the control values (ratio >1)

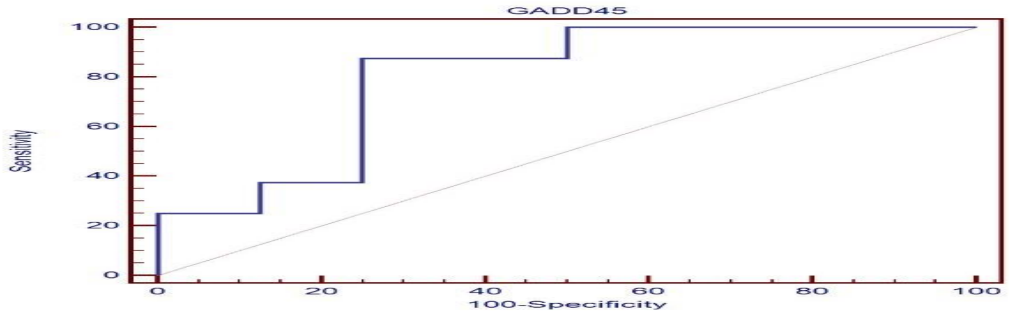

Figure 3. Strong discrimination power for *GADD45A* gene between the MGUS and healthy groups (AUC=0.797 and *p*=0.015)

Discussion

Monoclonal gammopathy of uncertain significance (MGUS), smoldering multiple myeloma (SMM), and multiple myeloma are all monoclonal gammopathies, and approximately 10% of SMM and 1% of MGUS cases progress to MM each year [7]. MGUS is a precancerous condition characterized by an asymptomatic increase in plasma cells. MGUS is observed in 3.5% of individuals over 50 years of age [8, 9]. Various pathophysiological conditions such as kidney failure, anemia, hypercalcemia, thrombocytopenia, lytic bone lesions, and bone pain occur because of the extra protein and monoclonal antibodies produced as a result of conversion from MGUS to MM, which complicates the patient's life [10]. Specific biomarkers are still needed to predict the conversion of MGUS to MM. The importance of *TP53* in tumor suppression in malignancies is well established. *TP53* dysregulation is involved in the pathogenesis of many malignancies [8]. On the other hand, the importance of other genes that regulate the cellular response to DNA damage and stress by being in the same pathway as p53 in MGUS MM transformation is not clear enough [3, 5].

The Growth Arrest and DNA Damage-inducible 45 (*GADD45*) family of proteins are important in the regulation of cellular responses to various stress factors. The *GADD45* family members (*GADD45A*, *GADD45B*, and *GADD45G*) are ubiquitously expressed in small amounts under physiological conditions in human tissues. However, their expression increases in response to various stress factors and is involved in the regulation of various cellular functions, such as cell cycle, DNA repair, and apoptosis. *GADD45* proteins lack enzymatic activity; therefore, they perform modulating functions by interacting with partner proteins [11, 12]. Although *GADD45* family members are involved in carcinogenesis in different tissues, the roles of these proteins in cancer development are not fully understood. Low expression of *GADD45* has been reported in lung [13], stomach [14], and breast [15] cancers, whereas *GADD45* overexpression has been reported in glioblastoma [16], cholangiocarcinoma [17]. In addition, *GADD45A* expression has been shown to be regulated by many transcription factors, including p53.

MGUS and smoldering MM (SMM) are benign diseases that occur before MM and are clonal plasma cell (PC) malignancies. Many oncogenes and chromosomal abnormalities found in MM PCs are also present in MGUS and SMM PCs, despite the fact that MGUS and SMM PCs do not grow rapidly. Borges et al. [18] hypothesized that MGUS/SMM PCs may be in an aging-like state, as oncogenic stress is known to induce cellular senescence. From their examination of a previously published human dataset (GSE5900), they deduced that MGUS/SMM PCs exhibit higher levels of the aging markers *CDKN1A* and *GADD45A* than healthy PCs do. *GADD45A* was identified as the most important upregulated gene in clonal PC compared to normal plasma cells (NPC) [19]. López Corral et al. [19] reported down-regulation of the *GADD45A* gene in the healthy group, in their RNAseq study which is opposite to our study findings. This situation may have been caused by the lack of confirmation by qRT-PCR in their study. Also, it may be related to the small number of samples in our study groups. But in their study, the number distribution in the comparison groups seems to be quite uneven (20 patients with MGUS, 33 with high-risk SMM, and 41 with MM were compared with only 5 healthy donors).

Plasma cells that produce an aberrant monoclonal protein, often known as the M protein, are a defining characteristic of MGUS. Even though MGUS does not cause any symptoms in itself, there is a 1% chance that it will progress into MM each year. It is unknown what causes MGUS or why certain instances of MGUS develop into MM. According to our RT2-Profiler PCR analysis of 22 genes, *GADD45A* expression was significantly decreased in the MGUS group compared to the control group (p=0.027). To address this uncertainty, it is important to identify genes that distinguish benign from malignant gammopathies. We believe that *GADD45A* may be involved in disease progression from MGUS to MM and can be used as a biomarker to distinguish benign from malignant gammopathies. Increases in *GADD45A* transcript levels have been observed under stressful growth arrest conditions and after treatment with DNA-damaging agents [20]. It is known that there is a significant correlation between *GADD45A* expression and apoptosis. Our results on *GADD45A* expression

may guide the elucidation of the complex genetic mechanism of MGUS. The decreased expression of *GADD45A* suggests that this gene may be the underlying cause of increased abnormal M protein levels, in which cells with MGUS do not achieve adequate cell cycle arrest in a p53-dependent manner. In addition, since no treatment similar to MM was applied in individuals with MGUS, we can conclude that there was no increase in the level of *GADD45A* transcription with treatment and therefore no triggering of apoptosis in cells with MGUS. The characterization of the MM progression of MGUS was explored through meta-analysis on GEO datasets by Aljabban, et al. They reported that the upregulation of *GADD45A*, a DNA-damaging protein, was discovered to encourage DNA methylation [21].

The data from the present study suggest that *GADD45* plays a relevant role in the pathogenesis of MGUS, a plasma cell neoplasm. In this respect, the role of *GADD45* in other plasma cell disorders should also be investigated. In our study, we shared the view that *GADD45A* has an important effect on the cell death mechanism in the p53 pathway. We examined the decrease in the expression of *GADD45A*, which is an aging marker, in individuals with MGUS compared to healthy controls and how the cells with MGUS progress towards multiple myeloma, where MGUS cells do not exhibit aging characteristics.

The first limitation of the current study was the small sample size of the groups, and the second was the mean age difference between the patient and control groups. However, samples from bone marrow transplant donors were collected because of the difficulty and risk associated with obtaining bone marrow samples.

In conclusion, in our study, according to the ROC analysis results, the detection of a significant difference only in the *GADD45A* gene among 22 genes suggests that it can be used as a differential biomarker, especially for diagnosis in individuals with MGUS. Although equal numbers of bone marrow samples were taken from individuals in the MGUS and control groups, the number of samples can be increased in future studies. In addition, although no difference was observed in the mRNA levels of 21 genes in our study, a difference was detected in the protein levels in MGUS patients.

In our study, it was determined that the expression level of only the *GADD45A* gene, out of 22 genes whose expression levels were examined, decreased significantly in the MGUS group compared to the control group. According to Pearson correlation data, *GADD45A* gene expression was highly correlated with 12 other genes (*APAF1, CDK4, PCNA, BAX, CDKN2A, CASP9, CHEK2, MDM2, RB1, P53, BCL2, CHEK1*) examined in the p53 pathway. Thus, these 12 genes were down-regulated in MGUS.

As a continuation of this study, it may be possible to detect changes in protein levels associated with our genes in the p53 pathway and reveal their relationship at the M protein level. Thus, the functional processes underlying the unknown mechanism of MGUS in *GADD45A* could be determined, and the possible pathogenesis of MGUS in MM could be elucidated. The detection of genetic markers that can distinguish MGUS from MM tumor cells is important in the pathophysiology of MGUS. Therefore, the idea that *GADD45A* can be used as a genetic biomarker in our study may contribute significantly to the literature.

At the same time, using genetic biomarkers can provide effective treatment protocols that will significantly halt the progression of MGUS.

Conflict of interest: The authors declare no conflicts of interest.

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Authors' contributions to the article

I.S., A.D.A., and G.O. contributed equally to the construction of the main idea and hypothesis of the study, developed the theory and arranged the material and method section, evaluated the data in the results section, wrote the discussion section of the article, reviewed, corrected, and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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The effects of COVID-19 pandemic on paper participation in national ophthalmology meetings

COVID-19 pandemisinin ulusal göz hastalıkları toplantılarındaki bildiri katılımı üzerine etkileri

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Abstract

Purpose: The aim of the current study is to evaluate the effect of COVID-19 pandemic on paper participation in national ophthalmology meetings held by the Turkish Ophthalmology Association (TOA).

Materials and methods: The data for the previous national ophthalmology meetings held by the TOA were gathered retrospectively from the TOA website. The COVID-19 pandemic-related online sessions and meetings with a scheduled in-person follow-up were taken into consideration. The number of poster and oral presentations and subject areas of the papers were recorded.

Results: The total number of poster and oral presentations in online meetings was 1505, while it was 1294 in face-to-face meetings (a 14.0% difference). Regarding poster presentations, a total of 1001 posters were presented in online meetings, whereas number of poster presentations was 865 in face-to-face meetings. Similarly, in online meetings, the number of oral presentations was 504, while it was 429 in face-to-face meetings. This finding demonstrated both poster and oral presentation participation was higher by 13.5% and 14.8% (respectively) in online meetings than in the face-to-face meetings.

Conclusion: It appears that national ophthalmology meetings held online during the COVID-19 pandemic had a favorable impact on the paper submission rate, and online meetings made sure that scientific sharing and collaboration continued and made it accessible to wider populations.

Keywords: COVID 19, meeting, ophthalmology, presentation.

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Öz

Amaç: Bu çalışmanın amacı, Türk Oftalmoloji Derneği (TOD) tarafından düzenlenen ulusal oftalmoloji toplantılarındaki bildiri katılımına COVID-19 pandemisinin etkisinin değerlendirmesidir.

Gereç ve yöntem: TOD tarafından daha önce gerçekleştirilen ulusal oftalmoloji toplantılarına ait veriler TOD web sitesinden retrospektif olarak derlendi. COVID-19 pandemisi ile ilgili online ve planlanmış yüz yüze müteakip toplantılar dikkate alındı. Poster ve sözlü bildiri sayıları ve bildirilerin konu alanları kaydedildi.

Bulgular: Online toplantılarda toplam poster ve sözlü sunum sayısı 1505 iken yüz yüze toplantılarda bu sayı 1294 oldu (%14,0 fark). Poster sunumları ile ilgili olarak, online toplantılarda toplam 1001 poster sunumu yapılırken, yüz yüze yapılan toplantılarda poster sunumu sayısı 865 olarak gerçekleşti. Benzer şekilde online toplantılarda sözlü sunum sayısı 504, yüz yüze toplantılarda ise 429 oldu. Bu bulgu, çevrimiçi toplantılarda hem poster hem de sözlü sunum katılımının yüz yüze toplantılara göre (sırasıyla) %13,5 ve %14,8 oranında daha yüksek olduğunu göstermiştir.

Sonuç: COVID-19 salgını sırasında çevrimiçi olarak gerçekleştirilen ulusal oftalmoloji toplantılarının bildiri gönderim oranını olumlu yönde etkilediği ve çevrimiçi toplantıların bilimsel paylaşım ve iş birliğinin devam etmesini ve daha geniş popülasyonlara erişilebilir olmasını sağladığı görülmektedir.

Anahtar kelimeler: COVID 19, toplantı, göz hastalıkları, sunum.

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Introduction

The global health systems were drastically impacted by the Corona virus disease (COVID-19) pandemic, which began in 2019, and many industries underwent significant adjustments as a result [1]. Academic meetings were also affected and could not be held face-to-face due to the high risk of disease transmission person to person [2]. Under these circumstances, scientific events such international and national ophthalmology meetings had to be organized online on online platforms [3-9].

Traditional face-to-face meetings have been substituted with online ones, which also brought several advantages such as lower geographical restrictions for the participants, more flexible personal schedule, and lower costs associated with transfer and accommodation. On the other hand, it is also critical to evaluate the positive and negative impacts of the online meetings on scientific quality.

The primary objective of this study was to examine the statistical distribution and trends of the participants submitting papers at the national ophthalmology meetings organized online by the Turkish Ophthalmology Association (TOA). Understanding the effect of the COVID-19 outbreak on academic activities will be an important source of information for healthcare professionals, researchers and congress organizers working in the field of ophthalmology [10-14].

Furthermore, the present study also aimed to dive into the impact of online ophthalmology meetings on the attendees, and to weigh the benefits and drawbacks of this platform. With the results of the study on how online meetings affect many aspects of event organization, participant experiences, knowledge sharing, and networking, recommendations can be made for more effective and efficient design of future meetings under challenging conditions.

Materials and methods

This retrospective descriptive cross-sectional study was carried out to evaluate the effect of the COVID-19 pandemic on the participation of papers in national ophthalmology meetings held online. The TOA website was used to collect the data related to the past national ophthalmology meetings organized by the TOA [15]. This study does not require ethics committee approval.

The TOA website has a comprehensive congress archive and past meetings can be accessed through this archive.

In this study, the meetings held online due to the COVID-19 pandemic *(2019 Summer Meeting, 2020 March Meeting, 2020 National Meeting, 2021 Spring Meeting, 2021 Winter Meeting)* and face-to-face versions of the aforementioned meetings *(2021 Summer Meeting, 2022 March Meeting, 2021 National Meeting, 2022 Spring Meeting, 2022 Winter Meeting)* were compared. Data such as the papers presented in meetings and the number of participants were obtained. For the analysis of the paper participation, among the meetings online, those who have a booklet were primarily determined. These booklets included abstracts of the presented papers, the names of the researchers and their institutions.

The Statistical Package for Social Sciences (SPSS) version 24 (IBM SPSS Statistics Inc., Chicago, IL, USA) was used for statistical analysis. Data was presented as frequency and percentages. Chi square test was used to compare categorical data between the online and face-to-face meetings. A p value <0.05 indicated statistical significance at a 95% confidence interval.

Results

The findings were evaluated over the five national meetings held by the TOA. It has been observed that online meetings reveal a significant difference in paper participation compared to face-to-face meetings. Considering the total number of papers, while the total number of poster and oral presentations presented in online meetings was 1505, this number was found to be 1294 in face-to-face meetings. These findings show that total paper participation in online meetings was higher by 14.0% compared to the face-to-face meetings. Focusing on poster presentations, the number of poster presentations presented in online meetings was 1001, whereas 865 posters were presented in face-to-face meetings.

Similarly, the number of oral presentations was 504 in online meetings, while this number was 429 in face-to-face meetings. This data reveals that both poster and oral presentation participation was higher by 13.5% and 14.8% in online meetings than in the face-to-face meetings. Chi square analysis showed no

statistically significant difference between online and face-to-face meetings regarding type of the presentation (i.e. poster or oral presentation) (p=0.851). Figure 1 shows comparison of number of presentations between the online and face-to-face meetings.

This study also evaluated distribution of the presentations regarding subject area (retina, cataract and refractive surgery, glaucoma, cornea, pediatric ophthalmology and others) between online and face-to-face meetings. Briefly, there was a reduction in paper participation in all the aforementioned subject areas in face-to-face meetings when compared to the online meetings. However, there was no difference between the online and face-to-face meetings in terms of subject area of the presentations (p=0.977, Chi square test). Figure 2 demonstrates the details of the distributional data regarding subject area of the papers.

Discussion

The COVID-19 pandemic had a profound impact on the healthcare industry and academic activities around the world. As part of the measures taken to prevent the spread of the

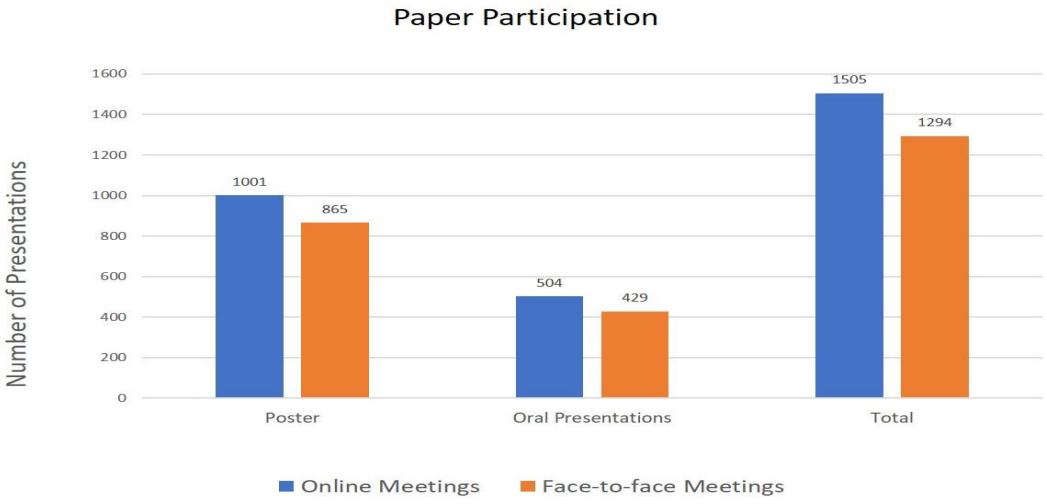

Figure 1. Comparative graph showing paper participation between online and face-to-face national ophthalmology meetings

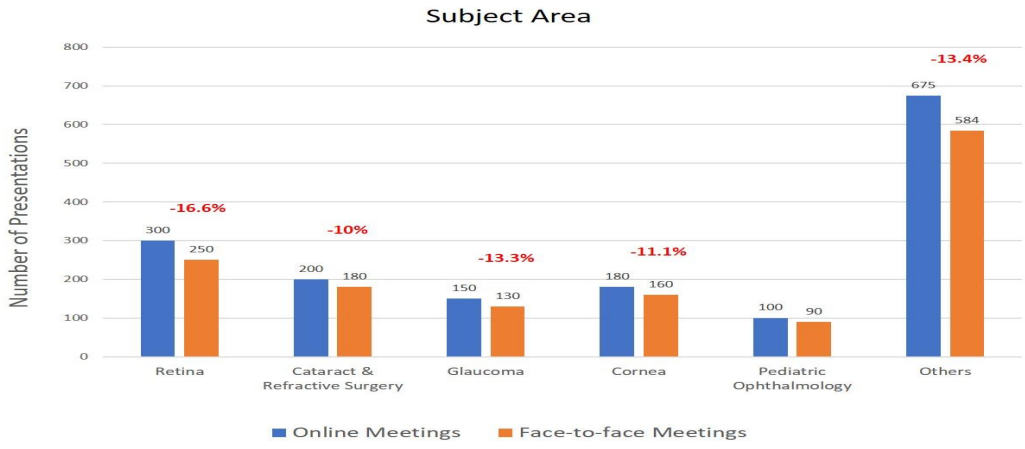

Figure 2. Subject area distribution of the presentations in online and face-to-face national ophthalmology meetings

pandemic, many ophthalmology meetings were held online [4, 11-14]. In this study, the effect of the COVID-19 pandemic on the participation of papers in national ophthalmology meetings was assessed.

The current study showed that the total paper participation was 14.0% higher in online meetings compared to face-to-face meetings. In addition, the number of poster and oral presentations presented in online meetings were also higher by 13.5% and 14.8% (respectively) than in the face-to-face meetings. Several factors might have caused the increase in paper participation in online meetings. First of all, it was difficult or impossible to attend face-to-face meetings due to travel restrictions and social distance measures during the pandemic. Online meetings, on the other hand, eliminated the need for transfer, accommodation and related expenses and provided a more flexible schedule [4-11, 16-20]. These factors encouraged more people to attend the online meetings. In addition, thanks to the technological opportunities offered by online media, participants were able to participate in events even from different geographical regions and different time zones [16-22].

Furthermore, online meetings provide an international platform by enabling scientists and experts from different countries to share their knowledge and experience. This, in turn, contributes to the acceleration of scientific development and the wider perspective of the scientific community [4-8, 16-22].

However, the importance of personal interactions and concrete experiences provided by face-to-face meetings should not be overlooked. It offers participants a different experience with elements such as live presentations, discussions, applications that require manual dexterity, and social interactions. Such events enable scientists to come together to exchange ideas, form new collaborations, and develop their practical skills related to their areas of expertise [4-8, 14, 16, 17].

It should also be stated that online meetings also have some limitations and challenges. The above-mentioned face-to-face interactions, in-depth discussions and social connections cannot be fully achieved in online meetings. Important elements such as, one-by-one interactions and networking are limited in online meetings. In addition, factors such as technical problems, internet connection problems and difficulty of simultaneous interaction between participants in different time zones can affect the online congress experience and hinder some participants [4-8, 14, 16, 17, 20].

Therefore, it is important to see online meetings as platforms that complement each other and can coexist, rather than completely replacing face-to-face events. New work should focus on developing models and approaches where online and face-to-face activities can coexist and complement each other. In this way, scientific communities can experience a more comprehensive and diverse interaction and learning [9-11, 20, 21].

The potential advantages and limitations of online meetings should be considered when planning and organizing future meetings. It is necessary to improve the technological infrastructure, develop platforms that support interaction, and make innovations that will enrich the participants' experience. In this way, the effectiveness of online meetings can be increased and scientific information sharing can be realized more effectively. Nevertheless, the importance and value of face-to-face meetings should not be forgotten because such events support personal interaction, networking and in-depth discussions [9-11, 20-22].

The findings of this study shed light on the changes in the COVID-19 pandemic process that affect the organization of national meetings in the field of ophthalmology and the structuring of scientific sharing. Although the importance and effectiveness of online meetings have been proven, more research and development studies are required in the future. Improving the technological infrastructure, developing features such as interactive sessions and poster presentations will enable online meetings to be held more effectively and efficiently.

On the other hand, lack of data regarding the types of studies presented in the meetings (cross-sectional, case-control, interventional, etc.), the institutions participating in the research (public or private hospital, university-based, etc.) and gender distribution of the participants might be considered as the limitations of the current study.

In conclusion, it seems that national ophthalmology meetings held in online media during the COVID-19 pandemic process had a positive effect on the participation of papers and online meetings ensured the continuation of scientific sharing and cooperation and provided access to large populations. However, the importance and value of face-to-face activities should not be forgotten. Future work should focus on developing models and approaches where online and face-to-face activities can coexist and complement each other. In this way, scientific communities can experience a more comprehensive and diverse interaction and learning.

Conflict of interest: The authors declare no conflict of interest

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Authors' contributions to the article

I.T. and D.K constructed the main idea and hypothesis of the study, developed the theory and arranged/edited the material and method section, did the evaluation of the data in the Results section. Discussion section of the article written by I.T.

I.T. and D.K reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Ureteral stent-related symptoms in 4.0 Fr versus 4.8 Fr double J stents: a questionnaire-based comparative study

Üreteral stent ilişkili semptomlarda 4.0 Fr'e karşın 4.8 Fr double J stentler: ankete dayalı karşılaştırmalı bir çalışma

Hakan Anıl, Umut Ünal, Ahmet Güzel

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Abstract

Purpose: The aim was to investigate the difference in Ureteral Stent-Related Symptom Questionnaire (USSQ) scores with the use of different stent diameters (4.0 Fr versus 4.8 Fr).

Materials and methods: Between August 2022 and January 2023, patients with double J stent insertion after endoscopic ureteral stone and retrograde intrarenal surgery in two different centers were included in the study. The patients were divided into two groups according to stent size of 4.0 Fr and 4.8 Fr. All of the patients were called for check-ups in the 2nd week after discharge and were questioned using the USSQ.

Results: A total of 228 patients, 112 in the 4.0 Fr group and 116 in the 4.8 Fr group, were included in the study. At the 2nd week visit, the total USSQ scale scores were 73.9±8.9, and 80.0±9.8 for the 4.0 Fr and 4.8 Fr groups, respectively (p<0.001). Stent dislocation was detected in 10 (8.1%) patients in the 4.0 Fr group and in 3 patients (2.5%) in the 4.8 Fr group (p=0.049). The symptom score scale was analyzed separately based on subdomains. The mean value for the urinary index score was 24.5±3.6 for the 4.0 Fr group and 27.6±3.4 for the 4.8 Fr group (p<0.001). Body pain index score was 16.4±3.8 and 18.6±3.8 for the 4.0 Fr and 4.8 Fr groups, respectively (p<0.001). The general health index score, work performance index score, and sexual matter score were not statistically significantly different between the groups.

Conclusion: Our study reported that ureteral stent-related symptoms favor the 4 Fr ureteral stent. In contrast, 4 Fr ureteral stents had a higher migration rate.

Keywords: Ureteral stents, stent-related symptoms, USSQ score, urolithiasis, quality of life.

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Öz

Amaç: Farklı üreteral stent çaplarının (4.0 Fr-4.8 Fr) kullanımıyla Üreteral Stentle İlişkili Semptom Anketi (USSQ) skorlarındaki farkı araştırmaktır.

Gereç ve yöntem: Ağustos 2022 ile Ocak 2023 tarihleri arasında iki farklı merkezde endoskopik üreter taşı ve retrograd intrarenal cerrahi sonrası double J stent takılan hastalar çalışmaya dahil edildi. Hastalar 4.0 Fr ve 4.8 Fr stent boyutlarına göre iki gruba ayrıldı. Hastaların tamamı taburcu olduktan sonraki 2. haftada kontrole çağrıldı ve USSQ ile sorgulandı.

Bulgular: Çalışmaya 4.0 Fr grubunda 112, 4.8 Fr grubunda 116 olmak üzere toplam 228 hasta dahil edildi. 2. hafta kontrolünde toplam USSQ ölçek puanları 4.0 Fr ve 4.8 Fr grupları için sırasıyla 73,9±8,9 ve 80,0±9,8 idi (p<0,001). 4.0 Fr grubunda 10 (%8,1), 4.8 Fr grubunda 3 (%2,5) hastada stent dislokasyonu saptandı (p=0,049). Belirti puan ölçeği alt alanlara göre ayrı ayrı analiz edilmiştir. İdrar indeks skorunun ortalama değeri 4.0 Fr grubu için 24,5±3,6 ve 4.8 Fr grubu için 27.6±3.4 idi (p<0,001). Vücut ağrı indeksi skoru 4.0 Fr ve 4.8 Fr grupları için sırasıyla 16,4±3,8 ve 18,6±3,8 idi (p<0,001). Genel sağlık indeksi skoru, iş performansı indeks skoru ve cinsel hususlar skoru gruplar arasında istatistiksel olarak anlamlı farklılık göstermedi.

Sonuç: Çalışmamız üreteral stent ilişkili semptomların 4 Fr üreteral stent lehine olduğunu bildirmektedir. Buna karşılık 4 Fr üreteral stentler daha yüksek migrasyon oranına sahipti.

Anahtar sözcükler: Üreteral stentler, stent ilişkili semptomlar, USSQ skor, ürolitiyazis, yaşam kalitesi.

Anıl H, Ünal U, Güzel A. Üreteral stent ilişkili semptomlarda 4.0 Fr'e karşın 4.8 Fr double J stentler: ankete dayalı karşılaştırmalı bir çalışma. Pam Tıp Derg 2023;16:610-616.

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Introduction

Ureteral stents are widely used in urology practice with the advancement of endoscopic treatments in recent years [1]. The primary purpose of using ureteral stents is to provide uninterrupted urine flow between the kidney and bladder [2]. After endoscopic ureteral stone treatment, it is recommended to insert a double J (DJ) stent in the presence of residual stones, suspected perforation, and bleeding [3]. In addition, these stents can be used in pregnancy-induced hydronephrosis, obstructive pyelonephritis, for pain relief, and after reconstructive urological procedures. Patients complain of irritative symptoms such as bleeding in the urine, flank pain, dysuria, and pollakiuria after DJ stent placement [4]. These adverse events impair the patient's quality of life, while they increase health-related costs [5]. In order to evaluate these complaints objectively, Joshi et al. [6] developed the Ureteral Stent-Related Symptom Questionnaire (USSQ) in 2003.

Many studies in the literature showed that ureteral stent-related symptoms are associated with stent material, design, size, and position [5]. Studies focusing on stent size evaluated stents between 4.7 Fr and 7 Fr with symptom scores [7, 8]. The general opinion in these studies is that as the stent diameter decreases, ureteral stent-related symptoms decrease [9, 10]. However, a randomized prospective study showed that small-diameter stents did not reduce stent-related symptoms; on the contrary, they involved more dislocation [11]. Studies in the literature include comparisons of 4.7 Fr and larger diameter stents. After a literature review, comparative studies using the 4.0 Fr DJ stent were not found, to the best of our knowledge.

In this study, we first hypothesized there would be a difference in USSQ symptom score between stent diameters (4.0 Fr versus 4.8 Fr). Second, we investigated whether smaller stent diameter is associated with higher rate of stent dislocation.

Materials and methods

Patient cohort

Following approval of the local ethics committee between August 2022 and January 2023, patients with double J stent insertion after endoscopic ureteral stone and retrograde intrarenal surgery in two different centers were included in the study. Informed consent was obtained from all patients. The data for the patients were collected prospectively and analyzed retrospectively. Patients with a previous history of URS, bilateral stones, using anticoagulants, under 18 years of age, with pregnancy, ureteric stenosis, renal failure, obstructive pyelonephritis, pyelonephrosis, malignancy, pre-stenting, and α-blocker therapy were excluded. In addition, the symptom score scale was not filled in by patients with stent migration after URS. The patients were divided into two groups according to stent size as 4.0 Fr and 4.8 Fr. Stone size and localization of the patients were determined by computed tomography.

Surgical technique

URS or flexible URS was used for all patients. Before the procedure, 2nd generation cephalosporin was administered to all patients as prophylaxis. The procedure was performed under general or spinal anesthesia in the lithotomy position with an 8/9.8 F fiber ureteroscope (Richard Wolf), 273 micron fiber and holmium laser. Flexible URS was performed with a 7.5 Fr fiber-optic flexible ureteroscope (Storz FLEX-X2) after a ureteral access sheath (9.5/11.5 F) was inserted under general anesthesia. A DJ stent was placed in the presence of bleeding, ureteral injury, clinical suspicion, and residual stone after the procedure. DJ stent was not inserted after uncomplicated URS. The collecting system was visualized by retrograde pyelography before DJ stent placement. All DJ stents were placed under fluoroscopy according to ureter size (24-26-28cm). During DJ stent placement, the upper end was placed so a full turn was in the renal pelvis and the lower end was placed so that it did not exceed the midline of the bladder. Polyurethane hydrophilic (Plastimed©) DJ stents were used in all procedures.

Postoperative evaluation

All patients were discharged on the same day or on the 1st postoperative day after being prescribed a non-steroidal anti-inflammatory (75 mg diclofenac). In order to evaluate patient symptoms during follow-up, the USSQ score, translated into Turkish by Tanidir et al. [12], and validated in Turkish by A.D., was used. This

questionnaire consists of 6 subdomains: urinary symptom index score, body pain score, general health index, work performance index, sexual matter score, and additional complaints. In our study, each subdomain score was recorded. All of the patients were called to the clinic in the 2nd week after discharge and were questioned using the USSQ. All stents were removed 3 weeks postoperatively. The presence of stent dislocation and hydronephrosis were evaluated with plain abdominal X-ray and ultrasonography before DJ stent extraction.

The primary endpoint of the study was completion of the USSQ symptom scale 2 weeks postoperatively. The secondary endpoint was the evaluation of the presence of stent dislocation by imaging methods.

Statistical analysis

Continuous variables are presented as mean ± standard deviation, and categorical variables as n (%). Normal distribution was evaluated with the Shapiro-Wilk test. Categorical variables were compared between the two groups with the chi-square test, and continuous variables were evaluated with the Student t-test. A value of $p<0.05$ was considered statistically significant. All analyses were conducted using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY) and GraphPad Prism 8.0.2.

Results

A total of 228 patients, 112 in the 4.0 Fr group and 116 in the 4.8 Fr group, were included in the study. The mean age of the patients was 42.0±12.1 and 42.1±11.7 years for the 4.0 Fr and 4.8 Fr groups, respectively ($p=0.951$). There was no statistical difference between the groups in terms of preoperative clinical and demographic characteristics of the patients (Table 1). The stone-free rate for patients was 93.7% in the 4.0 Fr group and 92.2% in the 4.8 Fr group ($p=0.655$). The stent lengths inserted in the 4.0 Fr and 4.8 Fr groups showed similar distribution ($p=0.941$).

Table 1. Preoperative clinical characteristics of the patient cohort

	4.0 Fr group	4.8 Fr group	*p* value
No. of patients	112	116	
Age , mean ± sd	42.0±12.1	42.1±11.7	0.951
Female/Male	40/72	42/74	0.938
BMI (kg/m²), mean ± sd	29.1±4.1	28.7±3.9	0.451
Lateralization (Left/Right)	54/58	57/59	0.889
Stone location, n (%)			0.659
Proximal	26 (23%)	32 (28%)	
Middle	35 (31%)	31 (26%)	
Distal	51 (46%)	53 (46%)	
Stone size (cm), mean ± sd	9.6±2.1	10.1±3.1	0.156
Operation type, n (%)			0.772
URS	83 (74.1%)	84 (72.4%)	
Flexible URS	29 (25.9%)	32 (27.6%)	
Length of the ureteral stent			0.941
24 cm	34 (30.3)	37 (31.9)	
26 cm	37 (33.0)	39 (33.7)	
28 cm	41 (36.7)	40 (34.4)	

After discharge and before the first visit, 5 patients (4.4%) in the 4.0 Fr group and 9 patients (7.7%) in the 4.8 Fr group were admitted early due to ureteral stent complaints (p=0.300). At the 2nd week visit, the total USSQ scale scores were 73.9±8.9 and 80.0±9.8 for the 4.0 Fr and 4.8 Fr group, respectively (p=0.001). The symptom score scale was analyzed separately by subdomains. The mean value for the urinary index score was 24.5±3.6 for the 4.0 Fr group and 27.6±3.4 for the 4.8 Fr group (p=0.001). Body pain index score was 16.4±3.8 and 18.6±3.8 for the 4.0 Fr and 4.8 Fr groups, respectively. This difference was found to be statistically significant in favor of 4.0 Fr (p=0.001). General health index score, work performance index score and sexual matter score did not have statistically significant difference between the groups. Comparisons of patients between groups according to USSQ subdomains at the 2-week visit are summarized in Figure 1. Stent dislocation was detected in 10 (8.1%) patients in the 4.0 Fr group and in 3 (2.5%) patients in the 4.8 Fr group (p=0.049). No fever or complicated urinary tract infection was observed during the follow-up of the patients. Daily analgesic use was 2.2±1.9 tablets per day in the 4.0 Fr group, and 2.6±1.1 tablets in the 4.8 Fr group (p=0.133). The USSQ symptom score values and additional complaints for the patients are summarized in detail in Table 2.

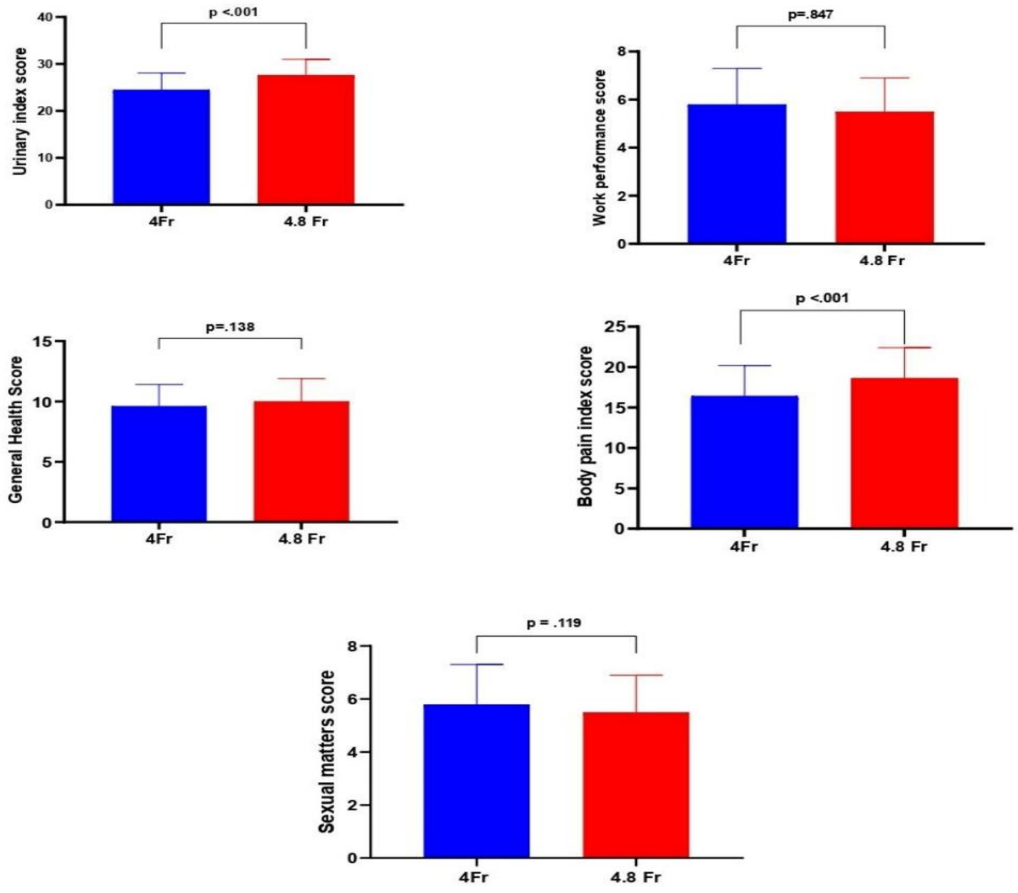

Figure 1. Comparison of domain scores between the two groups

Table 2. Comparison of subdomain scores and postoperative data of patients

	4.0 Fr group	4.8 Fr group	*p* value
USSQ Urinary index score (U1-U12)	24.5±3.6	27.6±3.4	<0.001
USSQ body pain index score (P3-P9)	16.4±3.8	18.6±3.8	<0.001
Overall pain score (P3, VAS)	6.9±3.8	7.1±4.4	0.714
USSQ general health index score (G1-G6)	9.6±1.8	10.0±1.9	0.138
USSQ work performance score (W5-W7)	7.6±1.7	7.7±2.0	0.847
Sexual abstinence due to stent (n, %)	24 (21.4)	32 (27.5)	0.280
USSQ sexual matters score (S3-S4)	5.8±1.5	5.5±1.4	0.119
USSQ stent related-additional problems (A1-A4)	5.4±1.7	5.7±1.8	0.197
Global quality of life with the stent in situ (GQ)	4.6±2.1	4.9±1.9	0.258
Stent migration ratio*, (%)	10/121 (8.1)	3/119 (2.5)	0.049
Analgesic usage per day	2.2±1.9	2.6±2.1	0.133

Discussion

Ureteral stent placement is one of the interventions most commonly performed by urologists. In addition to this common use, 80% of patients complain of some symptoms [13]. These side effects cause problems for both urologists and patients, such as deterioration in patient quality of life, loss of labor and increased health-related costs. In order to reduce these complaints, recent studies focused on stent material structure and stent diameter. The main finding of our study demonstrates that ureteral stent-related symptoms decrease as the stent diameter decreases.

The most appropriate approach to prevent ureteral stent-related symptoms is not to insert a DJ stent. Neither the EAU guidelines nor the AUA guidelines routinely recommend ureteral stent placement. In addition, EAU guidelines recommend DJ stenting after URS in suspected cases and to avoid stressful emergencies. In their study, Muslumanoglu et al. [1] reported that ureteral stenting significantly reduced postoperative complications compared to those without ureteral stent insertion. The predictive factors for stent placement were the presence of impacted stones, duration of surgery, presence of solitary kidney, stone size, and age. Routine stenting is not performed in our own clinic. A ureteral stent is inserted in suspicious cases, with ureteral bleeding, suspected residual stone and perforation.

The USSQ score consists of urinary symptom score, body pain score, work performance score, general health score, sexual matter and additional complaints. Randomized prospective controlled studies with this scale in recent years show that small diameter stents reduce ureteral stent-related symptoms. In their study using the USSQ scale, Çubuk et al. [9] reported that 4.8 Fr ureteral stents had statistically significantly lower score than 6 Fr ureteral stents. In this study, subdomain scores were not included separately, and the total USSQ score was shared. Nestler and colleagues compared three different sizes of stents (4.7 Fr, 6 Fr, 7 Fr). They found that the USSQ score for the 4.7 Fr group was statistically superior to the 7.0 Fr group for all subdomains. In the comparison of 4.7 Fr and 6 Fr groups, they reported that the only statistically significant difference was for the urinary symptom score [10].

Contrary to this, Damiano et al. [11] reported that there was no difference between stent diameters in terms of urinary symptoms. In our study, we found that the urinary system symptom score and body pain index score among the USSQ subdomains were statistically significantly lower in the 4.0 Fr ureteral stent group. Study performance score, general health index score, sexual matter score and additional complaints did not differ statistically between the groups.

Although small diameter stents are superior in terms of ureteral stent complaints, they are controversial in terms of drainage efficiency and stent migration. Damiano et al. [11] reported a higher rate of migration for 4.8 Fr ureteral stents compared to 6 Fr. In a series of 1258 patients, the stent migration rate was reported to be 5.6% for 4.7 Fr urethral stents [14]. In our study, the stent migration rate was 8.1% in the 4.0 Fr ureteral stent group and 2.5% in the 4.8 Fr group.

Our study has some limitations. The first is that it had retrospective design. Secondly, some of our patients were asylum seekers and their native language was not Turkish. For this reason, some patients were questioned by a hospital translator. Third, a control group was not included in the study. However, the number of subjects was sufficient compared to other studies in the literature, and the data were prospectively recorded in the system.

In conclusion, in our study comparing two different stent sizes (4.0 Fr versus 4.8 Fr), 4.0 Fr ureteral stents had fewer urinary system complaints. Similarly, overall body pain scores were in favor of the 4.0 Fr ureteral stent. However, 4.0 Fr stents had higher migration rate.

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

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Authors' contributions to the article

H.A. constructed the main idea and hypothesis of the study. A.G. developed the theory and arranged/edited the material and method section. U.U. has done the evaluation of the data in the Results section. Discussion section of the article written by H.A. and U.U.

A.G. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Knowledge levels and awareness of healthcare professionals on protection from chemical, biological, radiation, nuclear hazards, and emergency aid practices

Sağlık personellerinin kimyasal, biyolojik, radyasyon ve nükleer tehlikelerden korunma ve acil yardım uygulamaları ile ilgili bilgi düzeyleri ve farkındalıkları

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Abstract

Purpose: The accidental or intentional release of CBRN (Chemical, Biological, Radiological, Nuclear) substances into the environment causes significant loss of life and property and has adverse effects over a long time. This study was planned to raise awareness about protection from CBRN hazards and emergency aid practices, to create CBRN awareness, and to determine the knowledge level of healthcare professionals.

Materials and methods: After reviewing the literature and regulations, the questionnaire was prepared based on the training module on "Emergency Assistance in Chemical, Biological, Radiation, and Nuclear Hazards" for Emergency Health Services published by the Republic of Türkiye Ministry of National Education. The questionnaire was asked to participants before and after 10 hours of theoretical CBRN training, and the results were compared.

Results: The participants were 58.4% female, 41.6% male, and the average age was 38. Most participants were doctors or nurses, and approximately three-quarters of the participants were emergency service staff. 35.6% of them had been working in the emergency department for 1-5 years. 61.4% had not received CBRN training, and 84.2% thought they needed sufficient knowledge and experience. 77.2% had not experienced any CBRN incident nor performed any intervention for CBRN. When the 22 questions asked about the level of CBRN knowledge were evaluated, it was seen that the correct answer rate was above 50% in seven questions of 22 and was above 50% in all questions in the post-test applied after the training. Their level of knowledge was found to be low before CBRN training and good after training.

Conclusion: Theoretical training has a significant positive impact on creating CBRN awareness.

Keywords: CBRN, health knowledge, attitudes, practices, awareness.

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Öz

Amaç: KBRN (Kimyasal, Biyolojik, Radyolojik, Nükleer) maddelerin kaza ile veya kasıtlı olarak çevreye yayılması önemli can ve mal kayıplarına yol açmakta ayrıca uzun bir zaman dilimi boyunca olumsuz etkiler doğurmaktadır. KBRN tehlikelerinden korunma ve acil yardım uygulamaları ile ilgili farkındalık yaratmak, KBRN bilinci oluşturmak, bilgi düzeylerini tespit etmek amacıyla planlanmıştır.

Gereç ve yöntem: Literatür ve yönetmelikler incelendikten sonra, Türkiye Cumhuriyeti Milli Eğitim Bakanlığı tarafından yayınlanan Acil Sağlık Hizmetleri için "Kimyasal, Biyolojik, Radyasyon ve Nükleer Tehlikelerde Acil Yardım" konulu eğitim modülü temel alınarak anket hazırlanmıştır. Anket, katılımcılara toplam 10 saatlik teorik KBRN eğitiminden önce ve sonra sorulmuş ve sonuçlar karşılaştırılmıştır.

Bulgular: Katılımcıların %58,4'ü kadın, %41,6'sı erkek ve yaş ortalaması 38'dir. Katılımcıların çoğu doktor veya hemşireydi ve katılımcıların yaklaşık dörtte üçü acil servis personeliydi. Katılımcıların %35,6'sı 1-5 yıldır acil serviste çalışmaktadır. 61,4'ü KBRN eğitimi almamıştı ve %84,2'si KBRN konusunda yeterli bilgi ve deneyime sahip olmaları gerektiğini düşünüyordu. 77,2'si herhangi bir KBRN olayı yaşamamış ve KBRN'ye yönelik herhangi bir müdahalede bulunmamıştır. KBRN bilgi düzeyi ile ilgili sorulan 22 soru değerlendirildiğinde, eğitim öncesi 7 soruda doğru cevap oranının %50'nin üzerinde olduğu, eğitim sonrası uygulanan son testte ise tüm sorularda %50'nin üzerinde olduğu görülmüş, KBRN eğitimi öncesi bilgi düzeylerinin düşük, eğitim sonrası ise iyi olduğu tespit edilmiştir.

Sonuç: KBRN bilinci oluşturmak için teorik gerçekleştirilen eğitimin anlamlı düzeyde olumlu etkisi olduğu belirlenmiştir.

Anahtar kelimeler: KBRN, sağlık bilgisi, tutumlar, uygulama, farkındalık.

Babacan A. Sağlık personellerinin kimyasal, biyolojik, radyasyon ve nükleer tehlikelerden korunma ve acil yardım uygulamaları ile ilgili bilgi düzeyleri ve farkındalıkları. Pam Tıp Derg 2023;16:618-626.

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Introduction

As well as being used in many areas of daily life, especially in industry, medicine and scientific research, chemical, biological, radioactive and nuclear (CBRN) substances are also used as an instrument of war [1]. CBRN incidents are defined as events caused by the intentional or accidental release of chemical, biological, radioactive and nuclear substances, causing harmful and dangerous situations for humans and the environment [2]. Uncontrolled dispersal of CBRN agents through natural disasters, accidents and terrorist activities by humans, nature or technological sources poses great risks for the environment and humans. CBRN incidents can injure or even cause the death of many people if they do not receive urgent medical attention [1]. CBRN events have significantly affected the environment, climate, human life and social order in history. People are exposed to CBRN events and substances through industrial accidents such as the 2011 Fukushima Daiichi nuclear disaster, the 1986 Chernobyl disaster, the 1989 Exxon Valdez Oil spill; through wars such as the 1991 Gulf War, the 1945 atomic bombing of Hiroshima and Nagasaki, the use of mustard gas and tear gas during World War I; or terrorism events such as the 2001 US Anthrax attacks, the 1995 Tokyo sarin attacks. The Chernobyl accident was the most significant nuclear accident, and the Thrace and Eastern Black Sea regions were the most affected regions in our country.

The 1979 collision between a tanker and a dry cargo ship in the Bosphorus Strait in Istanbul, which resulted in the explosion of a tanker carrying 100 thousand tons of crude oil and causing damage to thousands of homes and businesses in the Bosphorus, the leakage of 6400 tons of Acrylonitrile during the 1999 Marmara earthquake, the 1986 explosion at the Kırıkkale MCI (Mechanical and Chemical Industry) corporation factory, and the explosion and fire caused by LPG cylinders in the Industrial Region of Ankara in 2011 are the CBRN incidents that have occurred in our country.

As a result of technological developments, rapid industrialization, an increase in weaponization, and developments in the industry, the production and availability of CBRN agents have increased and become more accessible. Inadequate knowledge, use and control of CBRN agents have brought the danger to the highest level today [3]. The geographical location of our country, being on the international transportation route and being surrounded by seas on three sides, nuclear facilities in surrounding countries, irregular urbanization, and industrialization increase the risk for our country [3]. The “Regulation No. 3033 on Chemical, Biological, Radiological, Nuclear (CBRN) Threats and Hazards” was published in 2020 to prevent or minimize the damage that may occur to human health and the environment in the event of any chemical, biological, radiological, nuclear threats and hazards that may occur in Türkiye or other countries. The responsibilities of the institutions and organizations that will take part in CBRN threats and hazards before, during, and after the incident are clearly defined by this regulation [4].

CBRN incidents are challenging and time-consuming events that require the cooperation of relevant institutions and organizations [3, 5]. The main task of healthcare personnel in CBRN incidents is to protect the injured people from the harmful effects of CBRN agents, to perform triage, first aid and decontamination, reporting, quarantine applications, advanced diagnosis, and treatment procedures [6, 7]. Healthcare organizations must determine the principles of healthcare services to be provided in these extraordinary events within the scope of the “Hospital Disaster Plan (HDP),” specially developed according to their organization. After an emergency, the affected community needs emergency intervention and long-term health services. It will lose functionality if the hospital staff is not prepared and trained and cannot perform medical intervention by providing the necessary occupational health and safety conditions. In order to develop the necessary knowledge, behaviors, and attitudes in the face of these events, training of hospital staff and testing of training through practices are of great importance [7].

The aim of this study was to determine the level of knowledge and awareness of healthcare workers working in the emergency service in our institution about protection from CBRN threats and hazards and emergency aid practices and to compare the level of knowledge before and after the training, and to evaluate the effectiveness of the training about CBRN awareness training.

Materials and methods

This descriptive study was planned to investigate the knowledge levels and awareness of healthcare personnel working in the emergency service of our hospital about protection from chemical, biological, radiation, and nuclear hazards and emergency aid practices. The ethics committee approval was obtained from Health Sciences University, Ankara, Dr. Abdurrahman Yurtarslan Oncology Training and Research Hospital. The questionnaire method was used for data collection. After reviewing the literature and regulations, the questionnaire was prepared based on the training module on "Emergency Assistance in Chemical, Biological, Radiation, and Nuclear Hazards" for Emergency Health Services published by the Republic of Türkiye Ministry of National Education [3]. A total of 10 hours of theoretical CBRN awareness training was given on CBRN introduction, personal protection from CBRN hazards (warning and alarm signs, PPE features and use, protection levels), chemical hazards, scene, front of hospital organization and triage in CBRN exposure, decontamination, biological agents, radiation and nuclear hazards, hospital organization in line with the HDP plan of our hospital. The questionnaire form, which consists of multiple-choice questions, was applied face-to-face before and after training to measure and evaluate the training module. The first section consisted of five questions about the sociodemographic characteristics of the participants, the second section consisted of three questions about CBRN training status, self-assessment of knowledge and skills, and history of experiencing an incident, and the third section consisted of twenty-two multiple-choice questions to assess the level of knowledge about CBRN. Correct answers were given a "1" point. In the third question, four questions were asked about CBRN risk perception, and they were asked to answer correctly or incorrectly. A total CBRN knowledge score was calculated by giving 1 point for each correct answer. Out of a total of 25 points; for the level of knowledge; 0-8 points were classified as low, 9-16 points as moderate, and 17-22 points as good. Participants who did not participate in CBRN awareness training and answered the survey questions incompletely were excluded from the study. One hundred and one health personnel participating in CBRN awareness training working in the emergency service completed the study.

Statistical analysis

The data were analyzed with SPSS 25.0 (IBM Co®. USA). The Kolmogorov-Smirnov test was used to determine normal distribution. Categorical data are presented as numbers and percentages (%). Numerical variables not normally distributed are shown as the median and interquartile range (IQR: 25th-75th percentile). Wilcoxon signed-rank test was used to compare the pre-and post-training knowledge level questionnaire results. Mann Whitney U and Kruskal Wallis tests were used to compare the pre-and post-training questionnaire results according to gender, duty, place, and task duration.

Results

Of the participants, 58.4% were female, 41.6% were male, and the median age was 38. Most of the participants were doctors or nurses. Approximately three-quarters of the participants were staff of the emergency service. 35.6% of them had been working in the emergency department for 1-5 years. The demographic characteristics of the participants are given in Table 1.

61.4% of the participants had not received CBRN training, and 84.2% thought they needed more knowledge and experience. 77.2% had not experienced any CBRN incident nor performed any intervention for CBRN (Table 2).

When the 22 questions asked about the level of CBRN knowledge were evaluated, it was seen that the correct answer rates were above 50% in a total of seven questions in the pretest about knowledge of the CBRN codes, risk perception, institutions and organizations concerned with CBRN, danger warning signs, precautions that should be taken in the hospital in case of CBRN exposure, the route of entry of biological agents into the body and the most potent toxin, and radiation beams. However, their level of knowledge could have been higher in general evaluation. The correct answer rates were above 50% in all questions in the post-test applied after the training, and their knowledge levels were found to be good in the general evaluation (Table 3).

Table 1. The demographic characteristics of the participants

		N/%	Median (IQR: 25th-75th percentile)
Age			38.0 (27.0-45.0)
Gender	Female	59 (58.4)	
	Male	42 (41.6)	
Duty	Doctor	47 (46.5)	
	Nurse	41 (40.6)	
	EMT	6 (5.9)	
	Health officer	7 (6.9)	
Place of duty	Emergency service	74 (73.3)	
	Family medicine	27 (26.7)	
Duration of duty	1-5 years	36 (35.6)	
	6-10 years	12 (11.9)	
	11-15 years	12 (11.9)	
	16-20 years	9 (8.9)	
	21-25 years	16 (15.8)	
	25 years and above	16 (15.8)	

IQR: Interquartile range, EMT: Emergency medicine technician

Table 2. Questioning of the self-assessment of the knowledge and skills of the participants on Chemical Biological Radiological Nuclear Threats and the history of experiencing an incident (N=101)

Have you received CBRN training?	Yes	39 (38.6)
	No	62 (61.4)
Do you think you have sufficient knowledge and skill level about CBRN as a healthcare professional?	Yes	16 (15.8)
	No	85 (84.2)
Have you experienced and/or intervened in any CBRN incident in your occupational life?	Yes. I have, but I have not had any intervention	11 (10.9)
	Yes. I have and I have an intervention	12 (11.9)
	No. I have not	78 (77.2)

CBRN: Chemical Biological Radiological Nuclear Threat

Table 3. Questionnaire questions and correct response rates for the evaluation of the participants' level of knowledge about Chemical Biological Radiological and Nuclear Threats (N=101)

	Pre-test	Post-test
	Number and percentage of correct answers (N/%)	
1. In case of a CBRN incident which code is prescribed by the head of the HDP in the hospital?	68 (67.3)	102 (100)
2. In which of the following areas of the scene of CBRN is the healthcare professional assigned?	33 (32.7)	98 (96.1)
3. Which of the following are included in the definition of CBRN? (For each item it was asked to express as true or false)		
a. Use of dangerous and epidemic bacteria, viruses, and toxins as biological weapons	82 (81.2)	102 (100)
b. Nuclear station accidents	90 (89.1)	102 (100)
c. Tanker, truck, train, and ship accidents during transportation of chemicals	87 (86.1)	102 (100)

Table 3. Questionnaire questions and correct response rates for the evaluation of the participants' level of knowledge about Chemical Biological Radiological and Nuclear Threats (N=101) (continued)

	Pre-test	Post-test
	Number and percentage of correct answers (N/%)	
d. The technological accidents in scientific or industrial research laboratories	73 (72.3)	102 (100)
4. Which of the following is one of the institutions and organizations in our country concerning CBRN?	68 (67.3)	99 (97.1)
5. Hazard warning and alarm systems have been established to warn the public against danger and to ensure that necessary precautions are taken; which of the following statements about hazard warnings is incorrect?	76 (75.2)	98 (96.1)
6. The level of protection in CBRN incidents varies according to the hazard encountered; which of the following is applied when the highest level of protection of respiration and lower level of skin protection is required?	29 (28.7)	83 (81.4)
7. Which of the following is the level of protection used by the healthcare professional in the decontamination area?	24 (23.8)	80 (78.4)
8. Which of the following is the level of protection used by healthcare professionals in the area of low pollution?	26 (25.7)	92 (90.2)
9. Which of the following statements about decontamination is incorrect?	20 (19.8)	81 (79.4)
10. Which of the following statements about decontamination is incorrect?	12 (11.9)	86 (84.3)
11. Which of the following is not one of the precautions that should be required in a hospital following CBRN exposure?	64 (63.4)	100 (98.0)
12. Which of the following should be applied for exposure to nerve agents?	44 (43.6)	98 (96.1)
13. Which of the following chemical warfare agents is used as a nerve agent?	42 (41.6)	89 (87.3)
14. Which of the following is not one of the physiological effects of anesthetic gases?	28 (27.7)	54 (5.9)
15. Which of the following is the most effective route of entry for biological agents to achieve their goals?	74 (73.3)	94 (92.2)
16. Which of the following is the most potent toxin in the world?	59 (58.4)	96 (94.1)
17. Which level of protection is sufficient in case of exposure to biological agents?	26 (25.7)	82 (80.4)
18. Which of the following is not one of the viral agents used as a biological agent?	49 (48.5)	94 (92.2)
19. Which of the following is the leading cause of radiation damage?	30 (29.7)	84 (82.4)
20. Which of the following organs is not resistant to radiation?	36 (35.6)	80 (78.4)
21. Which of the following statements about radiation beams is incorrect?	52 (51.5)	79 (77.5)
22. Which of the following is the form of very high dose exposure in acute radiation syndrome?	21(20.8)	52 (51.0)

CBRN: Chemical Biological Radiological Nuclear Threat

When the pre and post-training test results over a total of 25 points were compared, the median score was 11.0 (8.8-13.0) before and 20.0 (18.0-22.0) after the training, and a significant difference was found between the two results (p<0.001). There was no difference in CBRN knowledge level score before and after the training according to gender (p=0.504 and p=0.414, respectively). Again, no significant difference was found in the CBRN questionnaire scores of the participants before and after the training according to their duties (p=0.896, p=0.327). While there was no significant difference between the pre-training CBRN scores of those working in the emergency department and family medicine (p=0.807), the CBRN scores of emergency service personnel were found to be higher in the post-training questionnaire (p=0.029). There was no significant difference in pre- and post-training CBRN knowledge scores according to the duration of duty (p=0.051 and p=0.380, respectively).

Discussion

In this study conducted to evaluate the level of CBRN knowledge and the effectiveness of the training, 58.4% of the participants were female, 41.6% were male, and the mean age was 38 years. The male-female ratio and median age were consistent with similar studies [8, 9]. There was no significant difference in the CBRN knowledge level scores of the participants before the training regarding gender and duty. Gurler et al. [9] and Ayvazoglu et al. [10] found that CBRN knowledge levels did not differ significantly according to gender in their studies. In the study of Dincer and Kumru [11], which investigated the preparedness of health personnel for disasters and emergencies, it was found that gender did not cause a significant difference in readiness for disasters and emergencies. The findings obtained from this study are in parallel with the results in the literature.

In this study, 38.6% of the participants stated that they had received CBRN training before. Dönmez [12] said that 38.2% of the participants received CBRN training in the study conducted with emergency medical personnel, and Kaynak [13] stated that 54.7% of the participants received basic CBRN training in 2020. Öner [14] reported that 46.9% of the participants received CBRN training in the thesis study to determine the level of knowledge about CBRN of family physicians and 112 emergency and first aid healthcare personnel. So, the rate of CBRN training in this study is similar to previous studies.

84.2% of the participants in this study thought that they needed more knowledge and experience on CBRN. 77.2% had not experienced any CBRN incident nor practiced any intervention. In the study of Günenç [15], 75.6% of the participants reported that they had not experienced a CBRN incident. Similarly, Eyison et al. [1] found that most of the participants had not experienced a CBRN incident. The cold area at the scene of CBRN exposure is the clean area that has never been affected by the event. It is the location of healthcare personnel with personal protective equipment and ambulances. In our study, for the question about basic CBRN knowledge level, “The code given by the head of the HDP; code orange,” the correct answer ratio was 67.3%, and the correct answer ratio to the question “In which area do health personnel work at the CBRN incident site; cold area” is 32.7%. There are limited studies in the literature on CBRN preparedness and knowledge level of hospitals and emergency services, and there is no study that we can compare the findings of our research.

For the question “Evaluate the given events in terms of CBRN events,” 81.2% of the participants thought that bacteria, viruses, and toxins that are the agents of dangerous and epidemic diseases could be used as biological warfare agents, 89.1%, 86.1%, and 72.3% thought nuclear station accidents, transportation of chemical CBRN agents and technological accidents in scientific or industrial research laboratories pose CBRN risk, respectively. It was observed that there was no significant difference in the CBRN risk perception of the participants in terms of age, gender, duty period, and occupational groups and that their risk perception was high. In the study by Kaynak [13] in 2020, the correct answer rates for similar statements ranged between 64-96%. The correct answer rates are over 50% in the questions about the institutions and organizations concerning CBRN and hazard warning signs in our country. The most critical step in approaching CBRN incidents is decontamination and using PPE. In our study,

the correct answer rates to the 6th, 7th, and 8th questions about protection levels were 28.7%, 23.7%, and 25.7%, respectively. We have not encountered a study in the literature to compare the results of this study. The correct answer rates of the participants to the 9th, 10th, and 11th questions about decontamination were 19.8%, 11.9%, and 63.4%. The knowledge level of the participants about decontamination and methods is found to be low. In his study conducted on emergency service personnel, Günenç [15] found that the rates of correct answers to the abovementioned questions were 53%, 70%, and 65%, respectively. The high knowledge rates in this study may be due to the study population, and the participants may have had more CBRN training.

The rates of correct answers for questions 12, 13, and 14 about the symptoms and signs that can be seen after exposure to chemical agents are 43.6%, 41.6%, and 27.7%. In the study of Kaynak [13], the correct response rate of the participants to the question “Atropine is administered in CBRN cases exposed to nerve agents,” which is similar to the 12th question of this study, was 44%, in accordance with this study. These studies show that especially the healthcare personnel involved in CBRN incidents were aware of the CBRN hazard, but the knowledge of the medical approaches still needs improvement.

The correct response rates of the participants to questions 15, 16, 17, and 18 about biological agents, the most effective route of entry into the body, and levels of protection were 73.3%, 58.4%, 25.7%, and 48.5%, respectively. In the study of Demirag et al. [16], the correct response rate to the question “C level protection is applied with type C clothing in biological agent exposure” was found to be 44.5%, and 96.3% of the students answered the question about the ways of entry of biological agents into the body correctly. In the study conducted by Günenç [15], 91% of the students had the correct answer to the question “What are the routes of entry of biological agents into the body?” and 67% of the students had the correct answer to the question “Clostridium botulinum is the strongest known toxin.” Our findings are similar to the studies mentioned above. However, the correct answer rate was found to be low in the question about the level of protection. As observed in the COVID-19 pandemic, healthcare personnel who intervene in CBRN incidents should wear PPE and have knowledge and skills about PPE because they are at high risk [17, 18].

The level of knowledge of the participants about radiation beams and their properties, affected organ structures, and acute radiation syndrome was evaluated in the 19th, 20th, 21st, and 22nd questions. The correct answer rates were 29.7%, 35.6%, 51.5%, and 20.8%. The knowledge level of the participants is considered to be low, but there is no comparable data in the literature. In this study, it was found that the basic CBRN knowledge level of the participants was low in the pre-test. Ayvazoğlu [10] found that the CBRN knowledge level of state hospital personnel and university students was intermediate in his study. In most of the studies conducted in our country and abroad, it has been observed that nurses have inadequate knowledge about what to do about CBRN threats and hazards, need training, and are worried about themselves, their families, and society [19] Woude et al. [20] also found that basic education and training on CBRN were lacking. Due to the lack of training, it was stated that healthcare personnel had problems with issues such as how to intervene in CBRN situations. The findings obtained from the literature and this study show that individuals consisting of healthcare personnel have low levels of CBRN knowledge.

The finding of a significant difference between the results before and after the training regarding the level of knowledge reveals the importance of training. The post-training score of those working in the emergency service was higher than those working in family medicine. This finding may be related to the fact that those working in the emergency department show more motivation for CBRN-related training and have a higher rate of encountering CBRN events. Gurler et al. [9] found that the pre-test and post-test results were compared, and a significant difference was found in knowledge levels after the training. They emphasized the importance of training programs to raise awareness about basic first aid and CBRN in their study and noted that the increased level of knowledge as a result of the training would prevent irreversible situations by intervening in a possible event on time. Kako et al. [21]

reported that scenario-based training models could significantly contribute to increasing the knowledge of emergency healthcare personnel and closing the gap in this field. Li et al. [5] emphasized that the challenges and complexities of intervention in Nuclear, Biological, and Chemical incidents should be realized, and cooperation between national security agencies, military/local/regional, health service providers, professional medical communities, military and local communities should be established as early as possible. It was highlighted that coordination of intervention to Nuclear, Biological, and Chemical incidents should be established, practical training and exercises should be conducted, and a continuous and integrated response system should be conducted.

As a result, this study and other similar studies indicate that training programs will significantly contribute to improving knowledge and skills. Therefore, intra-institutional CBRN coordination should be developed, and knowledge and awareness should be increased through repeated training and drills.

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

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Non-Operative management of acute appendicitis in children

Çocuklarda akut apandisitin ameliyatsız tedavisi

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Abstract

Purpose: Most studies addressing non-operative management for acute appendicitis have focused on adults, and there are limited data available for children. We aimed to evaluate the results of successful non-operative management in children with acute uncomplicated appendicitis with our "additional criteria" and find which factors could be affecting the success rate and which cases could be candidates for non-operative management.

Materials and methods: A total of 26 patients who were diagnosed with acute uncomplicated appendicitis and received non-operative management were re-evaluated retrospectively. Defining uncomplicated appendicitis was based on the duration of symptoms (<24 hours), clinical history, and radiologic findings. The radiologic evaluation was based on ultrasonography and computed tomography. The patients received an intravenous antibiotic combination (sulbactam/ampicillin, gentamicin, clindamycin) for five days at the hospital; the treatment was completed after 10 days with an oral antibiotic combination (amoxicillin/clavulanate, metronidazole). The cases have a follow-up period of up to two years.

Results: The mean patient age and follow-up time were 10.42±3.65 years and 30.15±5 months, respectively. The mean leukocyte count, C-reactive protein (CRP), and appendix diameter values were 15.82±5.4×109/L, 20.38±33.4mg/dL, and 7.87±1.4 mm on admission. None of the patients had an early failure, complication, or adverse event. Recurrent appendicitis occurred in only one case (4%) that was treated by laparoscopic appendectomy during the follow-up.

Conclusion: Non-operative management for acute uncomplicated appendicitis in children regarding long-term outcomes with our criteria was satisfactory and initial success rates were excellent.

Keywords: Acute appendicitis, appendectomy, children, conservative treatment, non-operative management.

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Öz

Amaç: Akut apandisit için ameliyatsız tedaviyi ele alan çoğu çalışma yetişkinlere odaklanmıştır ve çocuklar için sınırlı veri mevcuttur. Akut komplikasyonsuz apandisitli çocuklarda başarılı ameliyatsız yönetimin sonuçlarını "ek kriterlerimiz" ile değerlendirmeyi ve hangi faktörlerin başarı oranını etkileyebileceğini ve hangi vakaların ameliyatsız tedaviye aday olabileceğini bulmayı amaçladık.

Gereç ve yöntem: Akut komplikasyonsuz apandisit tanısı alan ve ameliyatsız tedavi uygulanan toplam 26 hasta retrospektif olarak yeniden değerlendirildi. Komplike olmayan apandisit tanımlaması semptomların süresine (<24 saat), klinik öyküye ve radyolojik bulgulara dayanıyordu. Radyolojik değerlendirme ultrasonografi ve bilgisayarlı tomografi ile yapıldı. Hastalara hastanede beş gün intravenöz antibiyotik kombinasyonu (sulbaktam/ampisilin, gentamisin, klindamisin) verildi; tedavi oral antibiyotik kombinasyonu (amoksisilin/klavulanat, metronidazol) ile 10 güne tamamlandı. Olguların ortalama takip süresi iki yıldı.

Bulgular: Ortalama hasta yaşı ve takip süresi sırasıyla 10,42±3,65 yıl ve 30,15±5 aydı. Başvuru anındaki ortalama lökosit sayısı, C-reaktif protein (CRP) ve apendiks çapı değerleri 15,82±5,4×109/L, 20,38±33,4mg/dL ve 7,87±1,4 mm idi. Hastaların hiçbirinde erken başarısızlık, komplikasyon veya yan etki görülmedi. İzlemde sadece bir olguda (%4) tekrarlayan apandisit gelişti ve laparoskopik apendektomi ile tedavi edildi.

Sonuç: Çocuklarda akut komplike olmayan apandisitin ameliyatsız yönetimi, kriterlerimize göre uzun vadeli sonuçlara göre tatmin ediciydi ve başlangıç başarı oranları mükemmeldi.

Anahtar kelimeler: Akut apandisit, appendektomi, çocuk, konservatif tedavi, ameliyatsız tedavi.

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Introduction

The most frequent abdominal surgical pathology in children is acute appendicitis [1]. The standard therapy for acute appendicitis in children is appendectomy. Surgical intervention has some complications that can result in morbidity and mortality [2]. The surgical approach has been questioned for uncomplicated appendicitis in recent years, and antibiotic therapy has been proposed as an alternative treatment [3]. Non-operative management for acute appendicitis has been developed in adult cases and has been safely adapted for children over time. Only a small number of publications have described non-operative treatment among children [4-16]. Specific criteria and various results were used in these research. This study aimed to evaluate non-operative management for uncomplicated cases and find which factors could be affecting success rate and outcomes.

Materials and methods

This study was retrospective and descriptive. After obtaining permission from the Pamukkale University Non-Interventional Clinical Research Ethical Committee, the records of 180 cases diagnosed with acute appendicitis from February 2019 to February 2020 were reviewed. A total of 154 out of 180 patients were managed surgically (77 open appendectomies and 77 laparoscopic appendectomies), and the rest (26 patients) were treated non-operatively. Of the non-operatively treated appendicitis cases, only those who completed their two-year follow-up were included in the study. Patients with complicated appendicitis, fever at the time of admission, signs of fecalith on radiologic evaluation, and a follow-up period of less than two years were excluded from the study.

Diagnosis of acute appendicitis

The diagnosis of acute appendicitis was based on history, physical examination, laboratory results, and radiologic evaluation. Radiologic scans were routinely used in suspected acute appendicitis cases. Ultrasound (US) is preferred as the first-choice imaging method. However, a CT scan was used when the appendix could not be seen on an ultrasonographic exam. The appendix diameter was higher than 6 mm, uncompressible appendix, and echogenicity of tissue around the appendix were confirmed as acute appendicitis in the ultrasonographic exam.

Definitions

Our inclusion criteria for non-operative management were defined as symptom duration of less than 24 hours, localized tenderness, no signs of fecalith on radiologic evaluation, and no fever at the time of admission (Table 1). The symptom duration of longer than 24 hours, generalized tenderness on physical exam, and radiologically suspected complicated appendicitis cases (abscess, phlegmon, irregular appendix wall) were managed operatively.

Table 1. Patient evaluation and inclusion criteria for non-operetive management

Patient evaluation	Inclusion criteria for non-operative management
Symptom duration	<24 hours
Clinical history	No fever and no additional disease
Physical examination	Localized tenderness
Radiologic evaluation (Ultrasonography and CT)	Without fecalith and perforation

Treatment protocol

The non-operative management option was applied to those who did meet the criteria for non-operative management. Oral intake was not permitted during the first 24 hours of antibiotic treatment and hydration was provided by intravenous (IV) crystalloid solutions. The IV antibiotic protocol was ampicillin-sulbactam (150 mg/kg/day, divided into four doses), gentamicin (5 mg/kg/day, divided into two doses), and clindamycin (40 mg/kg/day, divided into four doses). All cases were evaluated by a physical examination at 12-hour intervals. For the patients who responded to antibiotic treatment after 24 hours, oral feeding was initiated. IV antibiotic duration was five days in all cases at

the hospital, and all patients were discharged from the clinic with an oral antibiotic regimen (amoxicillin/clavulanic acid and metronidazole). Total antibiotic duration (IV and oral) lasted for 10 days.

Follow-up

All cases were re-evaluated by laboratory investigation and radiological examination. All of the patients were re-evaluated only by a physical exam on the second and seventh days of discharge at the outpatient clinic. Additional radiologic and laboratory screenings were not repeated at the outpatient clinic.

All procedures carried out during this study complied with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards, as well as the ethical norms of the institutional and/or national research committee. The parents were informed about the treatment protocol and complications.

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 22.0 (IBM Corp, Armonk, NY). Statistics are presented as weighted mean ± standard deviation. The Kolmogorov-Smirnov test was performed to assess normal distribution. Parametric variables were analyzed by independent t-test and non-parametric variables by Mann-Whitney U test. The homogeneity of variance was determined by Levene's test. The level of statistical significance for descriptive statistics was set at $p<0.05$.

Results

The mean patient age was 10.42±3.6 years (range: 5-17 years). A total of 12 (46%) cases were males and 14 (54%) were females; the male-to-female ratio was 0.75. The follow-up period of the cases ranged from 24 to 37 months, and the mean follow-up time was 30.15±5 months.

Initial white blood cell (WBC) and C-reactive protein (CRP) levels at admission were 15.82±5.4×10^9/L and 20.38±33.4mg/dL, respectively. All cases were evaluated by the abdominal US at admission. The main criteria of non-operative management of acute appendicitis was no signs of fecaliths in the appendix lumen; therefore, most cases were evaluated by a CT scan. If signs of fecalith were not clearly reported in the US exam, they were evaluated by a CT scan. Neither unresponsive cases nor complications (e.g. sepsis, ileus, perforation, and adverse drug events) were observed during the antibiotic treatment. Initial success rates were 100%. Readmission to the hospital was observed in one case at the 20th month of post-non-operative treatments, and they were subsequently treated laparoscopically. Histopathologic evaluations have revealed that no perforation signs were recorded in the specimen.

Discussion

Pediatric appendicitis has a high perforation rate, and removal of the appendix is a conventional surgical operation. Therefore, appendectomy is the first choice of treatment in children. However, surgical interventions and general anesthesia have some inevitable complications (e.g. bleeding, ileus, surgical site infection, and pneumonia). For these reasons, in recent years, non-operative management has been preferred in some cases of acute appendicitis [17]. The basic hypothesis is that other acute appendicitis-like conditions (e.g. uncomplicated diverticulitis, salpingitis, and necrotizing enterocolitis) regress with antibiotics with a high success rate, especially when the medical treatment is started early [18]. Few studies have addressed non-operative management for acute appendicitis among pediatric patients, while this is a well-known option in the adult patient population [19].

Previous studies have demonstrated widely different success rates. These varied results might be due to patient selection criteria and antibiotic therapy protocols [2, 4-16]. Antibiotic selection, antibiotic duration, and time for IV/per oral route have also been attracting research interest. A varied ratio of overall success is presented in the literature by the studies regarding children being managed non-operatively. The overall success rate in our study is higher than many studies in the literature. Among those studies, it is seen that the overall success rate was higher in studies where the patients were with short symptom duration (<36 hours) [4, 14, 15].

In this study, we reduced the symptom duration between the onset of complaints and admission (<24 hours), and we required

additional criteria such as the patients to be “fever-free” at the initial examination. Being fever-free at the time of admission is an important sign of a non-complicated inflammatory period. This approach provided early antibiotic initiation and suppressed the inflammatory process. To date, meta-analyses are demonstrating that being fever-free at the time of admission is not an inclusion criterion for non-operative management [20, 21]. Similarly, early antibiotic initiation has been reported to cause low recurrence rates of non-operative treatment [4, 14, 15].

The inclusion and exclusion criteria for non-operative management have been determined with/without fecalith and appendix diameter in imaging studies [4, 7-9, 14, 15]. One of the main criteria in our study was no signs of fecaliths in the appendix. Unlike in previous studies, we performed a CT scan in 16 (61.5%) of the cases in our series. This is because, in the US examination, only 6 (23%) appendices were detected and verified without fecalith in the imaging studies. CT scan has high sensitivity and specificity rate for the diagnosis of acute appendicitis; however, the routine usage of CT scan is not recommended due to the high radiation exposure. The reduction of ionizing radiation has provoked the increased usage rate of CT year on year [22, 23]. Sometimes CT scanning may be the first choice of radiologic evaluation for undiagnosed patients and obese children. The usage rates of CT imaging for the diagnosis of acute appendicitis vary according to clinical practice, surgeon preference, and institutions. The average rate is reported as 30-40% [24-26].

In some studies, to decide on non-operative management, the appendix diameter has been taken into consideration. It has been reported that the appendix diameter should be ≤9, ≤10, and ≤11 mm in various studies [7, 9, 15, 27]. In the current study findings, we did not consider appendix diameter. In contrast, the appendix diameter was found higher than 8 mm in 9 (34%) patients, and they were treated non-operatively. However, the cut-off value of appendix diameter for non-operative management remains controversial. A critical evaluation was that acute uncomplicated appendicitis is suppressed with antibiotics.

The selection of antibiotics (e.g. cephalosporin, carbapenem, and β-lactam) and the duration of the prescription/therapy might differ among the clinical series [4-16]. Antibiotic duration for IV and oral administration has been reported to vary in the earlier reports. In our series, we preferred triple and narrow-spectrum antibiotics by IV route administered in the hospital for five days. The duration of antibiotic therapy was longer than the other reported series. Even in the early responding treatments of cases, IV treatment was completed in five days, as reported earlier.

Perez Otero et al. reported that the antibiotic treatment was first applied in the emergency department and was provided to be used at home for two or three days in the total course. The same analyses have reported that the success rate of their treatment was 58-99%. In our study, the positive responses of all cases to the treatment might be a result of the long-term usage of antibiotics.

The case numbers and follow-up periods of the literature studies were evaluated similarly. For long-term results, follow-up periods between six months and 4.3 years were reported. Besides, it has long been established that recurrences are the main factor in the success rate in the follow-up period. The early failure rate of these studies was between 1.2% and 41.6%, and the long-term failure rate was 8-42% in children [2, 4-16, 20]. There was no early failure case in our study; however, the long-term failure rate was 9% due to five recurrences of appendicitis. A meta-analysis of previous studies reported that the rate of appendectomy due to recurrence appendicitis was 18-42% within a one-year follow-up period [27-30]. Therefore, we included cases that have a follow-up period of at least two years. The mean follow-up period was 30 months in our study, whereas a small number of studies had a longer follow-up period than ours.

The primary limitations of this study were its retrospective, uncontrolled, single-center design. Another limitation of our study is the longer duration of IV antibiotic therapy (five days) in the hospital. However, this can be interpreted as the learning curve of our clinic. In our current practice, we hospitalize patients for two or three days for IV antibiotic therapy.

In conclusion, in this observational study, we found that non-operative management in children for acute uncomplicated appendicitis in selected cases is a safe and effective treatment method. Based on our findings, we propose that the success rate of non-operative management for clinically and radiologically proven acute appendicitis cases could be improved by applying two significant treatment criteria, i.e, less than 24 hours of symptom duration and fever-free at the time of admission.

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

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Authors' contributions to the article

O.U. constructed the main idea and hypothesis of the study. O.U. developed the theory and arranged/edited the material and method section. O.U. and I.G.A. have done the evaluation of the data in the Results section. Discussion section of the article written by O.U.

O.U. and I.G.A. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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The effects of personality types and coping styles on coronavirus anxiety levels of the healthcare workers

Sağlık çalışanlarının kişilik tipleri ve başa çıkma tarzlarının koronavirüs kaygı düzeylerine etkisi

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Abstract

Purpose: Healthcare workers are exposed to long and stressful work shifts in pandemics. It was aimed to evaluate the coronavirus related anxiety levels of the healthcare workers, and to evaluate the relationship between their personality types and coping strategies.

Materials and methods: Study included 213 medical healthcare workers who were randomly selected and agreed to participate in the study on a voluntary basis. Sociodemographic data form, Coronavirus anxiety scale, Type A Behavior Test, and Coping styles scale were applied to all participants.

Results: The total coronavirus anxiety scores of the participants with type A personality traits were found to be significantly higher than with type B personality traits (p=0.006). The mean scores of helpless approach and seeking social support were found to be significantly higher in participants with Type A personality (p=0.002, p=0.007, respectively). Self-confident and optimistic approach were found to be higher in participants with Type B personality (p=0.041, p=0.023, respectively). Participants with helpless approach had higher anxiety scores (p=0.033). A negative correlation was found between coronavirus anxiety and self-confident approach (p=0.002, r=-0.212) and optimistic approach (p=0.002, r=-0.209), and positive correlation with helpless approach (p=0.044, r=0.138).

Conclusion: The results of this study showed that healthcare workers with type A personality use less self-confidence and optimistic approach, use more helpless approach, and have higher levels of dysfunctional coronavirus anxiety according to B type personality. Following - up the mental health of healthcare workers is crucial to global health in other possible pandemics.

Keywords: Coronavirus anxiety, personality types, coping styles.

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Öz

Amaç: Sağlık çalışanları pandemi gibi süreçlerde uzun ve stresli vardiyalara maruz kalmaktadır. Bu çalışmada sağlık çalışanlarının koronavirüse ilişkin işlevsel olmayan kaygı düzeylerinin değerlendirilmesi, aynı zamanda koronavirüs kaygısının bireylerin kişilik tipleri ile başa çıkma stratejileri arasındaki ilişkinin değerlendirilmesi amaçlanmıştır.

Gereç ve yöntem: Çalışmaya rastgele seçilen ve gönüllülük esasına göre çalışmaya katılmayı kabul eden 213 tıbbi sağlık çalışanı dahil edildi. Tüm katılımcılara Sosyodemografik veri formu, Coronavirüs Anksiyete Ölçeği, A Tipi Davranış Testi ve Başa Çıkma Tarzları ölçeği uygulandı.

Bulgular: Çalışmanın sonuçlarına göre A tipi kişilik özelliğine sahip katılımcıların koronavirüs anksiyete puanlarının, B tipi kişiliğe göre anlamlı düzeyde yüksek olduğu saptandı (p=0,006). A Tipi kişiliğe sahip katılımcılarda çaresiz yaklaşım ve sosyal destek arama puanları anlamlı düzeyde yüksek bulundu (sırasıyla p=0,002, p=0,007). B Tipi kişiliğe sahip katılımcılarda kendine güven ve iyimser yaklaşımın daha yüksek olduğu bulundu (sırasıyla p=0,041, p=0,023). Çaresiz yaklaşım sergileyen katılımcıların kaygı puanları daha yüksekti (p=0,033). Coronavirüs kaygısı ile kendine güvenli yaklaşım (p=0,002, r=-0,212) ve iyimser yaklaşım (p=0,002, r=-0,209) arasında negatif, çaresiz yaklaşım (p=0,044, r=0,138) arasında pozitif korelasyon bulundu.

Sonuç: Bu çalışmanın sonuçları, A tipi kişiliğe sahip sağlık çalışanlarının kendine güven ve iyimser yaklaşımı daha az kullandığını, çoğunlukla çaresiz yaklaşım sergilediklerini ve işlevsel olmayan koronavirüs anksiyete düzeylerinin B tipine göre daha yüksek olduğunu göstermektedir. Sağlık çalışanlarının ruh sağlığının izlenmesi ve sağlanması, olası diğer salgınlarda küresel sağlık açısından büyük önem taşımaktadır.

Anahtar kelimeler: Coronavirüs anksiyetesi, kişilik tipi, başetme stratejileri.

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Introduction

The outbreak of Coronavirus-2019 disease (COVID-19) in the city of Wuhan, China, at the end of 2019, spread rapidly across the world with increasing numbers of cases creating global concern, and was declared a pandemic by the World Health Organisation (WHO) on March 2020 [1]. Throughout the world, not only those with infection, but all sections of society were affected by the COVID-19 pandemic.

Previous studies have shown that outbreaks of highly infectious diseases such as COVID-19 cause psychological stress and symptoms of mental health disease [2]. One of the groups most affected in those difficult days, when there was an evident threat to life and mental health integrity, was undoubtedly healthcare workers who were working on the frontline and facing a high risk of becoming infected every day. In addition to the high risk of infection, healthcare workers dealing with COVID-19 were also working long and stressful shifts to meet the health needs of the community [3].

It can be said that healthcare workers were under great stress at that time for many reasons including the working hours and physical fatigue, insufficient personal protective equipment available, fears of becoming infected or infecting family and loved ones after contact with patients, having to remain distant from family, the high mortality rate of the disease, the grieving process for colleagues lost to the disease, and uncertainty of when the pandemic would end [4, 5]. It has been reported worldwide that the vast majority of healthcare personnel who were dealing with COVID-19 experienced psychological problems during the pandemic [6, 7]. The results of previous studies have also shown that depression and anxiety were experienced by healthcare workers during the pandemic at rates ranging from 13% to 47% [8-11].

The sensitivity of individuals, responses to problems experienced, and coping strategies for stress can take various forms. The coping styles of an individual in stressful situations can vary according to many factors such as personal characteristics, age, gender, culture, upbringing, and the disease [12, 13]. It has been reported that the coping styles of individuals in stressful situations or negative life events can mediate some outcomes such as anxiety, depression, psychological distress, and somatic complaints [14, 15]. To be able to be better prepared for future pandemics and increase productivity, it seems to be neceessary to know how beneficial the coping strategies are in conditions of severe stress and which strategies are less stressful for those using them.

In addition, certain personality types also affect the individual's response to stress. For example, Type A personality is a behaviour pattern often encountered in stress research. It has been reported that individuals with Type A personality are those who are organised and perfectionist, and they have less resistance to stress, can perceive even ordinary events as stressful, tend to experience more stress, and experience more burnout [16-18]. According to the classification of personality types, Type A individuals are generally introverted, do not like wasting time, try to do more than one task at once, and are therefore always fussy, are overly meticulous, controlling and competitive at work, forcing themselves and others to finish tasks, and can thus show anger, impatience, and displeasure towards others. Type B personalities do not like competition, are satisfied with their social standing and profession, are calm and tolerant, do not expect approval, are generally not fussy, rest periodically, and have sufficient areas of interest outside work and the home [19-21].

The aim of the current study was to evaluate the anxiety levels experienced related to COVID-19, and the relationships between coping strategies of health care workers who were faced not only with the threat of illness, but also with the threat of illness or loss of their relatives during the COVID-19 pandemic. It was also aimed to determine whether individuals with similar personality types used similar strategies to cope with stress and whether the stress coping strategy used was related to coronavirus anxiety. To be able to understand the potential psychological effects of a highly infectious, rapidly spreading pandemic, and to be prepared for other potential pandemics in the future, the early identificaton of problems is important to be able to prevent these. According to the results of this study, knowing the factors that are effective in coping with stress can be expected to provide guidance for future studies.

Materials and methods

Sample

The study included 213 medical health care workers who were randomly selected and agreed to partcipate in the research on a voluntary basis. The subjects included had no history of psychiatric treatment, and those with a current or previous psychiatric disease were excluded from the study. An online questionnaire was sent by email, and the subjects in the research who completed the questionnaire in full were enrolled in the study. Data were collected from a university hospital between July 2020 and December 2020.

All the study participants completed a Sociodemographic Data Form. The Coronavirus Anxiety Scale (CAS), the Type A Personality Test (TAPT) to determine personality traits, and the Coping Style Scale (CSS) to determine the methods used to cope with stress.

The Coping Style Scale (CSS)

The 30-item Coping Style Scale developed by Folkman and Lazarus (Ways of Coping Inventory) [12] and was adjusted by Şahin and Durak [13] and named the Coping Styles Scale (CSS). The items on the CSS are scored from 0-3 points with 4-point Likert-type responses, and separate scores are obtained for the subscales. Higher subscale points indicate which style is more used. The subscales are the optimistic, self confident, seeking social support, submissive and helpless approaches. Of these, the helpless approach and submissive approach are evaluated as ineffective strategies, and the optimistic, self confident and seeking social support as effective strategies.

Type A Personality Test (TAPT)

This test was developed by Ganster et al. [19], and the Turkish version was tested for validity and reliability by Durna [20]. The test has a total of 7 questions, each scored between 1 and 8 points. The scores for all 7 questions are totalled and then multiplied by 3. A final score of ≥100 points is accepted as a sign of Type A personality and a score of ≤99 points as Type B personality.

Coronavirus Anxiety Scale (CAS)

This scale was developed by Sherman A. Lee et al. [22] to determine cases of potentially dysfunctional anxiety associated with the COVID-19 crisis. The scale has been translated into various languages, including Turkish, and the validity and reliability studies for the Turkish version were performed by Evren et al. [23]. The CAS is a mental health screening scale for dysfunctional anxiety associated with COVID-19. The last 2 days are evaluated, with each item scored from 0 (never) to 4 (almost every day) points. Total CAS points of ≥9 indicate dysfunctional anxiety associated with COVID-19. A subject with high points for a specific item or high total points is evaluated as showing problematic symptoms which would require further evaluation and/or treatment.

Statistical analysis

The study data were analyzed using SPSS vn. 22.0 software. Continuous variables were mentioned as mean ± standard deviation (SD) values and categorical variables mentioned as number (n) and percentage (%). In the comparisons of the differences between independent groups of data, the Significance of the Mean Difference Test and One-Way Variance Analysis were used when parametric test assumptions were met, and the Mann Whitney U-test and Kruskal Wallis Variance Analysis were used when parametric assumptions were not met. Differences between categorical variables were examined with Chi-square analysis. A value of $p<0.05$ was defined as statistically significant.

Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study.

Results

Evaluation was made of the data of 213 healthcare workers, comprising 155 (72.8%) females and 58 (27.2%) males. There were 4 separate age ranges of the participants: 86 (40.4%) aged <29 years, 71 (33.3%) aged 30-39 years, 50 (23.5%) aged 40-49 years, and 6 (2.8%) aged ≥50 years. It was seen that 121 (56.8%) participants were married and

92 (43.2%) were single. The educational level was reported as primary school by 3 (1.4%), high school by 12 (5.6%), and university by 198 (93%). Of the total study participants, 97 (45.5%) were resident physicians, 17 (8%) were specialist physicians, 5 (2.3%) were faculty member physicians, 86 (40.4%) were nurses/ health technicians, and 8 (3.8%) were patient carers.

The place of residence was reported to be a rural area by 17 (8%) and an urban area by 196 (92%) participants. There was a history of migration for 56 (26.3%) participants and not for 157 (73.7%). A total of 59 (27.7%) participants stated that they lived alone, 150 (70.4%) that they lived together with their family, and 4 (1.9%) stated that they had other living conditions.

During the COVID-19 pandemic, 46 (21.6%) participants stated that they had to make a change in their living arrangements and 167 (78.4%) did not have to make any change. When the working conditions during the pandemic were examined, 5 (2.3%) were not working actively with patients, 42 (19.7%) stated that they were in contact with patients when on call, 127 (59.6%) were during normal working hours and on call, and 39 (18.3%) during flexible working hours.

The CAS scores of the study participants were determined as <9 points in 199 (93.4%) subjects and ≥9 points in 14 (6.6%). The total CAS points of the subjects showing A-type personality characteristics (2.45±3.92) were determined to be higher than those of the subjects showing B-type personality characteristics (1.25±2.30) (p=0.006). This showed that individuals with the A-type personality characteristics of being more particular, controlling, and agitated experienced a higher level of COVID-19-related anxiety, meaning that they were more affected by the pandemic.

When the stress coping styles were examined, the mean points of the helpless approach (p=0.002) and seeking social support (p=0.007) of the healthcare workers showing Type A personality characteristics were determined to be statistically significantly higher. The mean points of the self-confident approach (p=0.041) and optimistic approach (p=0.023) of the healthcare workers showing Type B personality characteristics were determined to be signficantly higher. These results showed that individuals with type A personaity characteristics used self-confident and optimistic approach stress coping styles less, and the helpless approach to events and need for social support were at a higher level (Table 1) (Figure 1).

Table 1. Coronavirus anxiety levels and coping styles of the groups according to their personality types

	Mean±SD		
	Type A Personality	**Type B Personality**	***p*[a]**
CAS Total Score	2.45±3.92	1.25±2.30	**0.006**
Self Confident Approach	22.11±3.56	23.17±3.68	**0.041**
Optimistic Approach	14.14±2.88	15.02±2.55	**0.023**
Helpless Approach	19.71±4.02	17.85±4.33	**0.002**
Submissive Approach	13.39±3.18	13.01±2.61	**0.348**
Seeking social support	11.77±1.46	11.12±1.73	**0.007**

[a]Independent samples test, * p<0.05 SD: Standart Deviation CAS: Coronavirus anxiety scale

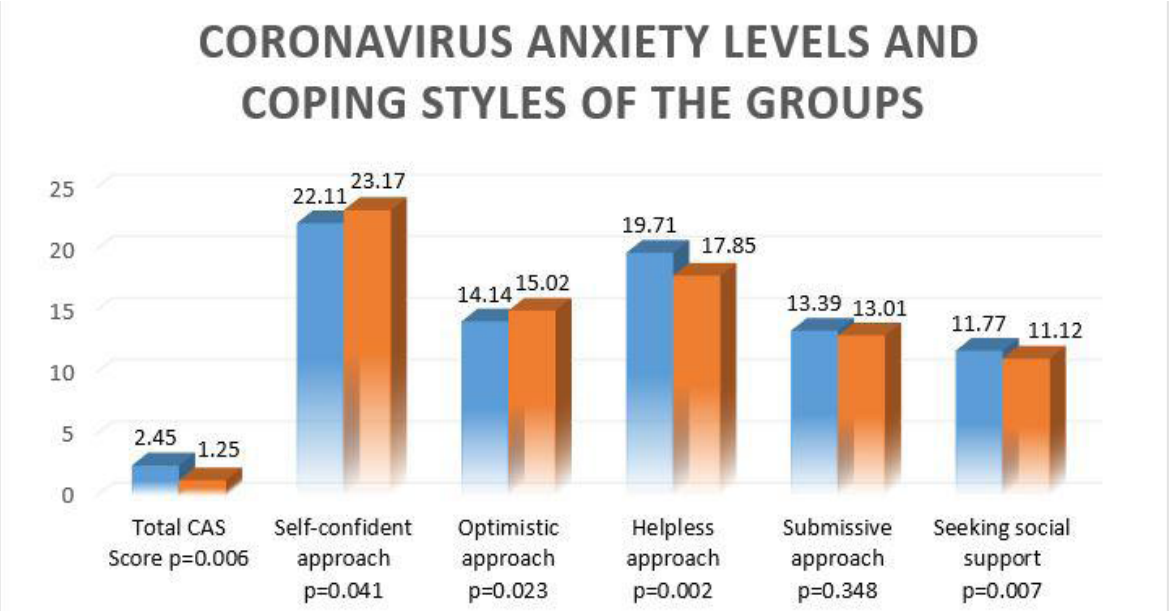

Figure 1. Coronavirus anxiety levels and coping styles of the groups according to their personality types

The relationships were examined between the sociodemographic characteristics and coronavirus anxiety and stress coping strategies, and it was determined that those who lived alone showed the helpless approach more (p=0.025), and those with a history of migration showed less submissive approach (p=0.002). The participants with high CAS points were found to have higher helpless approach points (p=0.033). Even if weak, some correlations were determined between coronavirus anxiety and coping styles. In the corelation analyses, a negative correlation was determined between coronavirus anxiety and the self-confident (p=0.002, r=-0.212) and optimistic approaches (p=0.002, r=-0.209), and a positive correlation was determined with the helpless approach (p=0.044, r=0.138). No relationship was found between coronavirus anxiety and sociodemographic data such as age, gender, educational level, working year, marital status, living alone or with family, and having any chronic disease.

Of the total study participants, 165 (77.5%) stated that they had burnout during the COVID-19 pandemic.

When coronavirus anxiety was examined according to gender, it was seen that female healthcare workers used the approach of seeking social support more than male healthcare workers, and no other significant difference was determined between the genders in terms of coronavirus anxiety or stress coping styles (Table 2).

Table 2. Coping styles and anxiety levels of male and female healthcare professionals

	Mean±SD		
	Female	**Male**	***p*[a]**
CAS Total Score	2.02±3.46	1.98±3.49	**0.936**
Self Confident Approach	22.57±3.77	22.31±3.26	**0.617**
Optimistic Approach	14.37±2.96	14.72±2.28	**0.363**
Helpless Approach	19.36±4.12	18.17±4.40	**0.078**
Submissive Approach	13.36±3.07	12.96±2.75	**0.368**
Seeking social support	11.76±1.53	10.91±1.60	**0.001**

[a]Independent samples test, * p<0.05 SD: Standart Deviation CAS: Coronavirus anxiety scale

Discussion

The first striking finding of this study was that the coronavirus anxiety points of the participants showing A-type personality characteristics were significantly higher than those of the participants showing B-type personality characteristics. Most findings in the literature have also shown higher anxiety levels sensitive to stress in individuals with an A-type personality [24, 25]. This suggests that because A-type individuals want to accomplish difficult tasks, their exposure to more stressful factors or overreaction to sources of environmental stress means that these are sources of more stress compared to other people.

The healthcare workers forming the sample of this study were selected at randomly, and the results showed a greater number of subjects showing A-type personality characteristics (n:135) than B-type (n:78). As the healthcare sector provides services which require meticulous management with no room for error, it can be expected that those who choose to work in this sector will show more A-type personality characteristics. However, it can also be said that this is a sign that healthcare workers with A-type characteristics who work meticulously are at risk of dysfunctional anxiety in times of crisis such as the COVID-19 pandemic.

No significant difference was found between the male and female participants in the current study with respect to the CAS total points. Some studies in the literature have reported that females are at greater risk in respect of coronavirus anxiety levels [7, 26]. In contrast to data from the general population, the fact that there was no difference between male and female healthcare workers in the current study could be due to the fact that professional skills are similar and a similar professional approach is shown without gender differentiation. Moreover, this could also be related to resilience. It is known that resilience to stress factors has a protective effect, which helps people to cope with difficulties in a positive way [27]. In a study by Liang et al. [28], the resilience of healthcare personnel working on the frontline, most of whom were female, was reported to be higher than that of the general population.

When the stress coping styles were examined in this study, it was seen that the healthcare workers showing A-type personality characteristics had significantly higher helpless approach mean points, and they sought social support more. Those with B-type personality characteristics were determined to have signficantly higher self-confident and optimistic approach mean points. Nuray and Fatih [29] reported positive correlations between A-type personality and ineffective coping strategies rather than effective coping strategies. In the same study, the stress symptoms experienced were found to increase as the A-type personality characteristics intensified. Similar to these findings in the literature, a positive correlation was determined between greater use of the helpless approach and coronavirus anxiety in the healthcare workers in the current study showing A-type characteristics, and a negative correlation between coronavirus anxiety and greater use of the self-confident and optimistic approaches in the healthcare workers showing B-type personality characteristics.

Depression and anxiety symptoms are known to be associated with family functions, social support, and coping style [30]. The helpless approach points were seen to be higher in the study participants with high CAS points, consistent with the literature. In addition, coronavirus anxiety was determined to be negatively correlated with the self-confident approach and the optimistic approach, and positively correlated with the helpless approach.

It has been similarly reported in the literature that in healthcare workers with positive coping strategies and an active coping style focussed on changing a stressful situation, there is typically a correlation with effective mood regulation, and correspondingly, negative coping strategies focussing on social isolation and avoidance of stressful situations are a passive coping style leading to negative evaluations [31]. In parallel with this, when the relationships between sociodemogaphic characteristics and stress coping styles were examined in the current study, those who lived alone were found to use the helpless approach more.

There are a great number of studies in the literature related to the sensitivity of migrants to mental health diseases [32, 33]. However, it has

been shown that positive coping strategies and social support (personal or community support) for individuals who have migrated have positive effects on their physical, psychological, and well-being [34]. The current study population was formed of subjects with no history of mental health disease, in other words in a state of psychological well-being, and consistent with data in the literature, those with a history of migration were found to use a submissive approach less.

The life cycle in which a stressful event occurs can also determine how it will be coped with. It can be considered that younger hospital personnel at the start of their careers will experience less anxiety because of a threat weighted towards the elderly population [35]. However, the results of this study showed no relationship between the level of coronavirus anxiety and the sociodemographic data of age, gender, educational level, and years of professional experience.

There were some limitations of this study, primarily that the relatively small sample prevents generalisation of the results. The stress coping styles questionnaire has forms of 66, 30, 28, and 20 items, and each form has separate subscales. A form of 30 items with 5 subscales was used in this study for the healthcare workers with an intense working tempo to be able to complete it in a short time, and these restricted comparisons with the literature as most other studies of the relationship between coronavirus anxiety and stress coping styles have used other forms. There is a need for further extensive studies to support the findings obtained.

In conclusion, the aim of this study was to determine the personality characteristics and the stress coping styles that are effective in combatting stress for healthcare workers in a global public health crisis, and the results demonstrated that those with A-type characteristics were at greater risk, and those using the self-confident approach and optimistic approach could cope better with stress. Ensuring and monitoring the mental health of healthcare personnel is very important for global health. Education in the areas of resilience and stress management is important for healthcare workers to be able to cope with future crisis situations, such as the COVID-19 pandemic [36]. The results of this study can be considered to be of guidance for precautions to be taken in the context of mental health protection, such as the education of healthcare personnel about stress management. There is a need for more of these types of studies to be able to be better prepared for future pandemics.

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Ethics committee approval: Permission was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committee for the study (approval date 23.06.2020, approval number 12).

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Turkish YouTube videos on erectile dysfunction as an informal information source: do they contain reliable content?

Resmi olmayan bir bilgi kaynağı olarak erektil disfonksiyon konulu Türkçe YouTube videoları: güvenilir içerik içeriyorlar mı?

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Abstract

Purpose: The purpose of this study was to evaluate the informative value of Turkish videos submitted to YouTube about erectile dysfunction (ED).

Materials and methods: The first 125 videos published on Youtube.com between January 11 and 18, 2023, accessed with the keyword "erectile dysfunction," published in Turkish, and displayed in search results in a standard order of relevance were studied. Videos that were less than 1 minute long, do not contain information, contains jokes, movie trailers, or product advertisements, were less than 1 month old since their publication, or were unrelated to ED were excluded from the study. The quality of the information content of the videos was assessed using DISCERN scoring. The obtained data were analyzed using SPSS Statistics 24 software.

Results: It was determined that out of the 100 videos that met the inclusion criteria, 74% were uploaded by healthcare professionals, 3% by the Pharmaceutical Industry, 5% by the Dietary Supplement Industry, 3% by psychologists, and 15% by non-healthcare professionals. When the videos were examined based on their content, it was determined that the topics of the published videos primarily focused on diagnosis and treatment. However, it was also found that there were videos that provided content on the etiopathology and symptoms of the disease. The total duration of the videos was 10 hours, 58 minutes, and 24 seconds (1 minute to 53.05 minutes). While the total number of views was 21.893.514 (15-1.700.000), the total number of likes was determined to be 130.340. The average views were 8.002.64 (1.998.76-11.953.26), and the average monthly likes were 47.30 (11.88-73.1). The average value for DISCERN was calculated to be 3.3 (1-5). There was a negative correlation between the DISCERN scores and the average monthly number of likes. It was found that there was a positive and significant correlation between the duration of videos and DISCERN scores. Videos uploaded by physicians had a high DISCERN score, while the content quality of the other videos was moderate to poor.

Conclusions: Overall, 50% of ED-related videos on YouTube have moderate to poor content quality. Videos uploaded by physicians had high DISCERN scores and high likes and view rates. A negative correlation existed between DISCERN ratings and average monthly likes and views.

Keywords: Erectile dysfunction, DISCERN, social media, Youtube.

Kaynak Y, Ugur S. Turkish YouTube videos on erectile dysfunction as an informal information source: do they contain reliable content? Pam Med J 2023;16:646-653.

Öz

Amaç: Bu çalışmanın amacı, YouTube'a gönderilen Türkçe videoların erektil disfonksiyon (ED) hakkında bilgilendirici değerini değerlendirmektir.

Gereç ve yöntem: Youtube.com'da 11-18 Ocak 2023 tarihleri arasında yayınlanan, "erektil disfonksiyon" anahtar kelimesi ile erişilen, Türkçe yayınlanan ve arama sonuçlarında standart bir alaka düzeyi sırasına göre gösterilen ilk 125 video incelenmiştir. 1 dakikadan kısa, bilgi içermeyen, fıkra, film fragmanı, ürün reklamı içeren, yayınlanmasının üzerinden 1 aydan az geçmiş veya ED ile ilgisi olmayan videolar çalışma dışı bırakıldı. Videoların bilgi içeriğinin kalitesi, DISCERN puanlaması kullanılarak değerlendirildi. Elde edilen veriler SPSS Statistics 24 programı kullanılarak analiz edilmiştir.

Bulgular: Dahil edilme kriterlerine uyan 100 videonun %74'ünün sağlık meslek mensupları, %3'ünün İlaç Endüstrisi, %5'inin Takviye Gıda Sektörü, %3'ünün psikologlar ve %15'inin sağlık meslekleri dışındaki meslek mensupları tarafından yüklendiği belirlendi. Videolar içeriklerine göre incelendiğinde yayınlanan videoların konularının öncelikli olarak teşhis ve tedavi odaklı olduğu belirlendi. Bununla birlikte hastalığın etiyopatolojisi ve semptomlarına yönelik içerikler sunan videoların da bulunduğu tespit edilmiştir. Videoların toplam süresi 10 saat 58 dakika ve 24 saniye (1 dakika ila 53,05 dakika) idi. Toplam izlenme sayısı 21.893,514 (15-1.700,000) olurken, toplam beğeni sayısı 130,340 olarak belirlendi. Ortalama izlenme sayısı 8.002,64 (1.998,76-11.953,26), aylık ortalama beğeni sayısı ise 47,30 (11,88-73,1) oldu. DISCERN için ortalama değer 3,3 (1-5) olarak hesaplanmıştır. DISCERN puanları ile ortalama aylık beğeni sayısı arasında negatif bir korelasyon vardı. Videoların süresi ile

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DISCERN puanları arasında pozitif ve anlamlı bir ilişki olduğu tespit edilmiştir. Doktorlar tarafından yüklenen videolar yüksek bir DISCERN puanına sahipken, diğer videoların içerik kalitesi orta ile zayıf arasındaydı.
Sonuç: Genel olarak, YouTube'daki ED ile ilgili videoların %50'si orta ila düşük içerik kalitesine sahiptir. Hekimler tarafından yüklenen videolar, yüksek DISCERN puanlarına, yüksek beğeni ve izlenme oranlarına sahipti. DISCERN derecelendirmeleri ile ortalama aylık beğeniler ve görüntülemeler arasında negatif bir korelasyon vardı.

Anahtar kelimeler: Erektil disfonksiyon, DISCERN, sosyal medya, Youtube.

Kaynak Y, Uğur S. Resmi olmayan bir bilgi kaynağı olarak erektil disfonksiyon konulu Türkçe YouTube videoları: güvenilir içerik içeriyorlar mı? Pam Tıp Derg 2023;16:646-653.

Introduction

Erectile dysfunction (ED) is the persistent inability to achieve or maintain a penile erection sufficient for satisfactory sexual performance [1]. The condition is quite common in men in their 40s with vascular risk factors [2, 3] and significantly affects their quality of life [4]. Vascular, neural, hormonal, anatomical, and psychological disorders and also some drugs are known to play a role in the etiopathogenesis of the disease. In many cases, several of these disorders play a combined role in the development of the disease [5]. The incidence of the condition is gradually increasing in all age groups [6]. ED not only affects the patient but also has a negative impact on the social and psychological life of their partner, resulting in a diminished quality of life for both individuals. Therefore, it is also recognized as a familial and social disorder [7-10].

Social media and the Internet play an increasingly important role in the healthcare system, and many patients rely on these resources to gather information [11]. According to the January 2023 report by the We Are Social digital platform, the number of active social media users in Türkiye is 62.55 million (73.1%), and this number is steadily increasing [12]. According to the report, users in Türkiye primarily use the internet for information gathering and reading news, with 39.5% of them using the Internet for researching health issues and healthcare products. YouTube, a video content platform, ranks third among the social media platforms where users spend the most time, with 18.5 hours. On this platform, which offers features such as likes, dislikes, and comments on videos, users can also access the number of times videos are viewed.

Since the Youtube platform does not provide any control mechanism for the content quality of the uploaded videos, it would be a mistake to believe that the shared videos are correct and reliable. Some studies that have examined the content of videos posted on the YouTube platform about various diseases and their treatment have found that the quality of information in these videos is low. They are not considered a reliable source of information for patients [13], and the most informative videos tend to have lower views [14]. In a study evaluating the quality of the information in videos related to ED uploaded in English on YouTube, it was reported that 80.4% of the videos were of low quality [15].

In reviewing the literature, it was found that no studies evaluated the content and quality of ED videos uploaded in Turkish. In this study, the content reliability of the videos with Turkish content on ED on the video platform Youtube was investigated.

Material and methods

In this study, designed as qualitative research, the content analysis method was used. During the analysis phase, in addition to video viewing, a thematic content analysis was conducted. The first 125 videos published on youtube.com between January 11 and 18, 2023, accessed with the keyword “erectile dysfunction,” published in Turkish, and displayed in search results in a standard order by relevance, were examined. Youtube can access the location of the person searching through google, with GPS, and sorts the results according to the location over the IP address. Measures taken to prevent this; making a call without logging in and connecting to the internet over a new IP. However, the device’s location services are also disabled. Based on the user’s ability to customize the search results on YouTube based on the history of the videos it interacts with, location, etc.; first, the registered data of all users in the browser

was cleared. As another precaution, the search was made without logging in to the any user. The data collected and analyzed for this study were obtained from the videos that individuals voluntarily took and uploaded to the social media platform youtube. Therefore, this study is not within the scope of any of the following studies that require ethics committee approval.

The videos were evaluated and scored by 2 urologists who are experts on ED and 1 clinical secretary who does not know this subject. We used a validated evaluation method called DISCERN developed by Charnock et al. [16] to determine the quality of reliability.

The evaluation process was conducted by both experts and non-experts to eliminate evaluator bias. The characteristics of the video uploaders, duration of time spent on the platform, total views, total number of likes or dislikes, content topic, and quality of content reliability were identified and recorded.

The DISCERN scoring system was developed to enable individuals seeking health information to assess the content quality level of the information in a publication they turn to for that purpose. The reliability of the information in the publication is evaluated based on the 16 questions in the scoring system, including the up-to-dateness of the evidence sources, verifiability, potential bias, and indication of alternative options if applicable. Each question is scored between 1-5 points. In the 16th question, a general quality score is given based on the total score obtained from evaluating the 15 questions. This overall quality score also ranges from 1 to 5 points. In this study, the rating of the overall content quality of the videos was determined based on the 16th question. Before scoring, both urologists and a clinic secretary familiarized themselves with the user manual of this scoring system, learning how to use it. They then watched the videos together and proceeded to score them, reaching a unanimous decision.

Videos that lasted less than one minute, do not contain information, contain jokes or joking, movie trailers or product advertisements, aired for less than one month, or were unrelated to ED were excluded from the study. Under these criteria, 25 videos were excluded: 2 containing magazine content, 3 lasting less than one minute, 3 uploaded less than one month ago, 6 containing sexual talk, 6 containing jokes, 2 containing movie trailers, and 3 unrelated videos. The remaining 100 informational videos were included in the study. The videos were categorized into four content categories (diagnosis, treatment, etiophysiopathology, and symptoms) and five uploader categories (physician, psychologist, pharmaceutical industry, dietary supplement industry, and non-healthcare uploaders).

Videos were analyzed in terms of uploaders, topics, duration of posting, monthly views, monthly likes or dislikes, and DISCERN scores.

SPSS Statistics 24 software was used to analyze the data. Standard deviation was calculated for the number of views and likes and DISCERN ratings of the videos included in the study. A correlation analysis was conducted using SPSS to determine the relationship between the durations of the videos and the DISCERN scores.

Results

The total duration of the 100 videos included in the study was reported as 10 hours, 58 minutes, and 24 seconds. It was determined that 74% of these videos were uploaded by healthcare professionals, 3% by the pharmaceutical industry, 5% by the dietary supplement industry, 3% by psychologists, and 15% by non-healthcare professionals. When the videos were examined based on their content, it was determined that 26% of the published videos were about Diagnosis, 14% were about Diagnosis and Treatment, 4% were about Diagnosis and Etiopathology, 1% were about Diagnosis and Symptoms, 38% were about Treatment, 1% were about Treatment and Etiopathology, 6% were about Etiopathology, 1% were about Etiopathology and Symptoms, 3% were about Diagnosis, Treatment, and Etiopathology, 3% were about Diagnosis, Treatment, Etiopathology, and Symptoms, and finally, 3% were about Diagnosis, Treatment, and Symptoms.

It can be seen that users did not evaluate any video negatively (dislike). The characteristics and user engagement of 100 scientific videos included in the evaluation are summarized in Table 1.

When the reliability quality of video content was evaluated according to the DISCERN scoring system, it was found that there were more videos with a DISCERN score of 5 (n=31) compared to other videos. These videos also had a higher percentage of total views (36.1%) and higher view counts (7.902.641). However, looking at the average number of views, it was found that DISCERN 1 videos were viewed more frequently than DISCERN 5 videos. Table 2 summarizes the distribution and viewing statistics of the videos according to this scoring system.

In the analysis of video likes based on the DISCERN score, it was found that DISCERN 5 videos had a higher like rate (37.27%) and received a higher total number of likes (48.578) compared to other videos. However, comparing the average likes, it can be seen that videos with a DISCERN rating of 1 received higher likes than other videos (2.307.43). Table 3 documents a summary of the DISCERN ratings and like statistics of the videos.

When the monthly views and likes of the videos are compared with the DISCERN ratings, Table 4 provides information about the duration of the videos depending on their DISCERN ratings, as well as the viewing and like status of the videos.

According to the table, videos with a duration of being online, videos with a DISCERN score of 2 have the highest monthly likes, while videos with a DISCERN score of 1 have the highest monthly views. Correlation analyses were performed between DISCERN and the video characteristics of the videos, the results are shown in Table 5.

Table 1. Video characteristics and user indicators

	Median (range)
Total time	658 min 24 sec (1 min-53 min 05 sec)
Total views	21.893.514 (15-1.700.000)
Monthly views	40.013.23 (1.998.76-11.953.26)
Total likes	130.340 (0-15.000)
Monthly likes	47.306 (11.88-73.1)

Table 2. Distribution of videos by DISCERN ratings and viewing statistics

DISCERN score	n (%)	Total views	Average views	Views percentage
DISCERN 1	16	6036400	377275	27.57
DISCERN 2	19	4107547	216186	18.76
DISCERN 3	15	725550	48370	3.31
DISCERN 4	19	3121376	164282	14.26
DISCERN 5	31	7902641	254923	36.10

Table 3. Likes of the videos according to DISCERN scores

DISCERN Score	n (%)	Total likes	Average likes	Likes percentage
DISCERN 1	16	36919	2307.43	28.33
DISCERN 2	19	21842	1149.57	16.76
DISCERN 3	15	4313	287.53	3.31
DISCERN 4	19	18688	983.57	14.34
DISCERN 5	31	48578	1567.03	37.27

Table 4. Duration of videos depending on their DISCERN / view ratings and likes of the videos

DISCERN Score	On Air Time	Total LIKES	Total VIEWS	Monthly Likes by Broadcast Time	Monthly Views by Airing Time
DISCERN 1	505	36919	6036400	163.50	11953.27
DISCERN 2	458	21842	4107547	188.06	8968.44
DISCERN 3	363	4313	725550	168.22	1998.76
DISCERN 4	420	18688	3121376	167.03	7431.85
DISCERN 5	818	48578	7902641	162.68	9660.93
Grand total	**2564**	**130340**	**21893514**		

Table 5. Correlation results

Correlation		Average likes per view per month	Monthly likes	Monthly views	DISCERN	On-air time
Average likes per view per month	Pearson	1	-.188	-.052	-.344	-.354
	Sig. (2-tailed)		.763	.934	.570	.559
	N	5	5	5	5	5
Monthly likes	Pearson	-.188	1	.991**	-.213	.556
	Sig. (2-tailed)	.763				.331
	N	5	5	5	5	5
Monthly views	Pearson	-.052	.991**	1	-.259	.517
	Sig. (2-tailed)	.934	.001		.673	.373
	N	5	5	5	5	5
DISCERN	Pearson	-.344	-.213	-.259	1	.521
	Sig. (2-tailed)	.570	.731	.673		.368
	N	5	5	5	5	5
On-air time	Pearson	-.354	.556	.517	.521	1
	Sig. (2-tailed)	.559	.331	.373	.368	
	N	5	5	5	5	5

** Correlation is significant at the 0.01 level (2-tailed)

The analysis conducted for correlation revealed a significant positive relationship between videos with a high DISCERN score and the proffesional uploaders. Accordingly, the videos of physicians with expertise in the field have a high DISCERN rating and many views and likes. The other correlation calculation found an inverse relationship between the average monthly number of likes per month view and monthly likes, monthly views, DISCERN rating, and posting duration. The variables that showed a significant positive relationship were monthly likes with monthly views and posting duration, monthly views with posting duration, and DISCERN rating with posting duration.

The distribution of DISCERN scores and video duration of the videos obtained after the analysis to determine the relationship between video duration and DISCERN scores is shown in Figure 1.

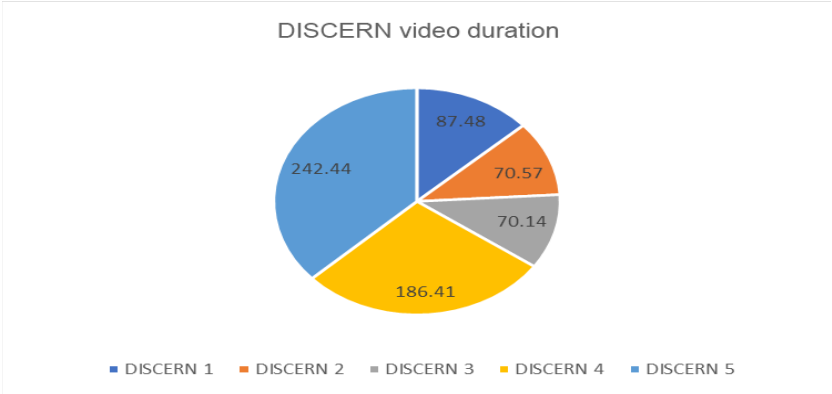

Figure 1. DISCERN-distribution of video duration

Upon examining the correlation of the data, a positive correlation was observed between the DISCERN scores of the videos and their durations. Accordingly, videos with a high DISCERN score were found to have a longer duration than other videos.

Discussion

Men with ED use platforms such as YouTube as a source of information because they cannot easily express their problems [17]. On the other hand, the analysis of content reliability in health-related videos on this platform has revealed a considerable proportion of low-quality videos [13, 14], indicating a potential danger to public health. In our literature review, we did not come across a study specifically reporting on the content quality of Turkish YouTube videos related to ED. In this study, we aimed to investigate the quality of content reliability of videos in Turkish uploaded to the YouTube platform regarding ED.

In the study, it was observed that the number of videos uploaded by physicians was higher, and their DISCERN scores were also higher (provide specific figures). We found that these videos were mostly designed to provide information to patients about the etiopathology and treatment of ED. We found that videos offering dietary supplement recommendations, mostly uploaded by the industry, were relatively few in number and had low DISCERN scores. In a study evaluating 71 English videos on ED on YouTube, it was found that 37% of the videos were uploaded by non-medical sources. In this study, the average DISCERN scores of the videos were found to be low (42.8/80), while videos uploaded by urologists for educational purposes had higher DISCERN scores [18]. In a recent study examining the scientific level of videos related to ED uploaded on the YouTube platform in English, researchers reported that 80% of the videos with a high level of scientific content were published on TV programs and medical websites. In this study, it was found that the majority of videos recommending natural herbal remedies and foods, personal experiences, and certain dances and prayers to enhance erection in the treatment of the disease were lacking scientific evidence. In addition, although not to the same extent as therapeutic videos, non-scientific information was found in about 40% of videos with etiopathophysiology content [19]. Therefore, it is considered that the uploading of videos in Turkish by physicians, especially videos with therapeutic and etiophysiopathological content, with a high score on DISCERN, contributes greatly to providing users with information corresponding to the current scientific reality. It is important that experts in the field and authoritative institutions should upload more high-quality content on popular platforms.

It was observed that users showed greater interest in videos related to the treatment and etiopathophysiology of the disease. It was determined that videos focusing on treatment received more attention in terms of average views and likes, based on the content of the videos. It was found that physicians mostly uploaded these videos and had high-quality content. It was also found that videos recommending dietary supplements had weak content quality. These findings are consistent with studies that evaluated YouTube videos on ED [18, 19].

When examining the relationship between the monthly average views and likes of videos with DISCERN scores, it was found that videos with poor content quality had higher average monthly likes and views compared to videos with high content quality. Although the total monthly views and number of "likes" are higher for videos with a high score from DISCERN because they were uploaded by physicians, the high interest of followers in videos with low content quality indicates that patients with ED are exposed to incorrect and incomplete information. Similar findings have been identified in previous studies conducted in this field, and warnings and recommendations have been expressed [18, 19].

When examining the relationship between the duration of videos and DISCERN scores, it was observed that videos with high DISCERN scores had longer durations compared to other videos. This situation can be interpreted as a reflection of the fact that videos with accurate and meaningful content, which are essential for ensuring their scientific and overall quality, take longer to be presented.

The videos were evaluated by 2 urologists who are experts on ED and 1 clinical secretary who does not know this subject, using a validated evaluation method called DISCERN. The evaluation process was conducted by both experts and non-experts to eliminate evaluator bias. We believe that these approaches make the study stronger. However, it should be noted that the evaluations are still subjective and pose a limitation. Moreover, the content reliability quality of the videos was determined only by the DISCERN scoring system. It would be better if we used JAMA and Global Quality Scoring as well. The absence of videos with dislikes in the cross-sectional sample we took is another limitation that may affect the results. In this study, only the keyword erectile dysfunction was entered to search the video in the Youtube search engine. Although we thought that most users would search with this word, a search with different keywords may have made the results of the study different.

In conclusion, overall, 50% of ED-related videos in Turkish on YouTube have medium to poor content quality. Videos uploaded by healthcare professionals, particularly those focusing on treatment and etiopathology, have high DISCERN scores and high rates of likes and views. There is a negative correlation between DISCERN scores and monthly average likes and views, and a positive correlation between DISCERN scores and video duration. The increased uploading of high-quality content videos by both individuals and institutional healthcare professionals on popular platforms like YouTube is crucial for ensuring that patients with Erectile Dysfunction (ED) have access to accurate and high-quality information.

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

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Ethics committee approval: The data collected and analyzed for this study were obtained from the videos that individuals voluntarily took and uploaded to the social media platform Youtube. Therefore, this study is not within the scope of any of the following studies that require ethics committee approval.

- All kinds of research carried out with qualitative or quantitative approaches that require data collection from the participants by using survey, interview, focus group work, observation, experiment, interview techniques,
- Use of humans and animals (including material/data) for experimental or other scientific purposes,
- Clinical studies on humans,
- Animal studies,
- Retrospective studies in accordance with the personal data protection law.

Authors' contributions to the article

Both authors took part in the Idea and design, Data collection and processing, Analysis and interpretation of data, Writing important parts of this article, by division of labor in the context of their expertise.

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F-Wave recorded from proximal and distal muscles innerved by the same nerve in the upper and lower extremities: could it be a new method?

Üst ve alt ekstremitede aynı sinir tarafından inerve olan proksimal ve distal kaslardan kaydedilen F dalgası: yeni bir yöntem olabilir mi?

Zeynep Ünlütürk

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Abstract

Purpose: The F- wave is a valuable measurement that provides information about both the proximal and distal parts of the nerve. Classical F-wave recording methods are performed from the distal muscles of the limb and so are affected from distal pathologies. Nerve conduction velocity of a nerve is affected by the diameter of the nerve. The diameter of a nerve gets thinner as it gives branches and travels distally. So it is expected that the nerve conduction velocity of a nerve is faster in proximal segment of the nerve than the distal part even they are the parts of the same nerve. The aim of this study is to compare the nerve conduction parameters of F waves recorded in proximal and distal muscles innervated by the same nerve which will provide additional information and may be valuable in detecting proximal pathologies accompanying background pathologies affecting the distal nerve.

Materials and methods: Twenty–six healthy volunteers who have normal routine nerve conduction studies are included in this study. The latencies of ulnar and peroneal F-waves of all participants were recorded from the proximal and distal muscles innervated by the same nerve.

Results: F-wave latencies recorded from proximal muscles were significantly later than the ones recorded from distal muscles.

Conclusions: Although the distances travelled by stimulation are shorter in F latencies recorded from proximal muscles, and the segment / branch of the nerve is expected to be thicker and faster, the latencies recorded from proximal muscles were longer than the ones recorded from distal muscles. This may be due to the distance of the recording electrodes effected by subcutaneous tissues in the proximal large mass muscles. One reason for this difference may be that the proximal relatively large mass muscles have higher desynchronization and temporal dispersions.

Keywords: F-wave, proximal F-response, distal peripheral neuropathy.

Unluturk Z. F-Wave recorded from proximal and distal muscles innerved by the same nerve in the upper and lower extremities: could it be a new method? Pam Med J 2023;16:656-660.

Öz

Amaç: F dalgası sinirin hem proksimal hem de distal kısımları hakkında bilgi sağlayan değerli bir ölçümdür. Klasik F dalgası kayıt yöntemleri ekstremitenin distal kaslarından yapıldığı için distal patolojilerden etkilenir. Sinir iletim hızı, sinirin çapından etkilenir. Sinirin çapı dallanıp distale doğru ilerledikçe incelir. Yani bir sinirin sinir iletim hızının, aynı sinirin parçaları olsa bile sinirin proksimal segmentinde distal kısmına göre daha hızlı olması beklenir. Bu çalışmanın amacı aynı sinirin innerve ettiği proksimal ve distal kaslarda kaydedilen F dalgalarının sinir iletim parametrelerini karşılaştırmaktır. Bu sinir distalini etkileyen arka plan patolojilerine eşlik eden proksimal patolojilerin saptanmasında değerli olabilir ve ek bilgi sağlayacaktır.

Gereç ve yöntem: Bu çalışmaya rutin sinir iletim çalışmaları normal olan 26 sağlıklı gönüllü dahil edildi. Tüm katılımcıların ulnar ve peroneal F dalgalarının latansları, aynı sinir tarafından innerve edilen proksimal ve distal kaslardan kaydedildi.

Bulgular: Proksimal kaslardan kaydedilen F dalgası latansları, distal kaslardan kaydedilenlerden önemli ölçüde daha uzundu.

Sonuç: Proksimal kaslardan kaydedilen F latanslarında uyarının kat ettiği mesafeler daha kısa olmasına ve sinirin segment/dalının daha kalın ve hızlı olması beklenmesine rağmen proksimal kaslardan kaydedilen latanslar, distal kaslardan kaydedilenlerden daha uzundu. Bunun nedeni, proksimal büyük kütleli kaslarda cilt altı dokuların fazlalığı ve kasın kayıt elektrotlarına uzaklığı olabilir. Bu farklılığın bir nedeni de, proksimal nispeten büyük kütleli kasların daha fazla senkronizasyon ve zamansal dağılıma sahip olması olabilir.

Anahtar kelimeler: F-dalgası, proksimal F-yanıtı, distal peripheral nöropati.

Ünlütürk Z. Üst ve alt ekstremitede aynı sinir tarafından inerve olan proksimal ve distal kaslardan kaydedilen F dalgası: yeni bir yöntem olabilir mi? Pam Tıp Derg 2023;16:656-660.

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Introduction

Peripheral nerves become thinner as they go from proximal to distal, giving their fibers to peripheral muscles [1-3]. The nerve fibers to different muscles travel together in the peripheral nerve but are separate bundles [1-3]. Generally, each peripheral nerve provides a sensation of a specific skin area, muscular innervation of a few muscles and sensory innervation of the deep structures [3, 4]. Thus, motor fibers from the same nerve root provide motor innervation of muscles with different peripheral nerves. Also, sensory fibers from the same nerve root provide sensory innervation of the skin in other peripheral nerve distribution areas [4]. The reason for the higher nerve conduction velocity in the proximal segments compared to the distal segments may be the thinning of the nerve fiber diameter from proximal to distal, the shortening of the internodal segments in the nerve fibers in the distal segments, and the lower extremity temperature in the distal compared to the proximal segments [5]. If a peripheral nerve is stimulated at the same site and electrophysiological recordings are made from two different muscles located proximally and distally, it is possible to comment on the conduction parameters of nerve fibers with the same course and in the same peripheral nerve but of different diameters [5, 6].

The F-response shows the conduction of antidromic motor impulses involving both distal and proximal segments of motor nerves and motor roots [1]. While the distal part of the motor unit can be examined with known classical motor conduction methods, the proximal part of the motor unit can only be examined with the F-response [1, 7]. It was considered advantageous to examine the F-response in proximal nerve and root involvement [7].

In the light of all this information, the aim of this study is to evaluate the F-response in proximally located muscles with relatively larger mass and distally located muscles with relatively smaller mass stimulated by the same nerve. By comparing the upper and lower extremity, distal and proximal values, it is aimed to discuss the use of these values in patients with concomitant peripheral motor lesions.

Material and methods

This study included 26 healthy volunteers with regular routine nerve conduction studies and between 18 and 80. Individuals were evaluated in the EMG laboratory of Prof. Dr. A. İlhan Özdemir Training and Research Hospital. In addition to routine nerve conduction studies, F-wave is studied from the ulnar nerve in the right upper extremity and the peroneal nerve in the right lower extremity. The ulnar and peroneal nerves were stimulated supramaximally. At least 10 F response recordings were recorded from each participant, those with a persistence above 50% and chronodispersion below 4 milliseconds (ms) for the upper limb and 6 ms for the lower limb were included in the study. In the upper extremity, the ulnar nerve was stimulated antidromically medial to the wrist. F-wave was recorded from the abductor digiti minimi (ADM) and flexor carpi ulnaris (FCU) muscles. In the lower extremity, the peroneal nerve was stimulated antidromically from the anterior ankle and the F-wave was recorded from the extensor digitorum brevis (EDB) and tibialis anterior (TA) muscles. Room temperature was kept between 25-28 °C in the study. The latencies of ulnar and peroneal F-wave of all participants were recorded from the indicated proximal and distal muscles and compared with ulnar and peroneal nerve conduction velocity and amplitude. The minimum F-wave latency is accepted to be below 32 ms for the ulnar nerve in the upper extremities and below 56 ms for the peroneal nerve in the lower extremities.

Individuals aged 18-80 years, with regular routine nerve conduction studies, without a chronic disease, and who agreed to participate were included. Patients under the age of 18 and over 80, with abnormal nerve conduction studies, with a chronic illness, who refused to participate or wanted to quit at any time were excluded from the study.

Informed consent was obtained from all subjects. The study was approved by Ordu University Clinical Research Ethics Committee. The data were analyzed with SPSS package program and p value less than 0.05 was considered statistically significant.

Results

The study included 26 subjects, including 15 women and 11 men. The mean age was 49.4 (±14.4) years. The mean age of women was 49.1 years and 49.9 years for men. In all participants, the mean ulnar F-response latency (FUD) recorded distally was 18.3 (±1.67) ms and the mean ulnar F-response latency (FUP) recorded proximally was 19.1 (±1.94) ms. These values were FUD 17.8 ms and FUP 18.7 ms in women and FUD 19.1 ms and FUP 19.8 ms in men. In all participants, the mean peroneal F-response (FPD) recorded distally was 31.9 (±3.45) and the mean peroneal F-response (FPP) recorded proximally was 32.5 (±2.88). These values were FPD 31.9 ms and FPP 32.1 ms in women and FPD 32 ms and FPR 33 ms in men. The velocities and amplitudes of the ulnar and peroneal motor nerves were recorded only from the distal muscles. The mean ulnar motor nerve velocity (UMV) was 54.9 (±2.7) and the mean ulnar motor nerve CMAP amplitude (UMA) was 8.3 (±1.2). The mean peroneal motor nerve conduction velocity (PMV) was 47.9 (±5.28) and the mean peroneal motor nerve CMAP amplitude (PMA) was 4.2 (±1.89).

There was no significant difference between the age and gender of the participants. No significant difference was found when the age and gender of the participants were compared with FUD, FUP, FPD, FPP values (p>0.05). Participants' FUD and FUP were compared, and the difference was statistically significant (p=0.03). Participants' FPD and FPP values were compared, and the difference was statistically significant (p=0.00). When other F response values were compared with each other and with UMA, UMH, PMA, PMH values, no statistically significant difference was found (Table 1).

Table 1. Electrophysiological findings of the individuals

	Female (n=15)	Male (n=11)	All (n=26)
Age	49.1	49.9	49.4
FUD (ms)	17.8	19.1	18.3
FUP (ms)	18.7	19.8	19.1
FPD (ms)	31.9	32.0	31.9
FPP (ms)	32.1	33.0	32.5
UMV (m/s)	55.7	53.9	54.9
UMA (mA)	8.2	8.4	8.3
PMV (m/s)	49.5	45.8	47.9
PMA (mA)	3.7	4.8	4.2

CMAP:compound muscle action potential, ms:milliseconds, mV:millivolt, mA:milliampere, m/s:meter/seconds, ADM:abductor digiti minimi, FCU:flexor carpi ulnaris, EDB:extensor digitorum brevis TA:tibialis anterior, FUD:distal stimulated ulnar F-response latency, FUP:proximal stimulated ulnar F-response latency, FPD:distal stimulated peroneal F-response latency, FPP:proximal stimulated peroneal F-response latency, UMV:ulnar motor nerve velocity, UMA:ulnar motor nerve CMAP amplitude, PMV:peroneal motor nerve conduction velocity, PMA:peroneal motor nerve BKAP amplitude

Discussion

The F-response is recorded by supramaximal antidromic stimulation of a motor nerve [1]. It is assumed that electrical stimulation of peripheral motor fibers results in antidromic activation of the motor neuron [1, 7, 8]. The most important benefit of the F-response is probably from some of its physiological features. The F-response shows antidromic motor impulses involving both distal and proximal segments of motor nerves and motor roots [8, 9]. While the distal parts of the motor unit can be examined with routine nerve conduction studies, the proximal part can only be examined with the F-wave. Examining F-wave in proximal nerve and root involvement was considered advantageous [10, 11]. In this study, participants minimal

F-latency was compared by recording from two different muscles located proximally and distally innervated by the same nerve. Four different F-wave minimal latencies (FUD, FUP, FPD, FPP) were recorded from each participant, and these four different F-wave latencies were found to be within normal limits.

When the minimum latencies of the F- wave recorded from the distal and proximal muscles in the lower and upper extremities were compared, it was found that the minimum latencies of the F-wave recorded from the proximal muscles (FUP and FPP) were longer than the minimum F-wave latencies recorded from the distal muscles (FUD and FPD). In previous studies comparing nerve conduction velocities, conduction velocity was found to be higher in proximal muscles with greater mass then the distal small muscles even they are innervated by the same nerve [6, 12, 13]. Considering the physiology of the F-wave, it is conceivable that the F-wave latency recorded from the proximal muscle should be shorter. In this study, the result was the opposite. This may be due to the distance of the recording electrodes from the muscle due to the excess of subcutaneous tissues in the proximal large mass muscles. One reason for this difference may be that the proximal relatively large mass muscles have higher desynchronization and temporal dispersions, which contain muscle fibers of different nerve conduction diameters [12, 14, 15].

Previous F-wave studies found that F-wave minimum latency increased with age by 0.03 ms/year in the upper extremity and 0.1 ms/year in the lower extremity. At the same time gender did not affect F-wave minimum latency [16]. In this study, a modest increase in the minimum F-wave latency is recorded with increase of the age.

It was observed that the mean F-wave minimum latencies of female participants were shorter than those of male participants. However, these differences were not statistically significant. The findings are consistent with the literature [16, 17].

The data obtained in this study are valuable because of the lack of studies in the literature examining F-wave recorded from proximal muscles and because of the exclusion of concomitant pathologies affecting the distal nerve. F-wave measurement by recording from proximal muscles can be used in clinical practice. However, larger studies with proximal stimulation and recording from proximal muscles are needed.

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Research Article

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Is there a relationship between TP-e/QT ratio and cardiovascular events due to spinal anesthesia in pregnant women?

Gebelerde TP-e/QT oranı ile spinal anesteziye bağlı gelişen kardiyovasküler olaylar arasında ilişki var mıdır?

İlker Coşkun

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Abstract

Purpose: Prolonged TPe interval has been reported to reflect the abnormal distribution of ventricular repolarization which can be used as a marker of ventricular arrhythmias. Since prolonged TPe/QT ratio is associated with cardiac pathologies, it is thought that it may also be associated with cardiovascular adverse events that occur during and after spinal anesthesia. The aim of this study is to investigate whether there is a relationship between prolonged TPe/QT ratio, which is routine preoperative non-invasive patient data that can be evaluated easily, and perioperative adverse cardiovascular events during cesarean section in pregnant women undergoing spinal anesthesia.

Materials and methods: Voluntary consent was obtained for our study in which 144 pregnant women who were planned for elective cesarean section were included. QT interval was measured based on the initial point where the Q wave or the R wave in the absence of the Q wave started to the last point where the T wave ended. TPe interval measurement was based on the peak point of the T wave and the end point of the T wave convexity. Lead V5 was primarily used for TPe measurement. TPe/QT ratios were calculated in Microsoft office excel program. Patients' demographic characteristics, heart rate, systolic, diastolic and mean arterial pressures were recorded every five minutes intraoperatively.

Results: A weak positive correlation was found between the height variable and the Tpe/QT ratio (p=0.022, r=0.191). As the height increased, the TPe/QT ratio increased. Although it did not reach the level of statistical significance, we found that the TPe/QT ratio was longer in cases with intraoperative bradycardia and hypotension than in cases without complications. The TPe/QT ratio was above 0.21 in patients who developed bradycardia and hypotension. Examination of the correlation between the amount of ephedrine use and TPe/QT ratio revealed a weak positive correlation (p=0.012, r=0.208).

Conclusion: TPe/QT ratio is a novel cardiac marker with high predictive power, is non-invasive, quite inexpensive, and very practical to measure in the early detection of cardiac events, especially arrhythmia. This novel predictive marker can be used in anesthesia practice, preoperative examination and patient follow-up in the intraoperative operating room to predict fatal cardiac arrhythmias or intraoperative hypo/hypertension.

Keywords: Spinal anesthesia, pregnancy, TPe/QT ratio, cardiovascular event.

Coskun I. Is there a relationship between TP-e/QT ratio and cardiovascular events due to spinal anesthesia in pregnant women? Pam Med J 2023;16:662-671.

Öz

Amaç: Tp-e süresinin uzaması, ventriküler repolarizasyonun anormal dağılımını yansıttığı ve ventriküler aritmilerin belirteci olarak kullanılabileceği bildirilmiştir. Uzamış TP-e/QT oranının kardiyak patolojiler ile ilişkisinin olması nedeniyle spinal anestezi sırasında ve sonrasında meydana gelen kardiyovasküler istenmeyen olaylar ile de ilişkisinin olabileceği akla gelmektedir. Bu çalışmadaki amacımız; noninvazif ve kolay değerlendirilebilen rutin bir preoparatif bir hasta verisi olan uzamış TP-e/QT oranı ile spinal anestezi uygulanan gebelerde sezaryen sırasında perioperatif istenmeyen kardiyovasküler olaylar arasında bir ilişki olup olmadığını araştırmaktır.

Gereç ve yöntem: Çalışmamıza gönüllü onamı alınmış, 144 elektif sezaryen operasyonu planlanan gebe dahil edilmiştir. QT intervalinin ölçümü, Q dalgasının veya Q dalgası yokluğunda R dalgasının başladığı ilk nokta ile T dalgasının bittiği son nokta baz alınarak yapılmıştır. Tp-e süresi ölçümü için, T dalgasının en zirve noktası ile T dalga konveksitesinin bittiği son nokta baz alınmıştır. Tp-e ölçümü için öncelikle V5 derivasyonu kullanılmıştır. Tp-e/QT oranları Microsoft office excel programında hesaplanmıştır. Hastaların demografik özellikleri, intraoperatif dönemde her beş dakikada bir olmak üzere nabız, sistolik, diastolik ve ortalama arter basınç değerleri kaydedilmiştir.

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Bulgular: Boy değişkeni ile Tpe/QT oranı arasında pozitif yönde zayıf düzey korelasyon tespit ettik (*p*=0,022, r=0,191). Boy arttıkça Tp-e/QT oranı artmaktaydı. İstatistiksel anlamlılık düzeyine ulaşmasa da intraoperatif bradikardi, hipotansiyon gelişen olgulardaki TPe/QT oranının, komplikasyon gelişmeyen olgulara göre daha uzun olduğunu tespit ettik. Bradikardi ve hipotansiyon gelişen olgularda TP-e/QT oranı 0,21'in üzerinde idi. Efedrin kullanım miktarı TPe/QT oranı arasındaki korelasyon incelendiğinde yine pozitif yönde zayıf düzey korelasyon tespit ettik (*p*=0,012, r=0,208).
Sonuç: Tp-e/QT oranı en başta aritmi olmak üzere, kardiyak olayların erken tespitinde prediktivite gücü yüksek, non-invazif, oldukça ucuz, ölçüm yapılması oldukça pratik, yeni bir kardiyak markırdır. Bu yeni prediktif markır; anestezi pratiğinde, preoperatif muayenede ve intraoperatif ameliyathanede hasta takibinde, fatal kardiyak aritmileri ya da intraoperatif hipo/hipertansiyonu öngörmede kullanılabilir.

Anahtar kelimeler: Spinal anestezi, gebelik, TPe/QT oranı, kardiyovasküler olay.

Coşkun İ. Gebelerde TP-e/QT oranı ile spinal anesteziye bağlı gelişen kardiyovasküler olaylar arasında ilişki var mıdır? Pam Tıp Derg 2023;16:662-671.

Introduction

Regional and general anesthesia techniques are used in cesarean section operations. Neuraxial blocks are preferred the most to avoid general anesthesia complications in pregnancy. Despite the rapid increase in the number of cesarean section operations, the low rate of anesthesia-related complications is due to the use of spinal and epidural anesthesia [1]. Spinal anesthesia is a form of anesthesia that is frequently used in all infraumbilical surgeries and has been shown to be effective due to some advantages such as preserving cognitive functions, reducing the amount of intraoperative bleeding and the risk of postoperative thromboembolism, and providing effective postoperative analgesia [2]. However, it may also bring disadvantages such as hypotension, bradycardia and delayed mobilization [3]. Hypotension secondary to vasodilation may increase perioperative mortality due to the sympathetic blocking effects of spinal anesthesia, especially in elderly patients [3]. Although elective cesarean section cases are young, female patients of reproductive age, bradycardia and hypotension that may develop after spinal anesthesia may disrupt the placental perfusion and cause undesirable effects on the fetus. Even in young female patients with long QT syndrome or Brugada syndrome, bradycardia and hypotension may result in sudden cardiac death. Preoperative detection of patients who are at risk to develop hypotension during surgery provides significant facilitation for the physician in terms of both preoperative and intraoperative intervention and surgical safety [4]. The depth of hypotension that may occur after spinal anesthesia mainly depends on 3 parameters. These include patient's intravascular volume, the amount of sympathetic activity, and peripheral vasomotor tone [5]. Of these, the intravascular volume value seems to be the parameter of the greatest significance due to both the feasibility of its measurement and the possibility of intervention [6]. Intravenous volume assessment, which can be measured both by various static (thermodilution, echocardiography, central venous pressure) methods and dynamic (arterial pressure, plethysmography, pulse change index) measurements, provides us with advantages in the prediction and treatment of hypotension [7]. It is thought that dynamic measurements can better detect volume by evaluating the effects of respiratory changes [8]. However, intravascular volume can be determined using hemodynamic monitoring devices that require expensive hardware equipment. These devices are difficult to obtain in daily practice, time-consuming, and disadvantageous due to expensive probes, which has paved the way for clinicians to find a simple, practical, and non-invasive method to predict bradycardia hypotension. Electrocardiography (ECG) is a simple and non-invasive test used in the diagnosis of diseases or conditions associated with the heart. As an example of ECG changes, QT dispersion (QTd), which is thought to show local heterogeneity in myocardial repolarization, has been shown to cause severe ventricular arrhythmias and sudden cardiac death [9]. QT dispersion defined as the difference between the longest (maximum) and shortest (minimum)

QT interval measured on a superficial 12-lead ECG. As another example of such ECG changes, Tpeak-Tend (TPe), which has been shown to be an arrhythmogenic marker in recent years, and the proportionally calculated TPe/QT ratio increase significantly. According to the QT interval, this interval is associated with ventricular arrhythmias, ventricular tachycardia, and ventricular fibrillation, both of which are life-threatening [10]. The TPe interval is the interval between the projection of the peak of the T wave on the isoelectric line (Tp) and the point where the line drawn tangentially to the descending part of the T wave intersects the isoelectric line (Te). The duration of this interval, the TPe interval, is suggested to indicate transmural dispersion of ventricular repolarization. It has been reported that prolonged TPe interval reflects the abnormal distribution of ventricular repolarization and can be used as a marker of ventricular arrhythmias [11-13]. Since prolonged TPe/QT ratio is associated with this type of pathologies, it is also thought to be associated with cardiovascular adverse events that occur during and after spinal anesthesia. In this study, our aim is to investigate whether there is a relationship between TPe/QT ratio, which is a non-invasive and easily evaluated routine preoperative parameter, and perioperative adverse cardiovascular events in elective cesarean section operations in pregnant women undergoing spinal anesthesia.

Materials ve methods

Ethical approval was obtained from Ordu University Clinical Research Ethics Committee (KAEK) for the study. Our prospective, observational and cross-sectional study was carried out between 01.12.2022 and 01.07.2023 in the operating room of Ordu University Training and Research Hospital, Gynecology and Children's Hospital. Voluntary consent was obtained and 144 pregnant women who were planned for elective cesarean section were included in the study. Power analysis was not performed and patients within a certain time interval were included in the study. Our study design was prepared in accordance with the Declaration of Helsinki and good clinical practice guidelines. Participating pregnant women were asked to fill in and sign the informed consent form. The inclusion and exclusion criteria in our study were as follows: cases over the age of 18, under the age of 50, who were planned for elective cesarean section, and whose ECGs were taken during the preoperative examination were included in the study, while cases under the age of 18, over the age of 50, who refused to participate in the study, who were morbidly obese (a body mass index of 35 kg/m^2), who had congenital heart disease, severe heart valve disease, advanced chronic kidney disease, severe respiratory disease, and chronic systemic inflammatory disease, who had a history of malignancy, who had complete and/or incomplete bundle branch block, atrial fibrillation, antiarrhythmic drug use and who underwent general anesthesia were excluded from the study. The patients' ECGs and intraoperative vital signs were evaluated by different people, thus providing blindness for the study. Patients' ECGs were scanned with an Epson brand Workforce DS-770 model device and transferred to the computer environment. Images transferred to the computer environment were enlarged with the help of Windows photo viewer and recorded by calculating the P wave, QT interval, T wave, TPe interval for each ECG with the help of the Pixel-Ruler program. P wave measurement was based on the first point where the P wave convexity started and the last point where it ended. T wave measurement was based on the first point where the T wave convexity started and the last point where it ended. QT interval was measured based on the initial point where the Q wave or the R wave in the absence of the Q wave started to the last point where the T wave ended. TPe interval measurement was based on the peak point of the T wave and the end point of the T wave convexity. On the 12-lead ECG, P wave, T wave and QT interval were calculated individually for each lead. TPe measurement was initially performed using lead V5, and if not suitable, lead V4 or V6. TPe/QT ratios were calculated in Microsoft office excel program. These measurements were calculated and recorded. ECG wave, interval and segments are shown in Figure 1, and QT interval and TPe interval are shown in Figure 2.

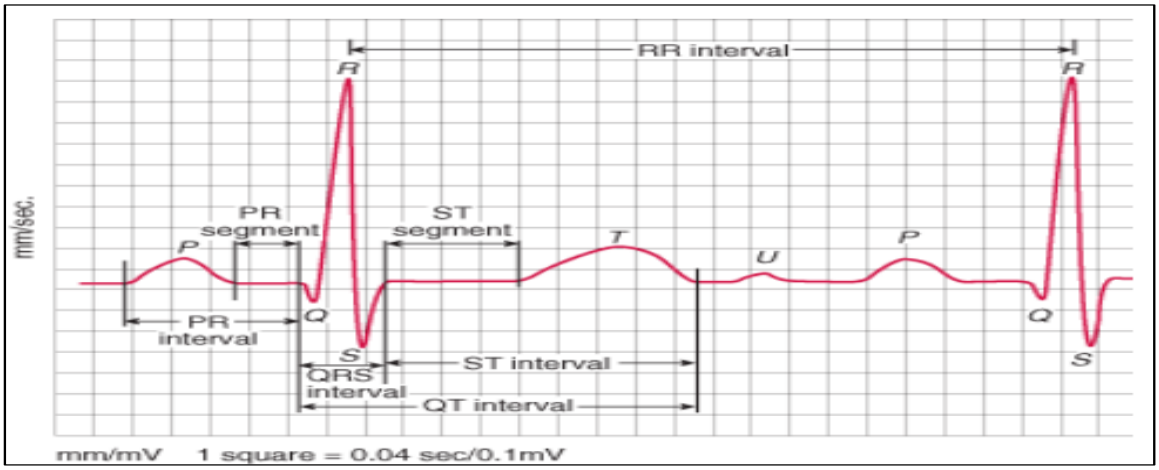

Figure 1. ECG wave, interval and segments

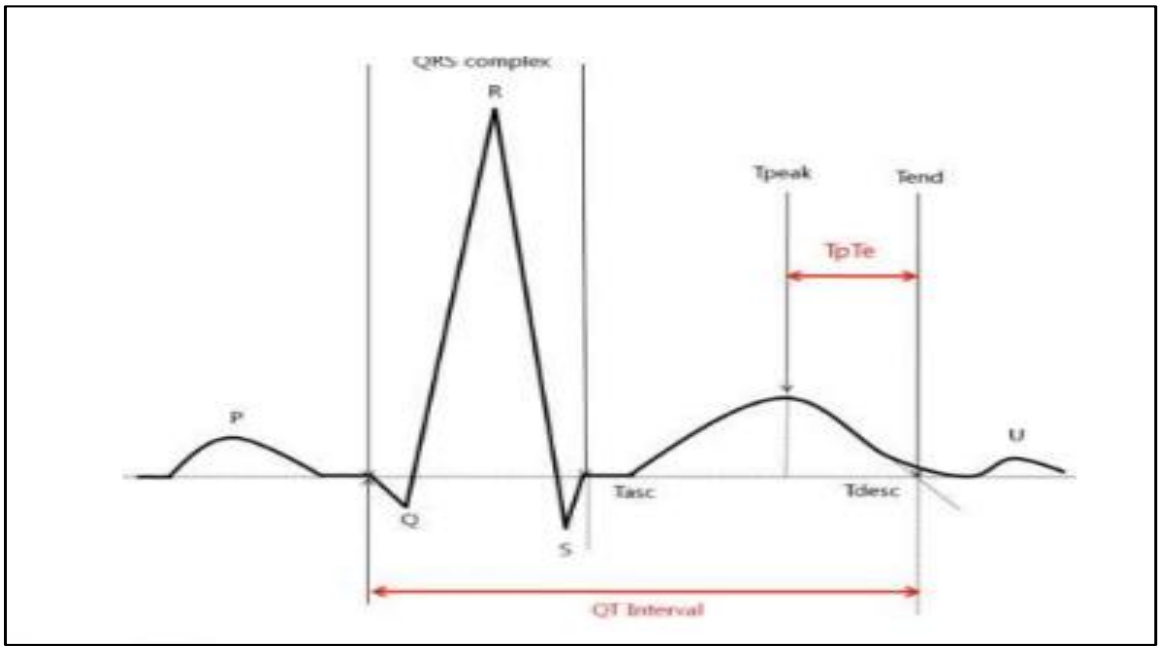

Figure 2. QT interval and TPe interval

When the patients were taken to the operating room, they were monitored with standard monitoring methods (ECG, pulse oximeter, pulse, and non-invasive blood pressure). None of the cases were premedicated. Vascular access was provided with a 22 Gauge intravenous cannula from the back of the right hand. Preoperative preload, that is, fluid loading, was not performed on the pregnant women. Hydration was achieved with 0.9% NaCl solution at a rate of 4 ml/kg/hour in the operating room environment. Pregnant women were placed in a sitting position, after the necessary treatment and covering procedures, spinal anesthesia was performed with a 25 Gauge Quincke spinal needle from the L3-L4 range. 12.5 mg of hyperbaric bupivacaine (Buvasin® 0.5% Spinal heavy ampoule, Vem İlaç, Istanbul, Türkiye) was given to the intrathecal (spinal) space when a clear flow of CSF was observed. Homogenization was achieved by applying the same local anesthetic and the same volume of bupivacaine to all cases. When the patient was taken to the operating room table, the vital findings (pulse, mean arterial pressure) were accepted as 0

minutes, and the vital findings immediately after spinal anesthesia were accepted as 1 minute. Then, following spinal anesthesia, pulse and mean arterial pressure (MAP) were intraoperatively recorded up to 40 minutes, every 5 minutes. In addition, the demographic characteristics of each patient (age, weight, height, body mass index, gestational week, family history of heart disease, accompanying systemic diseases) were recorded. During the follow-up of intraoperative vital findings, if the heart rate fell below 50 beats/min, bradycardia was accepted, 1 mg of atropine was planned to be administered and whether atropine was administered or not was recorded. The mean arterial pressure (MAP) was recorded at 0 minutes and, following spinal administration, a 20% decrease based on the initial MAP at each measurement time up to minute 40 (every 5 minutes), was accepted as hypotension, and 10 mg of ephedrine was administered. The amount of ephedrine was recorded in mg. Those who developed intraoperative bradycardia and hypotension complications were recorded as "complication developed". At the end of the operation, the patients were followed up in the recovery room for 30 minutes. The patients were sent to the service in the event that the block level decreased to T10, the Modified Bromage Scale was 2 and the Modified Aldrete score was 9-10.

Statistical method

Data were analyzed with IBM SPSS v23. Kolmogorov Smirnov and Shapiro Wilk tests were used to test normal distribution. Mann Whitney U test was used to compare the data that did not show normal distribution. The relationship between the measurements was analyzed with Spearman's rho test. The results of the analyses of quantitative data were obtained with mean ± sd. Significance level was accepted as $p<0.05$.

Results

Examination of the relationship between patients' demographic characteristics and TPe/QT is presented in Table 1.

Table 1. Examination of the relationship between demographic characteristics and TPe/QT

	r	*p*
Age	0.081	0.332
Weight	0.017	0.842
Height	0.191	**0.022**
BMI	-0.090	0.285

r: Spearman's rho (Correlation analysis of demographic characteristics and Tpe/QT ratio)

There is no statistically significant relationship between TPe/QT and age, weight, and BMI ($p>0.05$). There is a positive and weak statistically significant relationship between height and TPe/QT (r=0.191; $p=0.022$). As the height increases, the TPe/QT ratio also increases.

The comparison of TPe/QT values according to complications, comorbidities, and drug use is presented in Table 2.

The median TPe/QT value was determined as 0.2 in patients without intraoperative complications, and 0.222 in patients with complications with no statistical difference ($p=0.166$). While the median TPe/QT value was 0.2 in patients without postoperative complications, it was 0.225 in patients with complications with no statistical difference ($p=0.096$). While the median value was 0.214 in patients without co-morbidities, it was 0.2 in patients with co-morbidities with no statistical difference ($p=0.578$). While the median value was 0.2 in patients with a family history of cardiac diseases, the median value was 0.214 in patients without a family history, with no statistical difference ($p=0.690$). While the median value was 0.2 in patients who did not use ephedrine, it was 0.222 in patients who used it, with no statistical difference ($p=0.151$). While the median value was 0.2 in patients who did not use atropine, it was 0.235 in patients who used it, with no statistical difference ($p=0.169$).

Table 2. Comparison of TPe/QT values by complication, comorbidity, and drug use

	Mean ± s.s.	Median (min-max)	Test Statistics	*p**
Intraoperative Complication				
No (n=45)	0.202±0.07	0.2 (0.074-0.333)	1907.5	0.166
Yes (n=99)	0.222±0.084	0.222 (0.074-0.583)		
Postoperative Complication				
No (n=132)	0.212±0.078	0.2 (0.074-0.583)	562.5	0.096
Yes (n=12)	0.258±0.098	0.225 (0.143-0.526)		
Co-morbidity				
No (n=112)	0.215±0.071	0.214 (0.074-0.5)	1676.5	0.578
Yes (n=32)	0.219±0.108	0.2 (0.074-0.583)		
Familial Heart Disease				
No (n=118)	0.212±0.078	0.214 (0.074-0.526)	1457.5	0.690
Yes (n=26)	0.23±0.09	0.2 (0.1-0.583)		
Ephedrine Use				
No (n=52)	0.203±0.072	0.2 (0.074-0.333)	2048	0.151
Yes (n=92)	0.223±0.085	0.222 (0.074-0.583)		
Atropine Use				
No (n=141)	0.215±0.081	0.2 (0.074-0.583)	113.5	0.169
Yes (n=3)	0.248±0.026	0.235 (0.231-0.278)		

*Mann Whitney U

When the literature is examined, the TPe/QT ratio was found to be less than 0.21 among healthy volunteers and 0.21 and above among patients with cardiac disease in the studies comparing healthy volunteers and populations with cardiac problems [14, 15]. In our study, although it did not reach a statistically significant level, it was found to be above 0.21 in cases who developed intraoperative bradycardia and hypotension (patients who used intraoperative ephedrine and atropine due to hypotension), as well as in cases with a family history of heart disease.

Vital parameters during measurement times and TPe/QT ratio were analyzed by Sperman correlation test. Our results are presented in Table 3.

There is a positive and weak significant relationship between the amount of ephedrine use and TPe/QT (r=0.208; p=0.012). MAP differences and Pulse differences do not show a significant relationship with TPe/Qt ratio (p>0.05).

Descriptive statistical values of our patients are presented in Table 4.

The comparison of the vital signs measured before and after spinal administration in patients with and without prolonged TPe/QT ratio is presented in Table 5.

Table 3. Examination of the relationship between measurement values and TPe/QT ratio

	r	*p*
Amount of ephedrine# (mg)	0.208	**0.012***
PSMBP-POSMBP difference	0.034	0.689
PSMBP-POSMBP difference	0.191	0.135
PSMBP-POSMBP difference	-0.049	0.564
PSPulse-POSPulse difference	-0.158	0.059
PSPulse-PS5Pulse difference	-0.145	0.082
PSPulse-PS10Pulse difference	-0.121	0.147

r: Spearman's rho correlation analysis (Correlation analysis of vital signs and Tpe/QT ratio), mg: miligram, #: PSMBP: Pre-spinal mean blood pressure, POSMBP: Post-spinal mean blood pressure, POS5MAP: Post-spinal mean 5-minute blood pressure, POS10MAP: Post-spinal mean 10-minute blood pressure, PSPulse: Pre-spinal pulse, PSPulse: Post-spinal pulse, PS5Pulse: Post-spinal 5-minute, PS10Pulse: Post-spinal 10-minute pulse, Cases using intraoperative ephedrine were compared

Table 4. Descriptive Statistics

	Mean ± s.s.	Median (min-max)
Age (year)	28.556±5.419	28 (16-50)
Weight (kg)	78.931±13.374	76 (55-140)
Height (cm)	161.84±6.376	160 (149-178)
BMI (weight/heightxheight)	30.146±4.866	29.68 (20.7-48.04)
Gestational week	37.88±1.691	38 (29-42)
Operation time (minute)	38.958±9.75	40 (25-65)
TPE (ms)	2.215±0.931	2 (1-7)
QT (ms)	10.42±2.43	10 (5-22.5)
Amount of ephedrine (mg)	11.91±13.779	10 (0-100)
TPe/QT (ms)	0.216±0.081	0.205 (0.074-0.583)
PSMBP-POSMBP difference (mmHg)	9.035±13.47	8 (-42-52)
PSMBP-POSMBP difference (mmHg)	-25.917±584.453	21 (-6987-77)
PSMBP-POSMBP difference (mmHg)	20.528±15.801	19 (-11-73)
PSPulse-POSPulse difference (mmHg)	-0.847±15.505	-1 (-46-60)
PSPulse-PS5Pulse difference (mmHg)	4.653±23.203	4 (-52-62)
PSPulse-POSPulse difference (mmHg)	4.042±20.25	5 (-58-52)

Results of analysis Mean ± sd for quantitative data, BMI: Body Mass Indexmg, mg: miligram, mmHg: millimeters of mercury, PSMBP: Pre-spinal mean blood pressure, POSMBP: Post-spinal mean blood pressure ms: milliseconds, POS5MAP: Post-spinal mean 5-minute blood pressure POS10MAP: Post-spinal mean 10-minute blood pressure, PSPulse: Pre-spinal pulse, PSPulse: Post-spinal pulse, PS5Pulse: Post-spinal 5-minute, PS10Pulse: Post-spinal 10-minute pulse

Table 5. Comparison of vital signs measured before and after spinal administration in patients with and without prolonged TPe/QT ratio

	TPe/QT ratio <0.21		TPe/QT ratio >0.21		Test statistics	*p*
	Mean ± s.s.	**Median (min-max)**	**Mean ± s.s.**	**Median (min-max)**		
PSSBP	134.3±16.2	134 (105-171)	132.1±14.9	132 (102-174)	2421.000	0.494
POSSBP	122±17.9	124 (72-169)	120.1±17.7	120 (71-174)	2411.000	0.469
POS5SBP	107.1±21.4	109.5 (58-157)	108.4±20.1	109.5 (52-148)	2521.500	0.778
POS10SBP	113.9±16.4	114 (69-152)	113.1±16.7	113.5 (77-152)	2510.500	0.745
POS15SBP	115.7±13.3	114.5 (87-150)	114.1±15.8	115.5 (75-161)	2533.500	0.815
PO20SBP	113.9±13.4	114 (92-155)	114.9±13.7	113.5 (81-154)	2496.000	0.701
POS25SBP	114.1±13.3	113 (87-157)	117.9±13.4	117 (80-154)	2019.000	**0.030**
POS30SBP	116±13.6	116 (87-160)	118.2±12.3	119 (85-154)	1718.500	0.121
POS35SBP	116.7±14.1	114 (93-166)	117.6±12.3	115.5 (96-158)	1170.500	0.395
POS40SBP	117.4±12	117.5 (99-155)	121.7±11.5	122.5 (95-158)	441.000	**0.049**
POS25DBP	56.8±12.1	54 (35-101)	61.3±12.2	61 (37-92)	1932.500	**0.012**
POS30DBP	58.7±12.4	58 (34-96)	60.3±11.5	61 (27-85)	1766.000	0.185
POS35DBP	61.2±12.2	60 (40-104)	63.7±9.6	63 (44-87)	1018.500	0.062
POS40DBP	62.2±13.4	62 (28-95)	67.4±9.8	68.5 (42-91)	457.000	0.053
POS45DBP	57.1±10.7	56 (28-74)	69.6±11	70 (46-91)	78.000	**0.001**
POS40MBP	77.1±11.8	77 (55-110)	82.9±10.9	84 (59-110)	444.500	**0.017**
POS45MBP	73.2±10	72 (52-91)	84.9±10.4	82.5 (63-103)	88.500	**0.002**
PS50MBP	75.1±10.6	75.5 (56-90)	85.3±13.5	89 (52-101)	47.000	**0.023**

*Mann Whitney UResults of analysis Mean ± sd for quantitative data, POS: Post-spinal SBP: Systolic blood pressure DBP: Diastolic blood pressure, MBP: Mean blood pressure (All the lines that were significant were taken so that the table was not too long, some of the lines that were not, significant were included in the table)

Discussion

As a result of our study, we found a weak positive correlation between the height variable, which is one of our demographic characteristics, and the Tpe/QT ratio. As the height increased, the TPe/QT ratio increased. Although it did not reach the level of statistical significance, we found that the TPe/QT ratio was longer in cases with intraoperative bradycardia and hypotension than in cases without complications. The TPe/QT ratio was above 0.21 in cases with bradycardia and hypotension. Ephedrine, a short-acting non-selective beta-mimetic agent, is used in the operating room for the treatment of cases with intraoperative bradycardia and hypotension. When the correlation between the amount of ephedrine use and TPe/QT ratio was examined, we found a weak positive correlation. As the use of ephedrine increased, the TPe/QT ratio increased. When the vital findings were compared in the measured time periods, the systolic and diastolic blood pressures of the cases with a TPe/QT ratio above 0.21 were found to be higher and therefore the mean blood pressures were higher.

Studies have shown that the QT interval and TPe interval increase linearly with body mass [16]. In the same study, it was observed that the TPe/QT ratio did not change. It was observed that the TPe interval changed in heart rate changes, but the TPe/QT ratio did not change [12]. Therefore, the TPe/QT ratio is accepted as a more valuable parameter than the TPe interval. In our study, no significant relationship was found between the TPe/QT ratio and the weight variable. However, in our study, we found a positive correlation between the height variable and the TPe/QT ratio. As the height increased, the TPe/QT ratio increased. In the literature, the relationship between the age and weight variable and the TPe/QT ratio was examined in available studies. Our study is the first study to examine the height and TPe/QT ratio in the literature.

Tekinalp N. et al. [17] compared the TPe/QT ratios of the control group consisting of healthy volunteers with acute ischemic stroke and acute hemorrhagic stroke cases. They found that the TPe/QT ratios measured from the V5-V6 derivations increased significantly compared to the control group. In our study, the TPe/QT ratio was measured from the V5 derivations of the cases. Tekinalp et al. [17] conducted a study in elderly patients with comorbidities, whereas we conducted our study in pregnant patients consisting of young healthy women of reproductive age. In our study, we found that the TPe/QT ratios of the cases who developed hypotension increased, but it was not statistically significant. This difference may be due to the significant difference between study populations.

In a study comparing healthy volunteers (control group) and patients with coronary artery ectasia, Alsancak et al. [18] found that the TPe/QT ratios of patients with coronary ectasia were increased. In fact, the authors found that TPe/QT ratios were higher in patients with two-vessel-three-vessel ectasia compared to those with single-vessel ectasia. The fact that our results are conflicting is due to the fact that our study included a single group and the study population was very different.

Kayali and Demir [19] compared the TPe/QT ratios of young adults aged 16-19 years who smoked and did not smoke. The authors found the TPe/QT ratios were higher in smokers than in non-smokers. Our study was also conducted in young adult pregnant patients, and our study populations and results are partially similar to the studies of Kayali and Demir.

Hidayet et al. [20] compared the TPe/QT ratios, TPe intervals and TPe/QTc ratios of two groups including healthy volunteers and patients with Behçet's disease. The authors found that other mentioned ratios and TPe/QT ratios increased in patients with Behçet's disease compared to healthy volunteers. The authors emphasized that patients with Behçet's disease should go to cardiology outpatient clinic controls frequently in terms of arrhythmia. In our study, we found that there was a tendency to hypotension in our cases with increased TPe/QT rates.

Ucar et al. [21] compared the TPe/QT and TPe/QTc ratios of patients with acute myocarditis and healthy volunteers. Again, TPe/QT ratios were found to be increased in patients with myocarditis compared to healthy volunteers. The authors emphasized that these rates may have increased due to impaired ventricular repolarization in the heart. Again, our results do not coincide due to the differences in our populations.

In the literature, our study is unique in two aspects. There are no studies on the TPe/QT ratio in pregnant women. In the intraoperative period, no other study in which this rate was studied in the operating room has been found in the literature.

Our study had some limitations. First of all, the fact that there is no gender difference and the recruitment of pregnant female patients alone is the first limitation of the study. The low number of subjects included in the study is the second limitation.

In conclusion, the TPe/QT ratio is a novel cardiac marker with high predictive power, is non-invasive, quite inexpensive, and very practical to measure in the early detection of cardiac events, especially arrhythmia. This novel predictive marker can be used in anesthesia practice, preoperative examination and patient follow-up in the intraoperative operating room to predict fatal cardiac arrhythmias or intraoperative hypo/hypertension. We believe that our study will shed light on long-term studies with large populations to be conducted on this subject.

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

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Kidney transplantation in pediatric and young adults: a single - center experience

Pediatrik ve genç erişkinlerde böbrek nakli: tek merkez deneyimi

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Abstract

Purpose: Pediatric kidney transplantation (PKTx) is one of the most comfortable renal replacement therapies preferred in children with end-stage renal disease (ESRD) worldwide. Donor selection and identification of the underlying cause of renal failure in the recipient and individualisation of treatment are decisive factors for graft survival. The aim of this study is to present our results.

Materials and methods: This single-center, retrospective study was conducted at Pamukkale University, Faculty of Medicine, Organ Transplantation Center. The PKTx was performed in 11 patients between December 2014 and November 2019.

Results: The mean time from the beginning of the first dialysis session to transplantation was 40.2 months, and two patients were transplanted preemptively. The mean age of LD and DD transplants was 41.6 years and 17.1 years, respectively. This was attributed to the fact that, in the donation of cadaveric organs, donors under the age of 18 years are only registered for the waiting list for the recipients under the age of 18 years in our country.

Conclusion: Our study showed that patients who used basiliximab for induction treatment were more advantageous in terms of infections than patients using anti-thymocyte globulin (ATG).

Keywords: Basiliximab, ATG, pediatric transplantation.

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Öz

Amaç: Pediatrik böbrek nakli, dünya çapında son dönem böbrek hastalığı (SDBY) olan çocuklarda tercih edilen en konforlu böbrek replasman tedavilerinden biridir. Donör seçimi ve alıcıda altta yatan böbrek yetmezliğine neden olan sebebin ortaya konması ve tedavinin bireyselleştirilmesi, greft sağkalımı için belirleyici faktörlerdir. ve Bu çalışmanın amacı elde ettiğimiz sonuçları sunmaktır.

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Gereç ve yöntem: Bu tek merkezli, retrospektif çalışma Pamukkale Üniversitesi Tıp Fakültesi Organ Nakil Merkezi'nde yapılmıştır. Pediatrik böbrek nakilleri, Aralık 2014 ile Kasım 2019 arasında 11 hastaya uygulandı.
Bulgular: İlk diyaliz seansının başlangıcından transplantasyona kadar geçen ortalama süre 40,2 aydı ve iki hastaya önleyici olarak transplantasyon yapıldı. Canlı vericili ve kadavra vericili transplantlarının ortalama yaşı sırasıyla 41,6 ve 17,1 idi. Bu durum ülkemizde kadavra organ bağışında 18 yaş altı bağışçıların sadece 18 yaş altı bağışçıların bekleme listesine kaydedilmesine bağlanmıştır.
Sonuç: Çalışmamız indüksiyon tedavisi için basiliximab kullanan hastaların anti-timosit globülin (ATG) kullanan hastalara göre enfeksiyon açısından daha avantajlı olduğunu göstermiştir.

Anahtar kelimeler: Basiliksimab, ATG, Pediatrik böbrek nakli.

Özgen U, Özban M, Akbudak İH, Yüksel S, Girişgen İ, Aykota MR, Becerir T, Mete E, Yılmaz N, Doğa E, Uzunlu O, Çeri M, Birsen O, Aydın Ç. Pediatrik ve genç erişkinlerde böbrek nakli: tek merkez deneyimi. Pam Tıp Derg 2023;16:674-681.

Introduction

Pediatric kidney transplant (PKTx) is one of the most comfortable renal replacement therapies preferred in children with end-stage renal disease (ESRD) worldwide. With all the advances in organ transplantation over the past four decades, several strategies such as changes in the Kidney Allocation System, improvement of surgical techniques, advances in organ preservation and, particularly, novel immunosuppression regimens have emerged to optimize outcomes in pediatric renal allograft recipients. Recent data have shown that overall pediatric patient survival rates at one year, five years, and 10 years are about 99%, 98%, and 90%, respectively, and the one-year, five-year, and 10-year graft survival rates are 97%, 88%, and 69% from living donors (LDs) and 96%, 80%, and 55% from deceased donors (cadaveric) (DDs), respectively [1, 2].

Optimal recipient outcomes require adequate access to transplantation, particularly among pediatric patients, the presence of well-trained healthcare professionals, acceptable organ donation policies, and an impartial Organ Allocation System. Currently, it is extremely difficult to provide the requirements mentioned above in developing countries.

In our unit, a renal transplant program has been conducted in adult patients since 2006 and in pediatric patients since 2014. In the present study, we aimed to present our experiences in the pediatric patient group and share our follow-up results and patient outcomes.

Materials and methods

This single-center, retrospective study was conducted at Pamukkale University, Faculty of Medicine, Organ Transplantation Center. The PKTx was performed in 11 patients between December 2014 and November 2019. Those who developed ESRD in childhood (under 18 years) and were currently being followed in the pediatric nephrology clinic were included in the study. In our center, the immunosuppression protocol is induction with basiliximab in low immunological risk transplants from LDs and anti-thymocyte globulin (ATG) in high immunological risk transplants from DDs. In patients in whom basiliximab (12 mg/m^2) was administrated, the second dose was administrated at the same hour on the 4th postoperative day, following the first dose during anesthesia induction. For ATG, the first dose was administered as an infusion at a dose of 1.5 mg/kg over four hours following premedication with antihistamine and paracetamol during anesthesia induction.

On the first day following operation, CD3 level, platelet and lymphocyte count were monitored, and a total of ATG dose was administered as three or five doses depending on the immunological risk status of the patient. Post-induction triple immunosuppression as methylprednisolone (300 mg/m^2 starting four hours before the operation and during the operation, gradually decreasing the dose to 5mg at the end of the 12th week on the following days), tacrolimus (0.1-0.2 mg/kg/day in two doses when the creatinine value tended to decrease, usually on the postoperative 1st and 2nd days), and mycophenolate mofetil

(1200 mg/m^2/day, two doses one day before the transplantation) treatment protocols were applied.

Simultaneously, prophylactic treatments such as trimethoprim/sulfamethoxazole (3-5 mg/kg/day), fluconazole (10 mg/kg/day), and valganciclovir (15 mg/kg/day-maximum 450 mg/day) to prevent possible infections for three to six months after transplantation were applied. Cytomegalovirus (CMV) polymerase chain reaction (PCR), Epstein-Barr virus (EBV) PCR, and Polyoma PCR levels of all patients were evaluated every 15 days for the first six months, every month for the following six months, and every three months for the following years.

In all transplants, immunological evaluation, T and B cell flow cytometric (TFXM, BFXM) cross-match, as well as complement-dependent cytotoxicity (CDC) cross-match analyses were performed regarding the blood group transfusion compatibility principles. The human leukocyte antigen (HLA) test was performed using the technology based on PCR for Class 1 (locus A, B, C) and Class 2 (locus DR, DQ). Panel reactive antibody (PRA) counts of the patients were evaluated for Class 1 and Class 2. No protocol biopsy was performed for allograft in our clinic. However, during any period following PKTx, in case of graft dysfunction, protocol biopsy was performed and the biopsy results were evaluated regarding the Banff score [3]. The DDs assessment was conducted by the Republic of Türkiye, Ministry of Health regional coordination center in coordination with our center and donors with marginal criteria were excluded. It was preferred not to make high-risk transplants, particularly in our first experiences. In our country, pediatric donations are submitted to same age group recipients. In this study, the evaluation of LDs and recipients and the decision for transplantation were conducted by the Multidisciplinary Transplantation Council of our institution.

Urinary tract infection was defined as existence of symptoms like dysuria, fever, abdominal pain and positive urine culture in a midstream urine sample (10^5 colonies of microorganisms or more per ml).

Demographic characteristics of the recipients and donors, cold ischemia time, cross-match compatibility, surgical technical details, etiology of ESRD, the use of renal replacement therapy in recipients, duration and type of renal replacement therapy, comorbidities, induction protocol received during PKTx, complications during follow-up such as infection or rejection, and the final patient status were all recorded.

A written informed consent was obtained from the parents and/or legal guardians of the patient. The study was conducted in accordance with the Declaration of Helsinki and its amendments. (approved by Pamukkale University Non-Interventional Clinical Research Ethics Committee.

Statistical analysis

SPSS 22.0 (IBM Corp. Armonk, NY, USA) was used for performing statistical analysis. Analytical characteristics were given as percentage, mean and SD, or median. The Chi-Square test was used for univariate analysis of categorical variables. Values of $p<0.05$ were considered to be statistically significant.

Results

Demographic, clinical data and causes of ESRD of the patients are summarized in Table 1. Of the recipients, six were males and five were females with a mean age of 15.18 (range, 6 to 22) years at the time of transplantation. The mean time from the beginning of the first dialysis session to transplantation was 40.2 months, and two patients were transplanted preemptively.

Donor and immunologic data of transplant patients are summarized in Table 2. The mean age of LD and DD transplants was 41.6 years and 17.1 years, respectively. This was attributed to the fact that, in the donation of cadaveric organs, donors under the age of 18 years are only registered for the waiting list for the recipients under the age of 18 years in our country. One of the DDs was a 1.5-year-old infant with post-traumatic cerebral death and was included in our patient data as the youngest donor. The PRA positivity was detected in only one patient before transplantation in recipients. In tissue group compatibility, three mismatches were seen in seven patients, while five mismatches were detected in one patient. The CDC and flow cytometric cross-match tests were negative in all transplants.

Table 1. Demographic and pretransplant data of recipients

No	AGE	TX AGE	SEX	BLOOD GROUP	ESRD	RRT	RRTT (MONTH)
1	24	18	F	A+	UNKNOWN	PD	18
2	21	16	M	O+	CYSTINOSIS	HD	32
3	22	17	M	O+	VUR NEPHROPATHY	PD	24
4	14	10	F	A+	VUR NEPHROPATHY	PD	24
5	8.5	6	F	A+	FSGS	PR	-
6	21	20	M	A+	VUR NEPHROPATHY	PD	12
7	15	14	M	A+	FSGS	PR	-
8	21	20	M	O+	SPENCH SYNDROME	PD	36
9	22	22	F	O+	FSGS	PD	180
10	11	10	F	O+	CYSTINOSIS	PD	12
11	15	14	F	O+	VUR+RPGN	PD	24

F: Female, M: Male, VUR: Vesicoureteral reflux, FSGS: Focal Segmental Glomerulosclerosis, RPGN: Rapidly Progressive Glomerulonephritis TX: Transplantation, ESRD: End Stage Renal Disease, PD: Peritoneal dialysis, HD: Hemodialysis, PR: Preemptive, RRT: Renal replacement therapy, RRTT: Renal replacement therapy time

Table 2. Donor and immunologic data of transplant patients

No	TX TYPE	DONOR AGE	HLA MISMATCH STATUS	PRA STATUS	INDUCTION IMMUNSUPPRESSION
1	LIVING-RELATED	54	3	NEGATIVE	BASILIXIMAB
2	LIVING-RELATED	37	1	NEGATIVE	BASILIXIMAB
3	CADAVERIC	9	5	NEGATIVE	BASILIXIMAB
4	LIVING-RELATED	51	3	NEGATIVE	BASILIXIMAB
5	LIVING-RELATED	27	3	NEGATIVE	BASILIXIMAB
6	LIVING-RELATED	43	3	NEGATIVE	BASILIXIMAB
7	LIVING-RELATED	38	3	NEGATIVE	BASILIXIMAB
8	CADAVERIC	22	4	NEGATIVE	ATG
9	CADAVERIC	36	3	+CLASS 1 2% -CLASS 2 53%	ATG
10	CADAVERIC	1.5	4	NEGATIVE	ATG
11	CADAVERIC	17	3	NEGATIVE	ATG

Tx: Transplantation, HLA: Human Leucocyte Antigen, PRA: Panel Reactive Antibodies, ATG: Anti-thymocyte globulin

In our study, the mean cold ischemia time was 54.2 min in LDs transplants and 621.3 min in DD transplants. In all transplants, the graft was anastomosed on the external iliac artery and vein in the right iliac fossa. Eight of the allografts were anastomosed as a single renal artery, while three of them were performed as a double renal artery anastomosis. Ureteroneocystostomy was performed using a double J stent with the Lich-Gregoir extravesical ureteroneocystostomy technique. All patients were followed in the organ transplant unit after surgery. The urinary catheters of the patients were removed on postoperative Day 7. The creatinine values during follow-up are shown in Table 3.

Table 3. Serum creatinine levels of recipients periodically (mg/dl)

No	DGF	FOLLOW-UP TIME (MTH)	15. DAY	3. MTH	6. MTH	9. MTH	12. MTH	UP TO DATE
1	-	72	0.97	0.90	1.07	1.06	1.15	1.7
2	-	70	0.55	0.81	0.73	0.75	0.68	1.06
3	-	65	0.91	1.58	0.89	1	0.90	1
4	-	56	0.85	0.77	0.85	0.72	0.76	0.85
5	-	32	0.4	0.48	0.59	0.57	0.65	0.7
6	-	20	1.2	1.55	1.4	1.3	1.32	1.26
7	-	13	0.49	0.79	0.79	0.76	0.89	0.93
8	+	13	0.59	0.86	0.94	1.17	1.04	1.04
9	+	12	1.47	1.05	0.97	1.1	0.92	0.92
10	-	12	0.61	0.69	0.42	0.55	0.46	0.46
11	+	10	0.52	0.63	1.49	3.61	10	9.23

DGF: Delayed graft dysfunction, MTH: Month

During follow-up, the relatives of patient no. 7 with FSGS (*NPHS2-R229Q* mutation) were informed about the possibility of FSGS recurrence and perioperative plasmapheresis was performed. Since kidney biopsy performed for proteinuria at six months was compatible with cellular rejection, proteinuria regressed with steroid therapy. Following the recurrence of proteinuria at nine months, FSGS recurrence was detected in the re-biopsy, and the patient was administered plasmapheresis, rituximab, and tacrolimus of dose with gradually increasing. Although the degree of proteinuria decreased, it persisted at 17 months of transplantation (1000 mg-32 mg/m^2/hour). Delayed graft dysfunction was observed in three cases (patient no. 8, 9, 11) (Table 3). In patient no. 11, the kidney biopsy performed due to high creatinine in the postoperative sixth month was compatible with acute cellular rejection, and a diagnosis of humoral rejection was made with the detection of high serum PRA levels in the same period. As cellular and humoral rejection treatments were applied as follows: rituximab treatment was initiated after high-dose steroid and ATG therapy and plasmapheresis; however, renal functions did not improve and the graft loss was observed at the end of the first year. Additionally, two of the patients who developed acute rejection (patient no. 3, 7, 10, 11) could be controlled with pulse steroid therapy, while the other one recovered with steroid and ATG treatment. Proteinuria and hypertension findings of chronic allograft nephropathy were present in two patients whose transplantation periods were over five years, and the glomerular filtration rate (GFR) was 82 mL/min /1.73 m^2 in one patient (patient no. 2) and 96 mL/min /1.73 m^2 in another patient (patient no. 3).

In patient no. 8, polyoma PCR yielded a positive result (Table 3). During the same period, quinolone treatment was given due to the borderline high creatinine level and an improvement was observed. Since high CMV PCR levels were associated with high creatinine levels in two patients (patient no. 0 and 11), mycophenolate mofetil was discontinued, and tacrolimus doses were reduced. After treating with intravenous (IV) ganciclovir, the CMV PCR became negative and creatinine levels reached to normal value. The CMV staining was negative in kidney biopsies performed during this period. In this case series, all patients with viral infections were DD transplants who received ATG induction.

During follow-up, four patients had recurrent symptomatic urinary tract infections (UTIs) (one patient developed additional epididymitis) within the first six months, and VUR was detected on voiding cystourethrogram and did not develop UTIs following subureteric injection.

Discussion

The PKTx is the gold-standard treatment for pediatric patients with ESRD [4]. The prevalence of renal replacement therapy ranges from 18 to 100 per million in pediatric population [5]. The etiology in children with ESRD has changed over the years. Acquired diseases were at the forefront in developing countries, while the

causes of all ESRD cases in developed countries were reported to be congenital anomalies of the urinary system and hereditary nephropathies. Similarly, congenital kidney and urinary tract abnormalities were the main cause in the children with ESRD in the United States were reported [1]. According to the data obtained by the Turkish Society of Nephrology as of the end of 2019 from many pediatric nephrology centers across the country, primary glomerulonephritis and vesicoureteral reflux with UTIs is the first and second cause of etiology in patients with ESRD, 21 and 17.2%, respectively. According to the same data, kidney transplantation is the preferred treatment for 61.7% of all pediatric end stage renal disease [4]. In our study, 36.3% had VUR with UTIs, 27.2% of them had FSGS, and 18% had hereditary nephropathy such as cystinosis.

Acute rejection is the most serious complication after transplantation, often unresponsive to rejection therapy and may result in graft loss. The use of ATG, a polyclonal antibody, or basiliximab, a monoclonal antibody, in induction therapy to prevent rejection in PKTx has been adopted worldwide. In the literature, there are head-to-head studies comparing the effects and adverse effects of these two drugs used in induction. In a meta-analysis, while there was no significant difference in the acute rejection rate and graft survival rate between the ATG and basiliximab groups, secondary malignancies were found to be less in the basiliximab group [6]. In a study conducted by Acott et al. [7] the ATG and basiliximab were compared in pediatric patients and the rejection rates were found to be lower in the basiliximab group. In addition, serum sickness reaction and thrombocytopenia were not observed in the basiliximab arm, suggesting that basiliximab was superior to ATG. In our patient group, cellular rejection was detected in three patients and mixed (cellular and humoral) rejection in one patient who had graft lost. The ATG was used for induction in two of four patients with rejection, and basiliximab in two.

Post-transplant infections were the first cause of morbidity for our recipients during the first six months following PKTx. Cytomegalovirus disease was the most common viral infection for our recipients in the first six months following transplant. Infection rates between 8% and 32% have been reported in the literature [3]. One of the risk factors for the development of CMV disease is the serological incompatibility between the donor and recipient [8, 9]. All patients were categorized in the lowest risk as CMV D- / R-. The most important risk for post-transplant infections were the immunosuppressive drugs used. There are many studies comparing the viral infection frequency of drugs used in induction. In some studies, in the past years, more viral infections were found in the ATG groups than the basiliximab groups [7, 10, 11]. Contrary to these studies, a study evaluating the risk factors in post-transplant infections in adult patients suggested that CMV infection were more severe in patients receiving basiliximab [4]. In a meta-analysis that collected 8 studies in 2018; no significant difference was found between the groups in terms of viral infection in patients using ATG and basiliximab [6]. Cytomegalovirus infection was detected in two of our patients, and polyomavirus in one, CMV infections were treated with intravenously ganciclovir, and polyoma infection was treated with quinolone. All patients with viral infections were transplanted from DDs, and ATG was used for induction.

The existing data reveal a wide incidence range of UTIs among kidney allograft recipients, particularly in the first-year post-transplant, from 23% to 75%. However, there is still conflicting evidence regarding the effect and long-term outcomes of UTIs during the first year after [12]. Early acute pyelonephritis (APN) is significantly detrimental for graft outcome. APN may trigger the immune cascade, resulting in acute rejection and subsequent graft loss [13]. A recent large US cohort study by Naik et al. [14] demonstrated that first-year UTIs not only negatively affected patient and graft survival, but also significantly increased post-transplant costs. Therefore, the authors concluded that the prevention of UTIs was the key strategy to overcome this challenge [14]. In our study, symptomatic recurrent UTIs were observed in four patients in the first six months after transplantation, and elevated creatinine levels were observed during this period. Double J catheters were used in all patients and the catheters were removed at three months. Despite this, subureteric injection was performed in four patients due to persistent UTIs and VUR was

detected in all of these patients. Symptomatic UTIs were not seen in any of these patients after subureteric injection. Nonetheless, there are controversial opinions about the treatment of post-PKTx VUR in the literature. Previous studies have shown that the treatment decision of these patients should be individualized [15]. In patients with asymptomatic VUR, voiding training or short-term temporary antibiotic prophylaxis is recommended in patients with VUR that is diagnosed during the examination for hydronephrosis or with voiding dysfunction, while a surgical intervention is recommended in patients with symptomatic pyelonephritis, as it eventually disrupts the graft half-life by developing scarring [15]. Furthermore, there is ongoing debate on the surgical intervention, and it has been suggested that ureter reimplantation is superior to reflux injection. In the study of Sheth et al. [16], the rate of post-transplant VUR was 12.3% (35/285), 11 of these patients received deflux injection and seven of them had ureteral reimplantation. Vesicoureteral reflux and UTIs persisted in 10 of the patients who were injected with deflux, and half of these patients underwent reimplantation of the ureter. At the end of the study, reimplantation was more effective in post-transplant VURs. Three of the patients with VUR in our study had no voiding dysfunction, and still, regular voiding training was provided. Oxybutynin hydrochloride was initiated in patient no. 4 with voiding dysfunction. Deflux injection was used in all patients, as they had pyelonephritis episodes requiring hospitalization and causing elevated creatinine levels. There was no symptomatic urinary tract infection after subureteric injection in these patients. We suggest that patients with post-transplant VUR and pyelonephritis should be given a chance due to a less invasive deflux injection and its favorable results.

There are some limitations to this study. The sample size is small with a retrospective design. However, we found it meaningful to share our initial experience.

In conclusion, our study showed that patients who used basiliximab for induction treatment were more advantageous in terms of infections than patients using ATG. We suggest that subureteric deflux injection instead of more invasive intervention such as ureteric reimplantation can be used effectively in the children with VUR who suffered from symptomatic UTIs during the post-transplant period. Nonetheless, further large-scale, long-term studies are needed to gain a better understanding of the results of immunosuppressive treatment options in children.

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

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Author's contribution

Study conception and design: M.O., S.Y., U.O. Acquisition of data: U.O., I.G., T.B., N.Y. Analysis and interpretation of data: D.Y., M.A., E.M. Drafting of manuscript: O.U., M.C. Critical revision: M.O., S.Y., O.B. and C.A. All authors read and approved the final version of the manuscript.

Research Article

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Prognostic significance of systemic immune inflammation indices and prognostic nutritional index before CDK4/6 inhibitor therapy in hormone receptor positive, HER2 negative metastatic breast cancer patients

Hormon reseptör pozitif, HER-2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesi sistemik immün inflamasyon indekslerinin ve prognostik nutrisyonel indeksin prognostik önemi

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Abstract

Purpose: As systemic inflammatory indices and prognostic nutritional index are associated with poor prognosis in many tumor types, the goal of the present study was to ascertain their effect along with the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, C-reactive protein/albumin ratio, and systemic inflammatory response index on the progression-free survival (PFS) and overall survival (OS) of hormone receptor-positive HER2-negative (HR+/HER2−) metastatic breast cancer patients before CDK4/6 inhibitor treatment.

Materials and methods: The medical records of 79 patients with HR+/HER2− metastatic breast cancer who presented at the Medical Oncology Outpatient Clinic between January 2018 and May 2022 were retrospectively analyzed to gather relevant data measured before CDK4/6 inhibitor treatment in order to establish the effect of key markers on their PFS and OS.

Results: The median age of the participating patients, 70 (88.6%) of whom were postmenopausal, was 53 years (range 26-80 years). While 68 patients (86.1%) had a 0 performance score, 10 (12.7%) developed metastases during adjuvant endocrine therapy. Factors affecting PFS were age <50 (p=0.061), metastasis development during adjuvant endocrine therapy (p=0.09) and C-reactive protein/albumin ratio (p=0.019), while OS was primarily influenced by age <50 (p=0.069) and metastasis development during adjuvant endocrine therapy (p=0.012).

Conclusion: In the examined HR+/HER2− metastatic breast cancer patients, systemic inflammatory indices and prognostic nutritional index before CDK4/6 inhibitor treatment affected PFS. In addition, metastasis development during adjuvant endocrine therapy, progesterone receptor percentage, and age below 50 years emerged as prognostic factors for shorter overall survival.

Keywords: HR+/HER2− metastatic breast cancer, CDK4/6 inhibitors, systemic inflammatory indices, prognostic nutritional index, PFS.

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Öz
Amaç: Sistemik inflamatuvar indeksler ve Prognostik nutrisyonel indeks birçok tümör tipinde kötü prognoz ile ilişkilidir. Çalışmamızda hormon reseptörü pozitif HER2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesinde sistemik inflamatuar indeksi, prognostik nutrisyonel indeks, Nötrofil/Lenfosit oranı, Platelet/Lenfosit oranı, Lenfosit Monosit Oranı, C-reaktif protein/albümin oranı, sistemik inflamatuar yanıt indeksi gibi belirteçlerin progresyonsuz sağkalım ve tüm sağkalım üzerine etkisi araştırıldı.
Gereç ve yöntem: Ocak 2018-Mayıs 2022 tarihleri arasında Tıbbi Onkoloji polikliniğe başvuran hormon reseptörü pozitif HER2 negatif metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisi öncesi hastaların verileri retrospektif olarak incelendi. Bu belirteçlerin progresyonsuz sağkalım ve total sağkalım üzerine etkisi araştırıldı.
Bulgular: Çalışmaya 79 hasta dahil edildi. Hastaların ortanca yaşları 53 (aralık 26-80 yıl) idi. Yetmiş hasta (%88,6) postmenopozaldı. Hastaların 68'inin (%86,1) performans skoru 0'dı. Adjuvan endokrin tedavi sırasında 10 hastanın (%12,7) metastazı gelişti. PSK'yi etkileyen faktörler; yaş <50 (p=0,061), adjuvan endokrin tedavi sırasında metastaz gelişmesi (p=0,09) ve C-reaktif protein/albümin oranı (p=0,019) iken; TSK'ı etkileyen faktörler; yaş <50 (p=0,069) ve adjuvan endokrin tedavi sırasında metastaz gelişmesi (p=0,012) olarak bulundu.
Sonuç: Hormon reseptörü+/HER2 – metastatik meme kanserli hastalarda CDK4/6 inhibitörü tedavisinden önce hastaların sistemik inflamatuvar indeksleri ve prognostik nutrisyonel indeksi progresyonsuz sağkalımı etkilemektedir. Ayrıca hastalarda adjuvan endokrin tedavi sırasında metastaz gelişmesi, progesteron reseptör yüzdesi ve 50 yaşın altı olması tüm sağkalım için olumsuz prognostik faktörler olarak değerlendirildi.

Anahtar kelimeler: HR+/HER2- meme kanseri, CDK4/6 inhibitörü, sistemik inflamatuar indeksler, prognostik nutrisyonel indeks, PSK.

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Introduction

Breast cancer is the most common cancer in women and is the second leading cause of mortality after lung cancer [1]. In the molecular classification of breast cancer, the hormone receptor positive (HR+) and human epidermal growth factor receptor 2 negative (HER2−) group accounts for 60-65% of all breast cancers [2]. Endocrine therapy is the first-line treatment for women affected by HR+/HER2− metastatic breast cancer that have not experienced visceral crisis [3, 4]. However, only 20-40% of patients respond to aromatase inhibitors and 50% relapse within the first 8-14 months [5]. Therefore, due to the resistance to single-agent endocrine therapy, combination treatment strategies are increasingly being offered. As cyclin-dependent kinases (CDKs) are members of the serine/threonine kinase family that play a role in the regulation of the cell cycle [6], they have been shown to improve long-term survival when incorporated into the endocrine therapy [7-9]

The most important factors that play a role in the breast cancer prognosis are estrogen receptor (ER), progesterone receptor (PR), HER2 and Ki-67 percentage. It is known that neutrophils, platelets and lymphocytes, which play a role in the immune system and inflammation, contribute to tumor invasion, patient survival, and the development of distant organ metastases [10, 11].

In addition, the prognostic importance of ratios such as neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), and C-reactive protein/albumin ratio (CAR), as well as indices such as systemic inflammatory index (SII), systemic inflammatory response index (SIRI), and prognostic nutritional index (PNI) has been demonstrated in many tumor types [12-16]. For example, in a meta-analysis investigating the prognostic significance of NLR in breast cancer, higher NLR was associated with shorter PFS and OS [17]. Moreover, a meta-analysis of preoperative breast cancer patients indicated presence of a negative correlation between low LMR and incident-free survival [18]. Likewise, extant evidence shows that neoadjuvant breast cancer patients with high PNI had longer DFS and OS than those with low PNI [19].

However, the effects of these prognostic indices on the survival in patients with HR+/HER2− metastatic breast cancer receiving CDK4/6 inhibitor treatment has never been investigated. This gap in extant literature is

addressed in the present study by examining whether the SII, PNI, NLR, PLR, LMR, CAR, and SIRI values before the CDK4/6 inhibitor treatment influence the survival (PFS and OS) in HR+/HER2− metastatic breast cancer patients, and whether these parameters can be used as prognostic markers in clinical practice.

Materials and methods

Following the approval by the Pamukkale University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee, medical files of HR+/HER2− metastatic breast cancer patients who attended the Pamukkale University Medical Oncology Outpatient Clinic between January 2018 and May 2022 prior to commencing CDK4/6 treatment were retrospectively analyzed and pertinent data was recorded. The study sample included 79 female patients aged 18-80 years, who were pathologically diagnosed with invasive ductal carcinoma, ECOG PS 0-1, HER2− with ER and/or PR >1%, without evidence of visceral crisis, and who subsequently received CDK4/6 inhibitor with endocrine therapy. Age, menopausal status, previous treatments, ECOG performance status, ER, PR and Ki-67 percentages, number of metastases, and metastasis locations were obtained from their files, while neutrophil, lymphocyte, monocyte, platelet, CRP and albumin levels were obtained from their hemogram panels stored in the Hospital Laboratory Information System. Hemogram parameters were analyzed by electrical impedance and optical density method using Mindray CAL 8000 (Shanghai, China) auto analyzer, while CRP and albumin levels were established via electrochemiluminescence method in Cobas 702 (Roche Diagnostics, Manheim, Germany) analyzers. The obtained values were used to calculate PNI, SII, NLR, PLR, LMR, CAR and SIRI based on the following formulae:

PNI = serum albumin level (g/dL) × 10+lymphocyte count (/nL) × 0.005

SII = platelet count × neutrophil count / lymphocyte count

NLR= neutrophil count/lymphocyte count

PLR = platelet count/lymphocyte count

LMR = lymphocyte count/monocyte count

CAR = C-reactive protein/albumin level

SIRI = neutrophil count × monocyte count/ lymphocyte count

Overall survival (OS) was defined as the time that elapsed from the date of metastasis diagnosis until mortality, whereas progression-free survival (PFS) was defined as the time period from the date of metastasis diagnosis until disease progression.

Statistical analyses

Mann-Whitney U and Chi-squared or Fisher's exact test were used to determine the values and percentages of clinicopathological parameters. The PNI, SII, NLR, PLR, LMR, CAR and SIRI threshold values were established through Receiver operating characteristic (ROC) analysis, and Kaplan-Meier and log rank analysis were conducted to obtain PFS and OS values. Univariate and multivariate analyses were performed using Cox proportional hazards model, whereby hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were recorded for each factor. All analyses were performed using SPSS (version 23.0) software package (SPSS Inc., Chicago, IL, USA) and $p<0.05$ was considered statistically significant.

Results

The data of 79 female patients (median age 53 years, range 26-80 years) with metastatic HR+/HER2− invasive ductal carcinoma without visceral crisis obtained before CDK4/6 inhibitor + endocrine therapy was evaluated. As shown in Table 1, the sample comprised of 70 (88.6%) postmenopausal patients, 68 (86.1%) patients with ECOG 0 performance status, and 10 (12.7%) patients who developed metastasis during adjuvant endocrine therapy. Moreover, 15 (19%) patients had a single metastatic region, while ≥5 metastatic regions were noted in 54 (68.4%) cases. There were 25 (31.6%) patients with only bone metastases, while 30 (38.0%) had visceral metastases (but none experienced visceral crisis).

ROC analysis was performed to obtain the PNI, SII, NLR, PLR, LMR, CAR and SIRI

Table 1. Patient characteristics

	n	%
Age		
>50 years	45	57
≤50 years	34	43
Performance status 0	68	86.1
1	11	13.9
Menopausal status		
Postmenopausal	70	88.6
Premenopausal	9	11.4
Metastasis region		
Bone	25	31.6
Visceral	30	38.0
Both	24	30.4
Metastasis count		
Single	15	19.0
2	5	6.3
3	5	6.3
≥4	54	68.4
Treatment type		
Palbociclib+Letrazole	15	19.0
Ribociclib+Letrazole	33	41.8
Palbociclib+Fulvestrant	15	19.0
Ribociclib+Fulvestrant	16	20.2
Treatment before CD4/6 inhibitor		
Received	44	55.7
Not Received	35	44.3
Treatment before CD4/6 inhibitor		
1st line	12	15.2
2nd line	14	17.7
3rd line and onwards	18	22.8
CD4/6 treatment response		
Progression	18	22.8
No Progression	61	72.2
Patient's last condition		
Alive	68	86.1
Deceased	11	13.9

threshold values on the basis of pertinent laboratory findings and the results are reported in Table 2, along with the AUC, *p* values, and 95% CIs. As can be seen from the tabulated data, the threshold value for PNI was 48.65 (sensitivity 55.6%, specificity 77%); the threshold value for SII was 718637.6 (sensitivity 61.1%, specificity 67%); the threshold value for SIRI was 1134.9 (sensitivity 66.1%, specificity 62.7%); the threshold value for PLR was 184. 9 (sensitivity 66.7%, specificity 73.8%); the threshold for CAR was 2.14 (sensitivity 72.2%, specificity 78.7%); the threshold for NLR was 2.68 (sensitivity 61.1%, specificity 70.5%); and the threshold value for LMR was 3.4 (sensitivity 72%, specificity 69%).

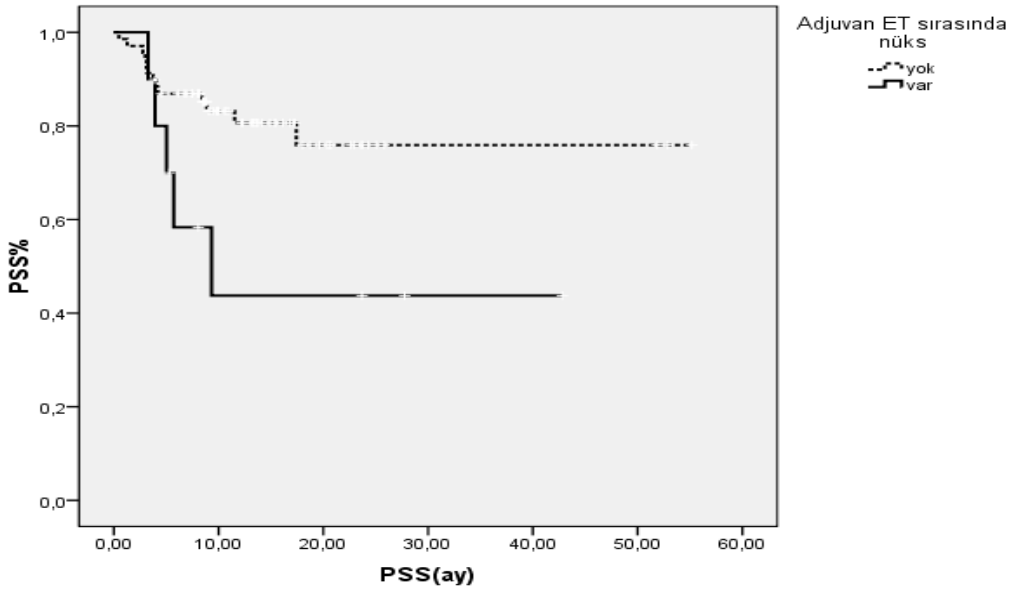
Table 2. ROC analysis values

Values	AUC	SE	*P* value	95% Confidence Interval
SII (718 637.6)	.637	.075	.080	.489
SIRI (1134.9)	.673	.077	.026	.521
PNI* (48.65)	.629	.078	.098	.476
PLR (184.9)	.682	.076	.019	.532
CAR (2.14)	.759	.069	.001	.623
NLR (2.68)	.679	.070	.022	.542
LMR* (3.4)	.679	.079	.021	.524

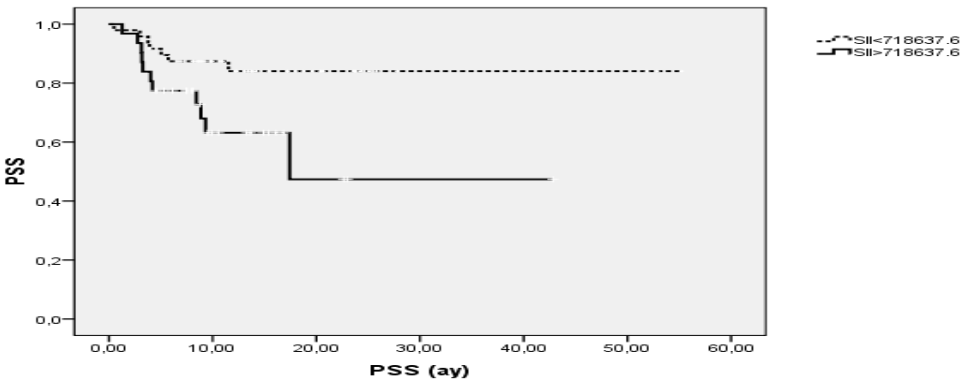
* Lower values in the ROC analysis indicate a positive test

For the examined cohort, the median follow-up was 66.2 months (11.3-308.4), while the median progression-free survival (mPFS) was 41.8+2.8 (95% CI 36.2-47.4) months, and the median overall survival (mOS) was 257.5+4.0 (95% CI 230.1-284.9) months. In addition, 18 (22.8%) patients progressed and 11 (13.9%) died during the investigated period. When the effect of clinicopathological and laboratory parameters on PFS was evaluated, metastasis development during adjuvant endocrine therapy (p=0.033), SII>718637.6 (p=0.01), SIRI>1134.9 (p=0.02), PNI<48.64 (p=0.006), PLR>184.9 (p=0.001), CAR>2.14 (p=0.000), NLR>2.68 (p=0.02) and LMR<3.4 (p=0.000) were found to adversely affect PFS duration Figure 1(a-h). Moreover, OS was shorter in patients with PR below 50% (p=0.028), those who developed metastases during adjuvant endocrine therapy (p=0.002), those that had PLR >184.9 (p=0.07) and those in whom CAR >2.14 was noted (p=0.09), as shown in Table 3, Figure 2(a-d).

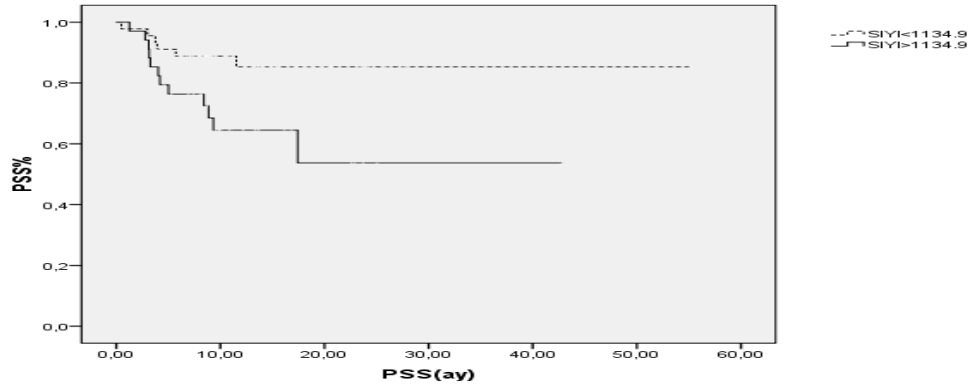
The findings yielded by the Cox proportional hazards model identified age <50 (p=0.061), metastasis development during adjuvant endocrine therapy (p=0.09) and CAR (p=0.019) as the factors affecting PFS (Table 4), while OS was influenced by age <50 years (p=0.069) and metastasis development during adjuvant endocrine therapy (p=0.012) (Table 5).



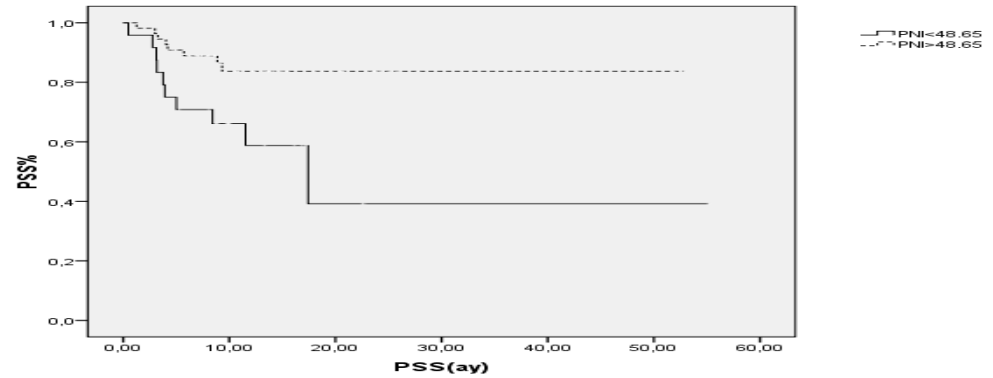
a. Presence of recurrence during adjuvant treatment (p=0.033)



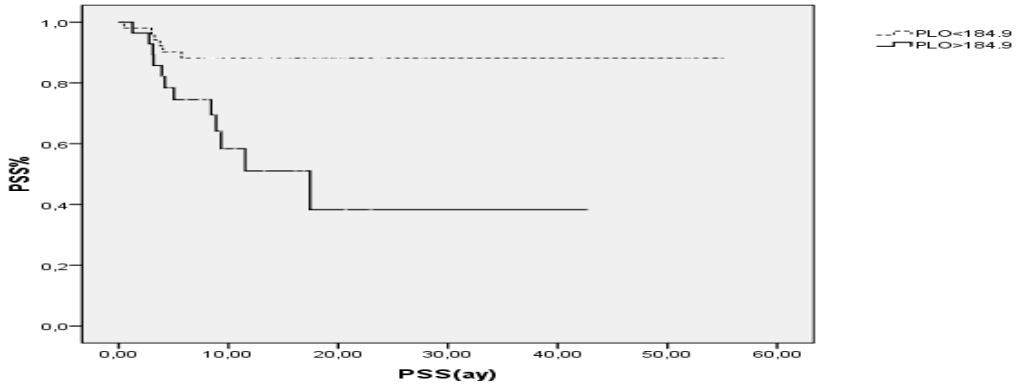
b. SII>718637.6 (*p*=0.01)



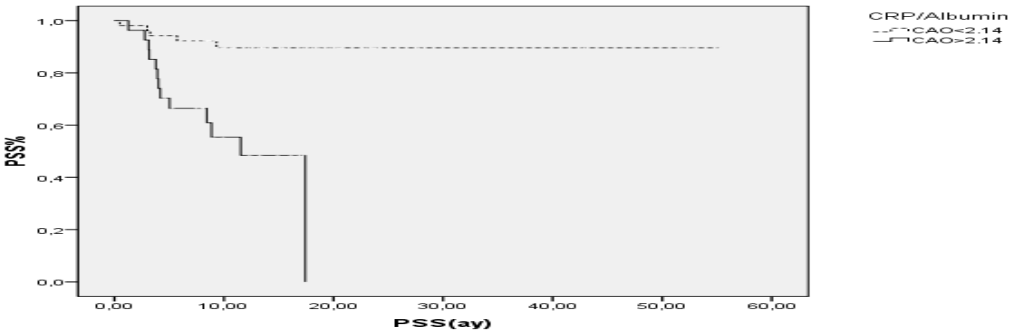
c. SIRI>1134.9 (*p*=0.02)



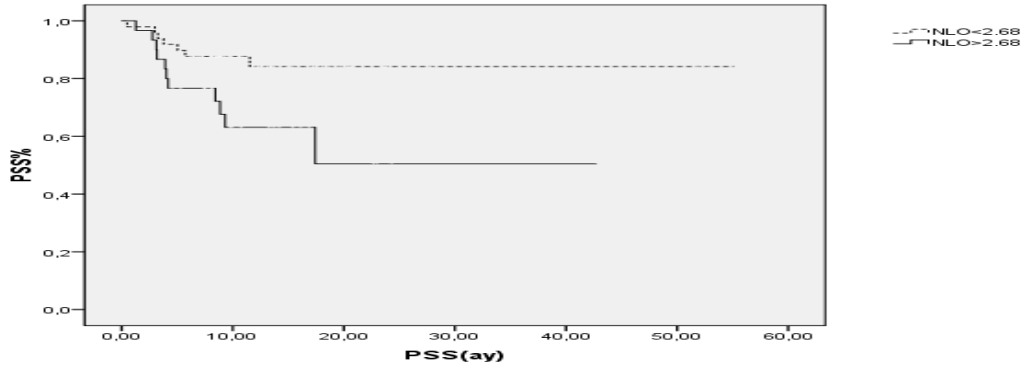
d. PNI<48.64 (*p*=0.006)



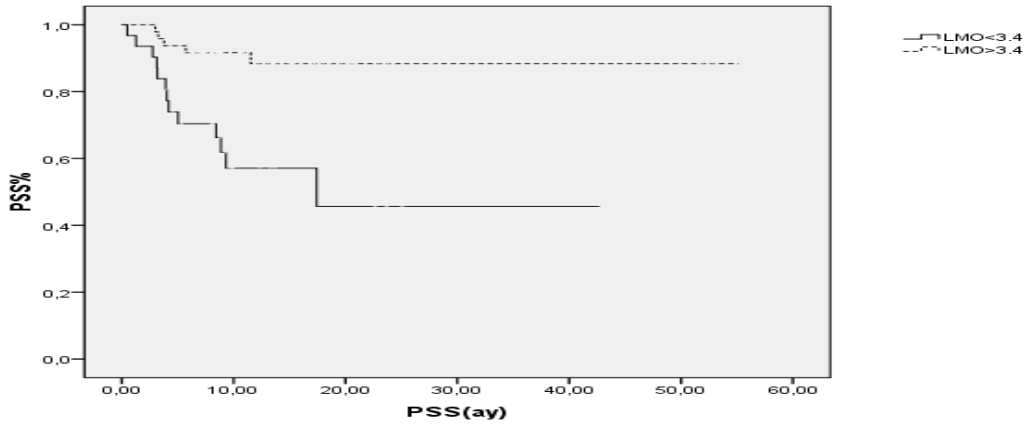
e. PLR>184.9 (*p*=0.001)



f. CAR>2.14 (*p*=0.000)



g. NLR>2.68) (*p*=0.02)

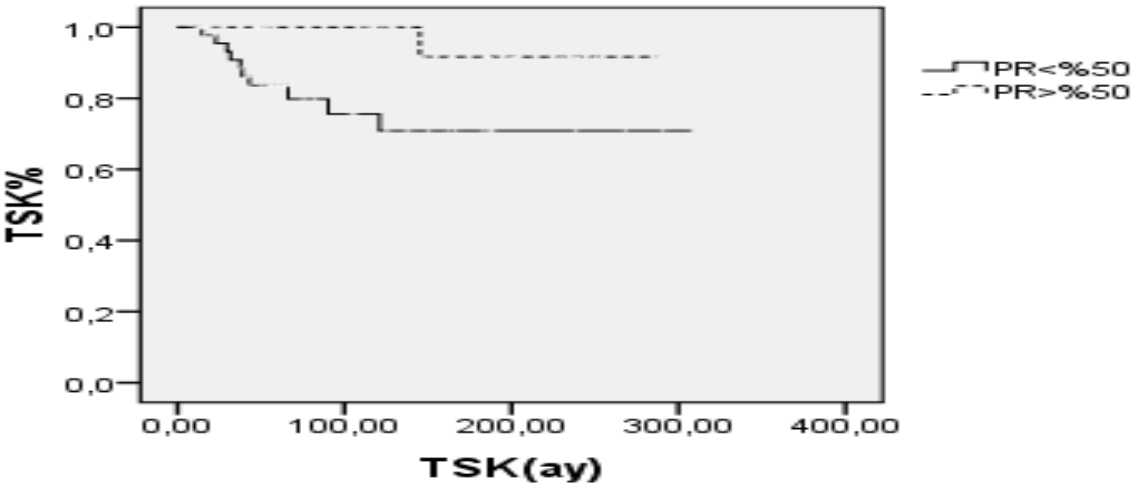


h. LMR<3.4 (*p*=0.000)

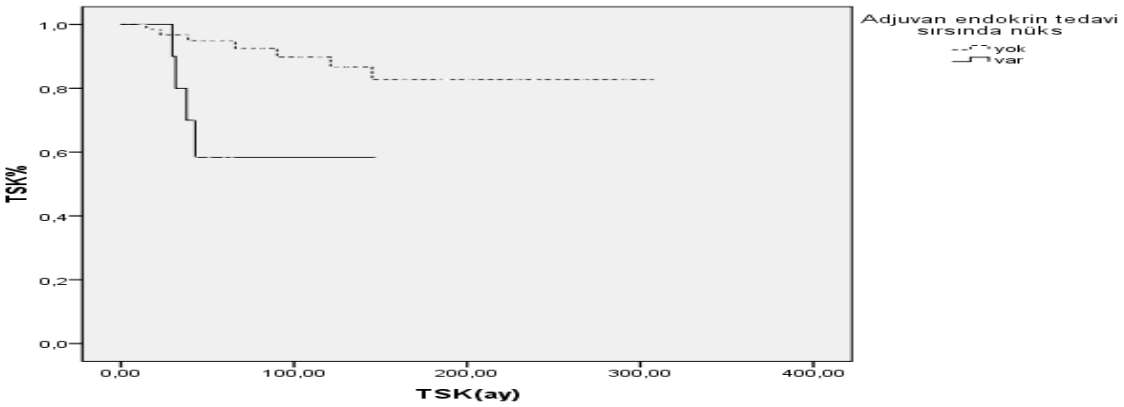
Figure 1. Kaplan Meier survival curves for factors affecting progression-free survival (PFS)

Table 3. PFS and OS values according to clinicopathological and laboratory values

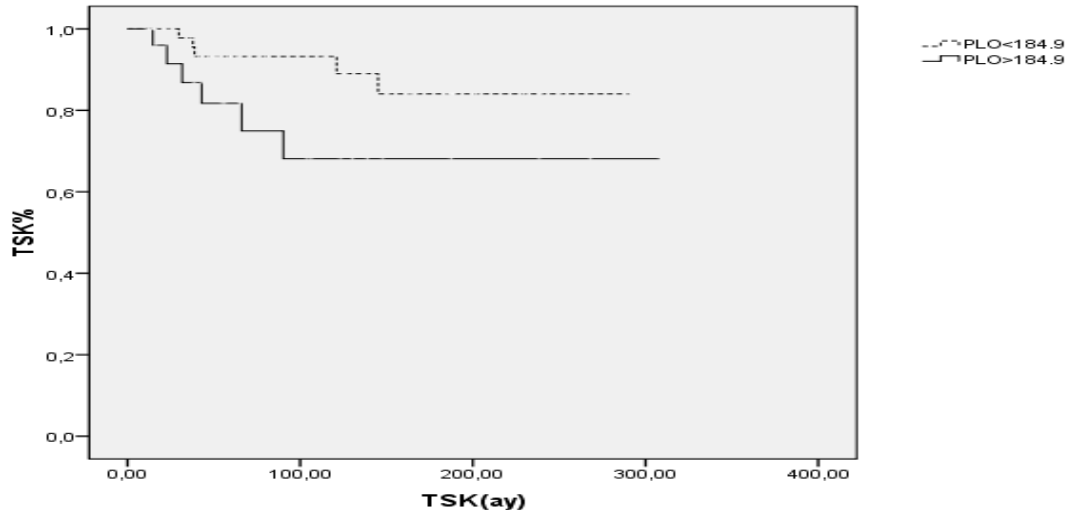
Parameters	Progression-free survival (months) (95%CI)	Overall survival (months) (95%CI)
Age ≤50 years (n=34)	34.6±5.3 (24.1-45.2)	247.9±2.8 (205.2-290.6)
Age >50 years (n=45)	44.7±2.8 (39.1-50.3) *p*=0.08	250.4±17.1 (217.1-283.8) *p*=0.49
ER <%50 (n=12)	41.7±6.7 (28.5-54.9)	251.4±25.7 (200.9-301.8)
ER ≥%50 (n=67)	40.3±2.9 (34.6-46.1) *p*=0.657	254.2±16.6 (221.5-286.8) *p*=0.71
PR <%50 (n=47)	39.5±3.6 (32.3–46.7)	235.7±20.1 (196.3-275.1)
PR ≥%50 (n=32)	41.5±4.7 (32.2-50.7) *p*=0.225	276.2±11.4 (253.8-298.5) *p*=0.028*
Ki67 <%20 (n=41)	44.3±3.4 (37.5-51.1)	255.7±21.5 (213.6-297.7)
Ki67 ≥%20 (n=38)	36.6±4.2 (28.2-44.9) *p*=0.444	242.6±16.7 (209.7-275.5) *p*=0.87
Metastasis during adjuvant endocrine therapy (n=10)	21.9+6.4 (9.4-34.5)	101.1±17.9 (65.8-136.2)
Metastatic at diagnosis (n=69)	43.7+2.9 (37.8-49.5) ***p*=0.033***	270.0±13.5 (243.5-296.4) ***p*=0.002***
SII <718637.6 (n=48)	47.2±2.7 (41.7- 52.7)	250.4±15.3 (220.4-280.4)
SII ≥718637.6 (n=31)	25.1±4.5 (16.1-33.9) ***p*=0.01***	249.4±23.6 (203.1- 295.6) *p*=0.428
SIRI <1134.9 (n=45)	47.8±2.8 (42.3-53.4)	241.5±18.3 (205.5-277.6)
SIRI ≥1134.9 (n=34)	26.7±3.8 (19.2-34.3) ***p*=0.02***	261.1±19.4 (223.0- 299.1) *p*=0.100
NLR <2.68 (n=49)	47.3±2.8 (41.8-52.7)	247.3±16.4 (215.2-279.4)
NLR ≥2.68 (n=30)	25.8±4.2 (17.7-34.0) ***p*=0.02***	253.2±22.2 (209.6- 296.7) *p*=0.65
PLR ≥184.9 (n=28)	21.7±4.4 (13.2-30.3)	226.0±28.5 (170.2- 281.8)
PLR <184.9 (n=51)	49.1±2.3 (44.4-53.6) ***p*=0.001***	259.4±13.3 (233.4-285.5) *p*=0.07
LMR ≤3.4 (n=31)	23.6±4.1 (15.6-31.6)	242.7±23.4 (196.8-288.6)
LMR >3.4 (n=48)	49.5±2.4 (44.7-54.3) ***p*=0.000***	233.6±14.3 (205.5- 261.6) *p*=0.36
PNI <48.65 (n=24)	27.2±7.3 (12.9-41.5)	244.9±24.9 (196.1-293.9)
PNI ≥48.65 (n=55)	45.1±2.5 (40.2-50.1) ***p*=0.006***	227.4±15.0 (198.2- 256.8) *p*=0.410
CAR <2.14 (n=52)	49.9±2.2 (45.5-54.3)	257.1±14.2 (229.4-284.8)
CAR ≥2.14 (n=27)	11.4±1.3 (8.7-14.0) ***p*=0.000***	232.5±26.7 (180.1- 284.8) *p*=0.09



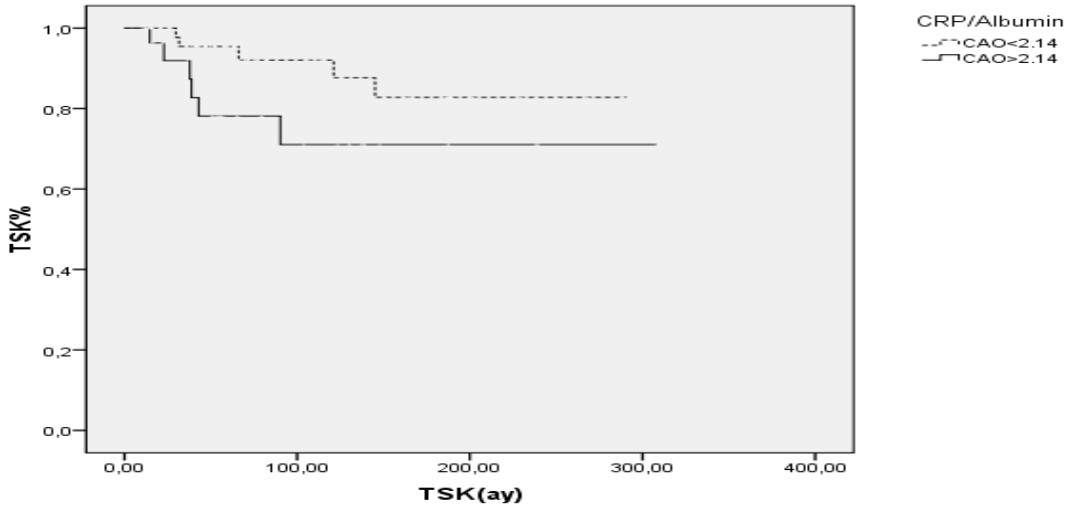
a. PR<%50 (*p*=0.028)



b. Recurrence during adjuvant treatment (p=0.002)



c. PLR >184.9 (p=0.07)



d. CAR >2.14 (p=0.09)

Figure 2. Kaplan Meier Survival curves for factors affecting overall survival (OS)

Table 4. Cox Proportional Hazard Model for progression-free survival (PFS)

Variables in the Equation								
							95.0% CI for Exp (B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Adjuvan ET met	-1.058	.631	2.813	1	.093	.347	.101	1.195
SII	-.583	.929	.394	1	.530	.558	.090	3.450
SIRI	.776	.885	.769	1	.380	2.173	.384	12.304
PNI	.049	.615	.006	1	.936	1.051	.315	3.506
PLR	-.723	.602	1.442	1	.230	.485	.149	1.579
CAR	-1.563	.669	5.456	1	.019	.210	.056	.778
NLR	.318	.823	.149	1	.699	1.374	.274	6.895
LMR	1.038	.778	1.780	1	.182	2.823	.615	12.964
Age	-.038	.020	3.497	1	.061	.963	.925	1.002

Table 5. Cox Proportional Hazard Model for overall survival (OS)

Variables in the Equation								
							95.0% CI for Exp (B)	
	B	SE	Wald	df	Sig.	Exp(B)	Lower	Upper
Adjuvan ET met	-2.054	.816	6.329	1	.012	.128	.026	.635
SII	-.691	1.049	.433	1	.510	.501	.064	3.919
SIRI	.495	1.012	.239	1	.625	1.640	.226	11.914
PNI	.312	.844	.136	1	.712	1.366	.261	7.144
PLR	-.927	.935	.984	1	.321	.396	.063	2.471
CAR	-1.188	.920	1.666	1	.197	.305	.050	1.851
NLR	1.472	1.256	1.373	1	.241	4.356	.372	51.054
LMR	.074	1.101	.005	1	.946	1.077	.125	9.308
Age	.013	.029	.209	1	.647	1.013	.957	1.073
PR%	2.676	1.470	3.315	1	.069	14.526	.815	258.858

Discussion

In our study involving 79 HR+/HER2− metastatic breast cancer patients, metastasis development during adjuvant endocrine therapy, as well as high SII, SIRI, PLR, CAR and NLR, and low PNI and LMR, were found to affect PFS. Factors influencing the overall survival were PR <50%, metastasis development during adjuvant endocrine therapy, high PLR and CAR >.

These findings are supported by the available evidence, indicating that SII—as a new inflammatory marker calculated using neutrophil, platelet and lymphocyte counts in peripheral blood—can be utilized as a prognostic factor in many tumor types [20-22]. In a meta-analysis conducted by Ji and Wang [23], high SII was found to be associated with adverse prognosis in patients with gynecological and breast cancer. When the available data was segregated by tumor type and race, the significant relationship with HCC and PFS remained. The authors further noted that patients with high SII had shorter OS duration. In patients with breast cancer receiving neoadjuvant treatment, Chen et al. [24] found that SII exhibited similar relationship with PFS and OS. On the other hand, in the present study, in the group without lymphovascular invasion, more frequent recurrence was associated with higher SII. However, thus far, no investigation has been conducted to ascertain the prognostic importance of SII in patients with HR+/HER2− metastatic breast cancer using CDK4/6 inhibitors. This shortcoming was addressed in the current study, in which high SII was associated with shorter PFS duration.

SIRI is another systemic inflammatory marker that plays an important role in the prognosis of many malignant tumors [25-27], prompting research into its relevance in breast cancer. In a study conducted by Hua et al. [27] including preoperative postmenopausal breast cancer patients examining the prognostic effect of SIRI, although the duration of HCC was shorter in patients with high SIRI, it was not statistically significant. However, high SIRI was correlated with shorter OS. On the other hand, Jiang et al. [28] investigated the prognostic significance of SIRI and LMR in breast cancer patients receiving neoadjuvant treatment, and noted that SIRI was a better prognostic factor than LMR. Still, the prognostic significance of SIRI in patients with metastatic breast cancer has never been investigated, making our finding

that high SIRI exerts a negative effect on PFS in metastatic HR+/HER2− patients using CDK4/6 inhibitors highly pertinent.

The prognostic nutritional index (PNI) is calculated using serum albumin level and total lymphocyte count. Although PNI has been frequently used to determine the treatment effect and survival in cancers of the gastrointestinal tract (such as colorectal cancer or hepatocellular cancer), its prognostic value has recently been demonstrated in other cancer types [29-31]. In contrast to other inflammatory markers, lower PNI was associated with worse prognosis, as well as shorter OS and DFS durations. In their study involving 785 patients, Chen et al. [19] aimed to ascertain whether PNI could be a prognostic marker in patients with neoadjuvant breast cancer and established a PNI threshold value of 51. The authors further noted that breast cancer patients with high PNI had longer HSK and OS than those with low PNI. In addition, Hua et al. [32] investigated the prognostic importance of PNI in patients with T1-2 N1 breast cancer and its potential as a predictor for guiding radiotherapy. Their patients were segregated into four groups and the PNI threshold value was 52. In the high-PNI group, the five-year survival rate was 94.9%, but declined to 87.3% in the low-PNI group. In addition, when survival in patients with T1-2 N1 breast cancer receiving radiotherapy was assessed in relation to PNI, the high-PNI group had a significantly longer OS than the low-PNI group (p=0.033; Hazards ratio [95% CI]=0.175 [0.035-0.868]). Although in extant research different threshold values were determined by ROC analyses, regardless of the threshold value, the general conclusion was that PNI has an effect on OS and PFS. In a study involving metastatic breast cancer patients using eribulin conducted by Zhu et al. [33], after multiple-line treatment, PNI was shown to be an independently associated with OS.

As PLR is an important proinflammatory marker, its effect on cancer prognosis has been extensively investigated. In a retrospective study conducted by Anwar et al. [34], the effect of PLR on PFS and metastasis development was found to be statistically insignificant. However, in our study, PLR above the threshold value determined by ROC analysis (>184.9) was found to be associated with shorter PFS. The differences in the obtained results likely arise due to the different threshold values, as well as the number of patients evaluated and the type of metastatic disease. Therefore, further studies with a larger number of patients are needed to resolve these inconsistencies. Anwar et al. [34] also established that shorter PFS and shorter duration of distant metastatic disease development were associated with higher NLR. In our cohort, those with higher NLR had shorter PFS. Similarly, based on their meta-analysis including 32 studies and 8.215 advanced cancer patients, Li et al. [13] found that higher PLR was associated with shorter OS and PFS.

CRP, which is an important acute phase reactant in infection and inflammation, is synthesized by the liver. As albumin is a protein involved in inflammation and has many functions in circulation, it has been subject to considerable body of research, indicating that CRP/albumin ratio (CAR) has negative effects on the quality of life and treatment efficacy in many cancers [35, 36]. Similarly, following their large-scale observational study involving large group of patients with different cancer types, Zhu et al. [37] concluded that only CRP and its increase and decrease patterns can predict malignancy. In Zhou et al. [38] retrospective study examining the prognostic impact of CAR in patients with non-metastatic breast cancer, multivariate analysis showed that high CAR was an independent risk factor for long-term outcome, as well as predicted short PFS and OS. However, CAR in HR+/HER2− metastatic breast cancer patients receiving CDK4/6 inhibitor treatment has never been studied. In our cohort, although CAR showed a similar relationship with PFS in patients with metastatic HR+/HER2− breast cancer, there was no statistically significant relationship with OS.

LMR has been analyzed as a prognostic factor in many cancer groups, and the findings suggest that low LMR may be associated with shorter PFS and OS. In a study conducted by Zhang et al. [39], in which the prognostic effect of LMR was analyzed in 938 patients with stage 1-3 breast cancer, low LMR was associated with more adverse prognosis. When the patients were segregated into the HR+, HR− and HER2− groups, low LMR was found to be a statistically significant predictor of HCC in the HER2− group only. As these findings do not align with the results obtained in the current study, there is

an evident need for more research involving much larger patient samples and longer follow-up periods to ascertain the prognostic value of LMR for OS.

Metastasis development while on adjuvant therapy was associated with shorter PFS and OS in our study, which is expected, as endocrine resistance (ER) is not uncommon in patients with hormone-positive breast cancer and may have multiple causes. For example, up to 30% of metastatic ER-positive breast cancers may have activating mutations in the estrogen-binding domain of the gene encoding ER (ESR1) [40]. Resistance to endocrine therapy may be de novo or acquired during treatment. Moreover, loss of estrogen dependence can be due to loss of ER, or can arise even when ER positivity persists. However, patients can also develop resistance to a specific therapy, although the tumor is still estrogen dependent as a result of ESR1 mutations, signaling pathways of growth factor receptors, activation of pP13K/AKT/mTOR and RAF/MEK/ERK pathways, and/or changes in cell cycle checkpoints [41]. In a study conducted by Grasic Kuhar et al. [42], hormone positivity was found to be an independent prognostic factor for cancer recurrence and mortality in the second decade after surgery in patients with early stage breast cancer. In other words, hormone-positive patients usually experience late recurrence. Grasic Kuhar et al. [42] similarly found that OS of recurrent patients was significantly shorter than that measured for non-recurrent patients. In our study, both PFS and OS were short in patients who developed metastases during adjuvant treatment, which is expected and consistent with the findings reported in extant literature.

Overall, the cumulative evidence in this field suggests that PNI, SIRI, SII, LMR, CAR, and NLR, which are easy to evaluate in clinical practice, may have prognostic significance. In all studies that have focused on these prognostic markers, data was analyzed retrospectively. However, this is the first attempt to determine whether immune-inflammation indices and prognostic nutritional index can be used as prognostic factors in HR+/HER2− metastatic breast cancer patients receiving CDK4/6 inhibitor treatment. Although the number of patients was relatively small and the follow-up period was short, the findings are still valuable as they focus on a specific group of patients. Nonetheless, our results should be validated through additional investigations involving a larger number of patients and longer follow-up durations.

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

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Authors' contributions to the article

B.C.D and A.Y. constructed the main idea and hypothesis of the study. B.C.D. and A.Y. developed the theory and arranged/edited the material and method section. B.C.D., T.D., T.G.K., M.O., and C.K. have done the evaluation of the data in the results section. Discussion section of the article written by B.C.D., A.Y., A.G.D., B.Y.T., S.D. and G.G.D. 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 thoracic computed tomography interpretation by emergency medicine residents with regards to accuracy and confidence

Acil tıp araştırma görevlilerinin, toraks bilgisayarlı tomografisi yorumlamada doğruluk ve özgüven açısından değerlendirilmesi

Alten Oskay

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Abstract

Purpose: Interpretation of thoracic computed tomography (CT) scans by emergency department (ED) physicians is important especially in crowded EDs. The aim of this study is to assess the proficiency and confidence of ED physicians with varying levels of experience in interpreting thoracic CT.

Materials and methods: A total of 25 pathological and 5 normal thoracic CT images were interpreted by 32 ED residents, initially without clinical information, then with. After each session the participants were asked to score their confidence on a scale of 1 to 10. At the end of the study, the results were compared between seniors and junior residents.

Results: The median age of the participants was 29 years (24-34). Twenty (62.5%) of the residents were junior residents. There were no significant differences between the two resident groups in terms of accurate diagnosis rates, regardless of the clinical information (p=0.307 and p=0.061). The physicians' certainty of their own diagnosis mostly does not seem to be statistically different in these diagnoses. The seniors are more confident in the diagnosis of the CT scans they evaluated without clinical information (p=0.004), while when the clinical information is added, the confidence of the junior physicians also increase (p=0.087).

Conclusion: Both senior and junior emergency medical residents are able to interpret thoracic CT images with a high degree of accuracy, both for COVID-19 and for other emergency diagnoses. Senior physicians were confident in their decisions regardless of whether they are accurate or not, solely by visual inspection, whereas junior residents displayed similar confidence when clinical information was available.

Keywords: Clinical information, confidence, emergency medicine, residents, thoracic computed tomography.

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Öz

Amaç: Özellikle kalabalık acil servislerde, toraks bilgisayarlı tomografisinin (BT) acil hekimleri tarafından yorumlanması önemlidir. Çalışmanın amacı, toraks BT'sinin yorumlanmasında farklı düzeylerde deneyime sahip acil tıp araştırma görevlisi hekimlerinin yeterliliklerini ve özgüvenlerini değerlendirmektir.

Gereç ve yöntem: Yirmibeş patolojik ve 5 normal toraks BT görüntüsü, başlangıçta klinik bilgi olmadan, daha sonra da klinik bilgi eklenerek 32 acil tıp araştırma görevlisi hekim tarafından yorumlanmıştır. Her oturumdan sonra katılımcılardan kararlarına olan güvenlerini 1 ila 10 arasında bir ölçekte puanlamaları istenmiştir. Çalışmanın sonunda, elde edilen sonuçlar kıdemli (2 yıl ve üzeri acil tıp tecrübesi olan) ve daha az tecrübesi olan araştırma görevlisi hekimlerin arasında karşılaştırılmıştır.

Bulgular: Katılımcıların ortanca yaşı 29 (24-34) idi. Araştırma görevlisi hekimlerin 20'si (%62,5) daha az tecrübesi olan gruptaydı. İki araştırma görevlisi hekim grubu arasında, klinik bilgiden bağımsız olarak, doğru tanı koyma oranları açısından anlamlı fark saptanmamıştır (p=0,307 ve p=0,061). Kıdemliler klinik bilgi olmadan toraks BT'lerini değerlendirirken, kendilerine, daha az tecrübesi olan araştırma görevlisi hekimlere göre, daha fazla güvenmektedirler (p=0,004). Klinik bilgi eklendiğinde daha az tecrübesi olan araştırma görevlisi hekimler de kıdemli hekimler kadar kendi tanılarına güvenmektedirler (p=0,087).

Sonuç: Hem kıdemli hem de daha az tecrübesi olan acil tıp araştırma görevlisi hekimler, toraks BT görüntülerini hem COVID-19 hem de diğer acil teşhisler için yüksek derecede doğrulukla yorumlayabilmektedir. Kıdemli araştırma görevlisi hekimler tanılarına, tanının doğruluğundan bağımsız olarak, klinik bilgi olmadığı durumda bile güveniyorken, daha az tecrübesi olan araştırma görevlisi hekimler ise klinik bilgi eklendiğinde benzer bir güvene sahip olmaktadırlar.

Anahtar kelimeler: Acil tıp, araştırma görevlisi hekim, klinik bilgi, özgüven, toraks bilgisayarlı tomografisi.

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Introduction

Thoracic CT scans account for 10% of the computed tomographies (CTs) ordered in the emergency departments (EDs) [1]. During the COVID-19 pandemic, admissions to EDs for respiratory tract symptoms have significantly increased, as well as the use of thoracic CT in EDs. Thoracic CT is an imaging tool that is easier to interpret and evaluate than other CTs, and has a significant impact on the clinical decision of new physicians [2].

In overcrowded areas, such as hospital EDs, patients are more likely to undergo laboratory and CT imaging tests [3]. Furthermore, the number of radiologists in the institutions with high patient admissions may be insufficient, and they may not be able to provide service in out-of-hours periods. In some such health institutions, images with teleradiology can be reported by radiologists outside the hospital during non-standard hours [4]. However, this process can be time-consuming. Both the presence of high patient admissions and the necessity of rapid patient evaluation, as well as the limited radiological support, often compels physicians from various specialties to evaluate the radiological images associated with their field. Although there are trainings on the interpretation of radiological images during the residency training process in many educational institutions, radiology residents are usually available in the institutions providing resident training and reporting the CTs. Interestingly, studies show that physicians who graduate from institutions without on-site radiologists and read their own radiographs during their training period have increased self-confidence in patient care after graduation [5].

The aim of this study was to assess the proficiency of ED physicians with varying levels of experience in interpreting thoracic CT, a commonly used imaging method in EDs.

Materials and methods

For the study, ethics committee approval was obtained from Pamukkale University Non-Interventional Clinical Research Ethics Committe. Following the ethics committee approval, all ED residents working in our institution who agreed to participate in the study were included after filling out the informed voluntary consent form. Demographic data of the residents, including their years of experience in the medical profession and in the ED, were recorded. A total of 25 pathological and 5 normal thoracic CT images were prepared by a Radiology specialist with at least 10 years of professional experience. The images were initially presented to the participating ED residents in the computer-based study without providing clinical information. The physicians were then tasked with identifying any pathological findings in these images, determining whether the images were normal or abnormal, and assigning a score out of 10 to represent their confidence level. The thoracic CT diagnoses included 14 cases of viral pneumonias (confirmed COVID diagnosis by PCR), 6 lobar pneumonias, 5 normal, 3 congestive heart failure, 3 traumas and 1 pulmonary embolism. After one month, the same thoracic CT images were shown to the participants with the addition of clinical information and they were asked to identify whether they were pathological or normal once more. Finally, the participants were asked to score their confidence on a scale of 1 to 10.

At the end of the study, the correct identification rates of the residents on the images on thoracic CT and the comparison between seniors and junior residents were described. In our institution, residents who have completed the second year of training in the ED are evaluated with an exam and given the title of “senior resident”, if he/she is successful. This title signifies their ability to assume responsibilites within the ED under expert supervision until their graduation.

Statistical analyses

All statistical analyses were performed using SPSS 23.0 (IBM SPSS Statistics 23 (Armonk, NY: IBM Corp.)) software. Continuous variables were defined by the mean ± standard deviation and the median (minimum-maximum values). Kolmogorov Smirnov and Shapiro Wilk tests were used for determination of normal distribution. When parametric test assumptions were met, Independent samples T test was used for comparison between independent groups. Mann Whitney U test was used when parametric test assumptions were not provided. Chi Square test was used for categorical variables. Statistical significance was determined as $p \leq 0.05$.

Results

Out of the 32 ED residents who participated in the study, 9 (28%) were female. The median age of the participants was 29 years (minimum 24 – maximum 34 years). Among the residents, 20 (62.5%) were classified as junior residents (Table 1). The average duration of residency training in the ED during the study period was 11.35 (±6.16) months for juniors and 38.50 (±8.32) months for seniors. All medical experience was 29.45 (±17.17) months for juniors and 55.33 (±13.59) months for seniors (Table 2).

All 32 participants evaluated all 30 scans. There were no significant differences between the two resident groups in terms of accurate diagnosis rates for images, regardless of the clinical information (p=0.307 and p=0.061). In pathological diagnoses, there were no discernible differences between the study groups, and the correct diagnosis rates in the presence and absence of clinical information (Table 2). In addition, the physicians' certainty of their own diagnosis mostly does not seem to be statistically different in these diagnoses (Table 3).

Table 1. Identification data of the residents participating in the study

Gender, female, n (%)	9 (28.1)
Age, years	28.69±2.15
Junior resident, n (%)	20 (62.5%)
Residency time in ED, months	21.53±15.04
Experience in medicine, months	39.16±20.20

ED: emergency department, * mean±SD

Table 2. Accurate diagnostic data of senior and junior residents

	Senior Resident	Junior Resident	*p*
Gender, female, n (%)	5 (41.7)	4 (20)	0.180
Age, years	30 (29-34)	28 (24-30)	**0.000**
Residency time in ED, months	38.50±8.32	11.35±6.16	**0.000**
Experience in medicine, months	55.33±13.59	29.45±17.17	**0.000**
COVID-19 Dx w/o CI	3.5 (0-12)	5 (0-13)	0.716
COVID-19 Dx with CI	4.5 (0-13)	6 (0-13)	0.924
Viral pneumonia Dx w/o CI	11.5 (4-13)	11 (0-13)	0.924
Viral pneumonia Dx with CI	12 (6-14)	12 (0-14)	0.985
Lobar pneumonia Dx w/o CI	3 (1-5)	3 (0-5)	0.893
Lobar pneumonia Dx with CI	3 (1-5)	3 (1-4)	0.774
Pulmonary embolism Dx w/o CI	1 (0-1)	1 (0-1)	0.408
Pulmonary embolism Dx with CI	1 (0-1)	1 (0-1)	0.893
Congestive heart failure Dx w/o CI	1 (0-3)	1 (0-3)	0.195
Congestive heart failure Dx with CI	1 (0-2)	1 (0-3)	0.893
Trauma Dx w/o CI	2 (1-3)	1 (0-3)	0.125
Trauma Dx with CI	3 (2-3)	3 (2-3)	0.833
Normal CT scan Dx w/o CI	4 (3-5)	4 (0-5)	**0.029**
Normal CT scan Dx with CI	4 (3-5)	2.5 (0-5)	**0.029**
Accurate final Dxs w/o CI	22.08±3.75	19.15±4.33	0.061
Accurate final Dxs with CI	23.5 (20-26)	22 (8-27)	0.307

ED: emergency department, CI: clinical information, CT: computed tomography, Dx: diagnosis, w/o: without, * Chi Square Test
** Independent Samples t-test (mean±SD), *** Mann Whitney U test (median (minimum-maximum))

Table 3. Data for scoring the self-confidence of senior and junior residents at the time of diagnosis

Confidence in	Senior Resident	Junior Resident	*p*
COVID-19 Dx w/o CI	31.5 (0-113)	41.5 (0-102)	0.985
COVID-19 Dx with CI	39.5 (0-130)	54 (0-119)	0.833
Viral pneumonia Dx w/o CI	99 (40-117)	90 (0-126)	0.116
Viral pneumonia Dx with CI	103 (53-136)	96 (0-121)	0.289
Lobar pneumonia Dx w/o CI	26.42±9.97	22.45±13.25	0.378
Lobar pneumonia Dx with CI	24.33±11.96	21.00±6.13	0.384
Pulmonary embolism Dx w/o CI	8.5 (0-10)	5 (0-10)	**0.024**
Pulmonary embolism Dx with CI	9 (0-10)	8 (0-10)	0.307
Congestive heart failure Dx w/o CI	9 (0-26)	5.5 (0-24)	**0.029**
Congestive heart failure Dx with CI	8 (0-17)	7.5 (0-23)	0.924
Trauma Dx w/o CI	17.17±8.04	10.90±8.83	0.054
Trauma Dx with CI	23.92±5.49	22.10±4.42	0.312
Normal CT scan Dx w/o CI	36.58±7.34	24.25±11.17	**0.002**
Normal CT scan Dx with CI	32.42±9.63	20.40±13.29	**0.011**
Final Dxs w/o CI	268.17±26.35	229.70±36.90	**0.004**
Final Dxs with CI	270.58±32.30	249.50±32.79	0.087

ED: emergency department, CI: clinical information, CT: computed tomography, Dx: diagnosis, w/o: without,
* Independent Samples t-test (mean±SD), ** Mann Whitney U test (median (minimum-maximum))

For normal images, with or without clinical information, senior physicians had higher rates of correct diagnosis in both scenarios (p=0.029) (Table 2). When it was questioned how confident they were about their "normal" diagnosis, senior physicians displayed significantly higher confidence in their own "normal" diagnosis than the junior residents (36.58±7.34 vs. 24.25±11.17; p=0.002). When the clinical information is added, this trend continued favoring the seniors (p=0.011). When all diagnoses are taken into account, the seniors are more confident in the diagnosis of the CT scans they evaluated without clinical information (p=0.004), while when the clinical information is added, the confidence of the junior physicians in their own interpretations of the CT images increases, and there is no longer a significant difference between the two groups (p=0.087) (Table 3).

Discussion

Physicians in departments that primarily handle patients' clinics and frequently assess patients can accurately evaluate the radiological images associated with their fields of expertise [4]. This allows physicians to be more practical in their patient care processes and have greater self-confidence [5]. Emergency medicine is one such department. In a study evaluating emergency medicine residents, physicians were required to obtain images such as pneumonia, aortic pathology, masses, metastases, pneumothorax, pulmonary embolism, pleural effusion, lung parenchymal pathology, pericardial effusion, mediastinal pathology, cystic lesions in the thoracic CTs, and intraabdomial free fluid, aortic pathology, splenic pathology, intra-abdominal free air, appendicitis, gynecological pathologies, renal pathologies, gallbladder pathologies, mesenteric embolism on abdominal CT. The results have indicated that the ED residents demonstrated similar success rates to radiologists [6]. In the evaluation of head CT scans, ED physicians have been found comparable to neuroradiologists, with no significant oversight of clinically significant patients [7].

Although there are studies that may suggest otherwise [8], it is generally expected that accurate diagnosis rates will improve with increased professional experience. However, professional experience alone is not enough for the radiological evaluation to be accurate. In this study, the rate of correct diagnosis of senior physicians was higher than that of juniors, but although the analysis was not performed because the number of subgroups was limited,

it was evident that the rate of correct diagnosis increased in both groups with the inclusion of clinical information.

The present study was conducted in the first months of COVID-19 in Turkey. The aim of the study was to determine the success of ED residents in interpreting thoracic CT. The images included cases involving trauma patients and many pulmonary emergencies, including viral pneumonias. Notably, during the evaluation, junior residents showed a tendency to diagnose COVID-19, a condition they frequently encountered in daily practice. Another study conducted among radiology physicians (specialists and residents) in the early period of COVID-19 showed that radiologists, even without knowing the patient's clinic, were able to distinguish the diagnosis of COVID-19 with thoracic CT from other viral agents, independent of their professional experience [8]. As professional experience increases, so does self-confidence in decisions [5]. In the study, junior residents were more cautious in their assessments without knowing the patient's clinic. However, they are equally confident as senior residents in the evaluations of patients with their clinical information. This situation once again reveals how important it is to have access to the patient's clinical information.

The study found that junior residents were significantly more cautious than senior ones in making normal thoracic CT diagnosis, and their current diagnosis rates decreased with the addition of clinical information. The reason for this may be multifactorial. Some physicians may hesitate or feel apprehensive to make a normal diagnosis in the presence of a positive clinical information. In addition, some may prefer to evaluate the patient in person before rendering a diagnosis.

The main limitation of the study is the relatively small number of participants. In our institution, as in many EDs, there is an average number of residents. A second limitation is that the number of CT images are insufficient to perform subgroup analysis. These limitations can be addressed in future multicenter studies.

In conclusion, both senior and junior emergency medical residents were able to interpret COVID-19 thoracic CT images with a high degree of accuracy, even though they had no formal training on COVID-19 radiology, during the early stages of the pandemic. Senior emergency medical residents diagnosed thoracic CT images with a high degree of accuracy. Senior physicians were confident in their decisions regardless of whether they are accurate or not, solely by visual inspection, whereas junior residents displayed similar confidence when clinical information was available.

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

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Research Article

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Determination of mTOR activity depending on donor age of mesenchymal stem cells isolated from adipose tissue

Adipoz dokudan izole edilen mezenkimal kök hücrelerin donör yaşına bağlı olarak mTOR aktivitesinin belirlenmesi

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Abstract

Purpose: Aging in living organisms is an inevitable physiological consequence. Cellular senescence occurs not only in cells that have completed their differentiation, but also in stem cells. Mammalian target of Rapamycin protein complex (mTOR) has an important role in cell growth and metabolism. The mTOR, which plays an important role in cell proliferation, also regulates cellular aging and directs the bioenergetic infrastructure. The aim of the study is to determine the mTOR expression of mesenchymal stem cell (MSC) obtained from adipose tissue depending on the donor age.

Materials and methods: Six-week-old pubertal rats were named Group 1 (n=6), 10-12-week-old reproductive period rats were named Group 2 (n=6), and 20-month-old rats were named Group 3 (n=6). The isolation of MSC was performed by primary explant culture method from adipose tissue taken from groups. Characterization and differentiation experiments were performed in MSC obtained. The activity of mTOR (mTORC1 and mTORC2) in MSC was determined by qRT-PCR method. Caspase 3, 8, 9, Bax and Bcl-2 expressions were evaluated by Real-time polymerase chain reaction (qRT-PCR) method.

Results: In our study, it was determined that the highest expression of apoptotic markers was in Group 1 and the lowest expression was in Group 2. When mTOR expression was evaluated, mTORC1 was found to be highest in Group 2 and lowest in Group 1. mTORC2 expression in Group 1 was lower than in other groups. Although the expression of mTORC1 and mTORC2 in Group 3 was not as high as in Group 2, it was statistically significant (p<0.05).

Conclusion: In this study, we found that both mTORC1 and mTORC2 are differentially expressed in stem cells depending on donor age. Further studies are needed to better understand the functional consequences of this difference.

Keywords: Aging, adipose tissue, mTOR, mesenchymal stem cells.

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Öz

Amaç: Canlı organizmalarda yaşlanma kaçınılmaz bir fizyolojik sonuçtur. Hücresel yaşlanma sadece farklılaşmasını tamamlamış hücrelerde değil, kök hücrelerde de meydana gelir. Rapamisin protein kompleksinin memeli hedefi (mTOR), hücre büyümesinde ve metabolizmasında önemli bir role sahiptir. Hücre çoğalmasında önemli rol oynayan mTOR, aynı zamanda hücresel yaşlanmayı düzenler ve biyoenerjetik altyapıyı yönlendirir. Çalışmanın amacı, donör yaşına bağlı olarak yağ dokusundan elde edilen mezenkimal kök hücrelerin (MSC) mTOR ekspresyonunu belirlemektir.

Gereç ve yöntem: Altı haftalık pubertal sıçanlar Grup 1 (n=6), 10-12 haftalık reprodüktif dönem sıçanları Grup 2 (n=6) ve 20 aylık sıçanlar Grup 3 (n=6) olarak isimlendirildi. Gruplardan alınan yağ dokusundan primer eksplant kültür metodu ile MSC izolasyonu yapıldı. Elde edilen MSC'de karakterizasyon ve farklılaşma deneyleri yapıldı. Kök hücrelerdeki mTOR aktivitesi (mTORC1 ve mTORC2) qRT-PCR yöntemi ile belirlendi. Caspase 3, 8, 9, Bax ve Bcl-2 ekspresyonları Real-time polymerase chain reaction (qRT-PCR) yöntemi ile değerlendirildi.

Bulgular: Çalışmamızda apoptotik belirteçlerin en yüksek ekspresyonunun Grup 1'de, en düşük ekspresyonun Grup 2'de olduğu belirlendi. mTOR ekspresyonu değerlendirildiğinde, mTORC1 en yüksek Grup 2'de, en düşük Grup 1'de bulundu. Grup 1'deki mTORC2 ifadesi diğer gruplara göre daha düşüktü. Grup 3'teki mTORC1 ve mTORC2 ekspresyonu Grup 2'deki kadar yüksek olmasa da istatistiksel olarak anlamlıydı (p<0,05).

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Sonuç: Bu çalışmada hem mTORC1 hem de mTORC2'nin donör yaşına bağlı olarak kök hücrelerde farklı şekilde eksprese edildiğini bulduk. Bu farkın fonksiyonel sonuçlarını daha iyi anlamak için daha fazla çalışmaya ihtiyaç vardır.

Anahtar kelimeler: Yaşlanma, yağ doku, mTOR, mezenkimal kök hücreler.

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Introduction

Aging in living organisms is an inevitable physiological outcome. Cellular senescence does not only occur in differentiated cells. It also happens in stem cells. Mesenchymal stem cells (MSCs), which are easy to obtain and have fewer ethical problems, have become a promising method for treating cartilage, bone and spinal cord injuries as well as metabolic diseases. However, many of the stem cells transplanted to treat tissue damage have been found to die after transplantation. Although molecular, epigenetic and metabolic activity-related changes have been demonstrated in studies suggesting that this problem may be related to stem cell aging, stem cell aging has not yet been fully elucidated [1].

Studies show that the Mammalian Target of Rapamycin (mTOR) pathway plays an important role in cellular and organismal aging. The mTOR is a protein that acts as a sensor in anabolic and catabolic processes in our body; coordinates adequate nutrient, energy, oxygen availability and growth factors; and plays a central role in cell proliferation. There are two signaling complexes called mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). Playing an important role in cell proliferation, mTOR also regulates cellular senescence and directs the bionergic infrastructure. Attenuation of mTOR signaling by rapamycin delayed senescence in many cell types [2]. The mTORC2 plays an important role in endothelial senescence, which is manifested by increased binding of mTORC2-directed mTOR to Ser2481 and Rictor, an important component of AKT (phospho-AKT) phosphorylation [3]. Rapamycin mTOR is a regulator of cell growth in mammals, depending on hormone, nutrient and oxygen levels. Activation of both complexes facilitates cell growth and survival. The mTORC1 is involved in protein and lipid synthesis and cellular growth and proliferation, early cellular senescence and autophagy. The mTORC2 is involved in the organization of the actin cytoskeleton, control of ion transport, and anti-apoptotic events through stimulation of the AKT-FOXO pathway. The mTOR complex rapamycin is effective in the treatment of cancer immunology and genetic diseases, and in the prevention of degenerative and age-related pathologies in the heart and brain [4, 5]. In particular, mTORC1 has been reported to be a regulator in events such as cellular aging, telomere attrition, genomic imbalance and mitochondrial dysfunction [5].

Studies on stem cell senescence are generally related to cell activity after advanced passage (such as passage 45). In our study, we aimed to investigate mTORC-1 and mTORC-2 signaling complexes in adipose tissues derived MSCs of puberty, adult and aged rats.

Materials and methods

With the decision of Pamukkele University Animal Experiments Ethics Committee dated 03/02/2020 and numbered PAUHADYEK-2020/11, 18 female 200-250 gr rats were used. The rats were kept at 22°C a for 12 hours in a light-dark cycle and their access to water and food was arranged ad libitum. Groups were designated 6-week-old puberty as Group-1 (n=6), 10-12-week old reproductive rats as Group-2 (n=6), and 20-month-old rats as Group-3 (n=6). Retroperitoneal adipose tissues of the rats were removed through laparotomy incision. The adipose tissues were washed in 50 ml phosphate buffered saline (PBS). Adipose tissue pieces of the groups were transferred to the Cell Culture Laboratory under sterile conditions. Adipose tissue was dissected with sterile thin tissue scissors into the smallest pieces that could be separated in a petri dish containing complete medium. Each group was placed in 5 ml of medium Dulbecco's Modified Eagle's Medium (L-DMEM), 10% Fetal Bovine Serum (FBS), 50 U/ml penicillin, 50 µg/ml streptomycin, 0.1 mM nonessential amino acids and 2 mM L-glutamine) in the culture flask prepared for initial inoculation and incubated

separately at 37°C in a humid environment with 5% CO_2. Subculture was initiated when cells reached 70% confluence. At passage 3, cells were harvested with 0.25% trypsin. Cell counts were done. Flow cytometry analysis and differentiation assays were performed.

Flow cytometry analysis

Cells from Group 1 and Group 2 were sent to Pamukkele University Hospitals Tissue Typing Laboratory for mesenchymal stem cell characterization. Cells in Group 3 could not be analyzed because they could not be obtained sufficiently. The cells were characterized using CD34, CD73, CD90, mesenchymal stem cell surface markers in Flow Cytometry (Navios EX, Beckman Coulter Life Sciences, Houston, Texas).

Mesenchymal stem cell differentiation assays

Adipogenic differentiation

Cells from Group 1 and Group 2 at the third passage at 70% confluent were seeded in 12 well plates with 1×10^4 cm² cells. Since the cells in Group 3 could not be obtained sufficiently, differentiation experiments could not be performed. For 15 days, adipogenic culture was induced in media. The medium was changed twice a week with adipogenic medium (45 ml Basal Medium, 5 ml Adipocyte Supplement, 25 µl penicillin-streptomycin). At the end of 15 days, adipogenesis was demonstrated by oil red O. Cells were washed twice in PBS and fixed in 10% formalin. Cell staining was performed in filtered Oil Red O for 1 hour. At the end, the cells were washed under running water, Hemotoxylene was added to wells, left for 1 minute and rinse in distilled water. Cells of each group were examined and photographed under phase contrast microscope.

Osteogenic differentiation

At the third passage, $3.5x10^6$ live cells were added to the cells of Group 1 and Group 2 from 1 ml of cell suspension prepared after cell counting. Medium and 20µl of cell suspension were added to the culture dish and incubated. Twice a week, the medium was changed. At the end of the 21st day, the medium was removed. Cells were fixed (4% formaldehyde) and incubated for 30 minutes. The cells were stained with a solution of Alizerin Red S for 2 to 3 minutes. Cells of each group were examined and photographed under phase contrast microscope.

Chondrogenic differentiation

Viable cells ($1.6x10^7$ /ml) from 1 ml of the prepared cell suspension was added to the center of the 12-well plate. It was incubated at 37°C for 2 hours. The prepared chondrogenic differentiation medium was added and placed in the incubator. The medium was changed twice a week. At the end of the 14th day, 4% formaldehyde was added to the cells and kept for 30 minutes. The fixed cells were kept in 1% Alcian blue dissolved in 0.1 N HCl. After removal of Alcian blue and washing with 0.1N HCl, cells from each group were examined and photographed under a phase-contrast microscope.

Real-time polymerase chain reaction (qRT-PCR)

The RNA isolation by TRIzol Reagent was performed on cells obtained from Group 1, Group 2 and Group 3. Cells were resuspended in 500 µl TRIzol and Total RNA was extracted. Complementary DNA (cDNA) synthesis was performed with cDNA Synthesis Kit with Rnase Inhibitor. After cDNA synthesis, expression level differences in mRNA levels were determined by qRT-PCR using SYBR green assay. The data obtained were recorded as Cq. The primary sequences of the genes were analyzed and the housekeeper gene (beta-actin) was used as a reference gene for normalization (Table 1).

Statistical analysis

The analysis of the data was quantified by using the ΔΔCT method with a computer program. Volcano Plot in the "RT2Profiles™PCR Array Data Analysis" program was used to compare the groups. The groups were statistically evaluated by "Student's t-test" analysis. Statistical significance was determined at $p \leq 0.05$.

Table 1. Real Time PCR forward and reverse primer sequences

Gene names	Primer Sequence
Beta Actin	F: GCGAGTACAACCTTCTTGCAGCTC R: TGGCATGAGGGAGCGCGTAA
CD 34	F: AGCCATGTGCTCACACATCA R: CAAACACTCGGGCCTAACCT
CD 45	F: TTGCTCCCCATCCGATAAGAC R: AGCGTGGATGAAAAACCATCG
CD 73	F: TGCATCGATATGGCCAGTCC R: AATCCATCCCCACCGTTGAC
CD 105	F: ACTGAGTTGCACATCTGGGG R: TTCCGAAGTGGTGGTAAGCC
CD 106	F: GGTGGCTGCACAGGTTGGGG R: ACCCACAGGGCTCAGCGTCA
Bcl 2	F: ATCGCCCTGTGGATGACTGAGT R: GCCAGGAGAAATCAAACAGAGGC
Bax	F: TCAGGATGCGTCCACCAAGAAG R: TGTGTCCACGGCGGCAATCATC
mTOR	F: TGAGAGAGGAGATGGAGGAA R: TTCAGAGCGGAGAAAGCA
mTORC 1	F: TGACTTACCGAGAGCACACA R: ACATTCACAGACTCAGGCATC
mTORC 2	F: GAAGGTGCTAAAACTGAAGGTG R: CAGAACTCGGAAACAAGGAA
Caspase 3	F: GGAAGCGAATCAATGGACTCTGG R: GCATCGACATCTGTACCAGACC
Caspase 8	F: AGAAGAGGGTCATCCTGGGAGA R: TCAGGACTTCCTTCAAGGCTGC
Caspase 9	F: GTTTGAGGACCTTCGACCAGCT R: CAACGTACCAGGAGCCACTCTT

Results

Cells isolated from adipose tissue taken from the retroperitoneal region of Groups rats were observed to adhere to the plastic surface in the first 24 hours and had a fibroblast-like appearance. At the second and third passages, fibroblast-like cells were homogeneous and dense. In group 3, adhesion to the plastic surface occurred on the 8th day (Figure 1). In the following days, it was observed that the cells did not proliferate and deaths started and these deaths increased day by day. Therefore, since the cell density required for characterization and differentiation experiments could not be reached, these analyses could not be performed in this group. Only RT- PCR analyses could be performed.

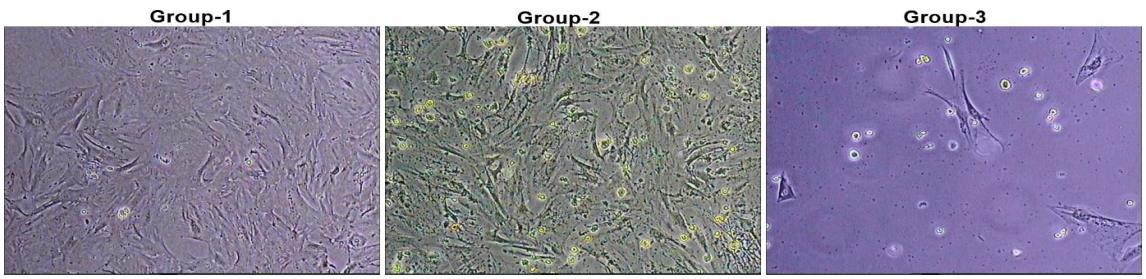

Figure 1. Mesenchymal stem cells obtained from rat adipose tissue by primary cell culture. X20, inverted microscope

Flow cytometry analysis

In flow cytometry analysis performed for stem cell characterization, CD73 and CD90, which are mesenchymal stem cell markers, were measured as 86.08% and 83.76% in Group 1. In Group 2, CD73 was 86.46% and CD90 was 90.46%. CD34, a hematopoietic stem cell marker, was negative (0%) in both groups (Figure 2). According to flow cytometry analysis, surface markers of MSC were demonstrated in Group 1 and Group 2. In Group 3, analysis could not be performed because of insufficient number of cells.

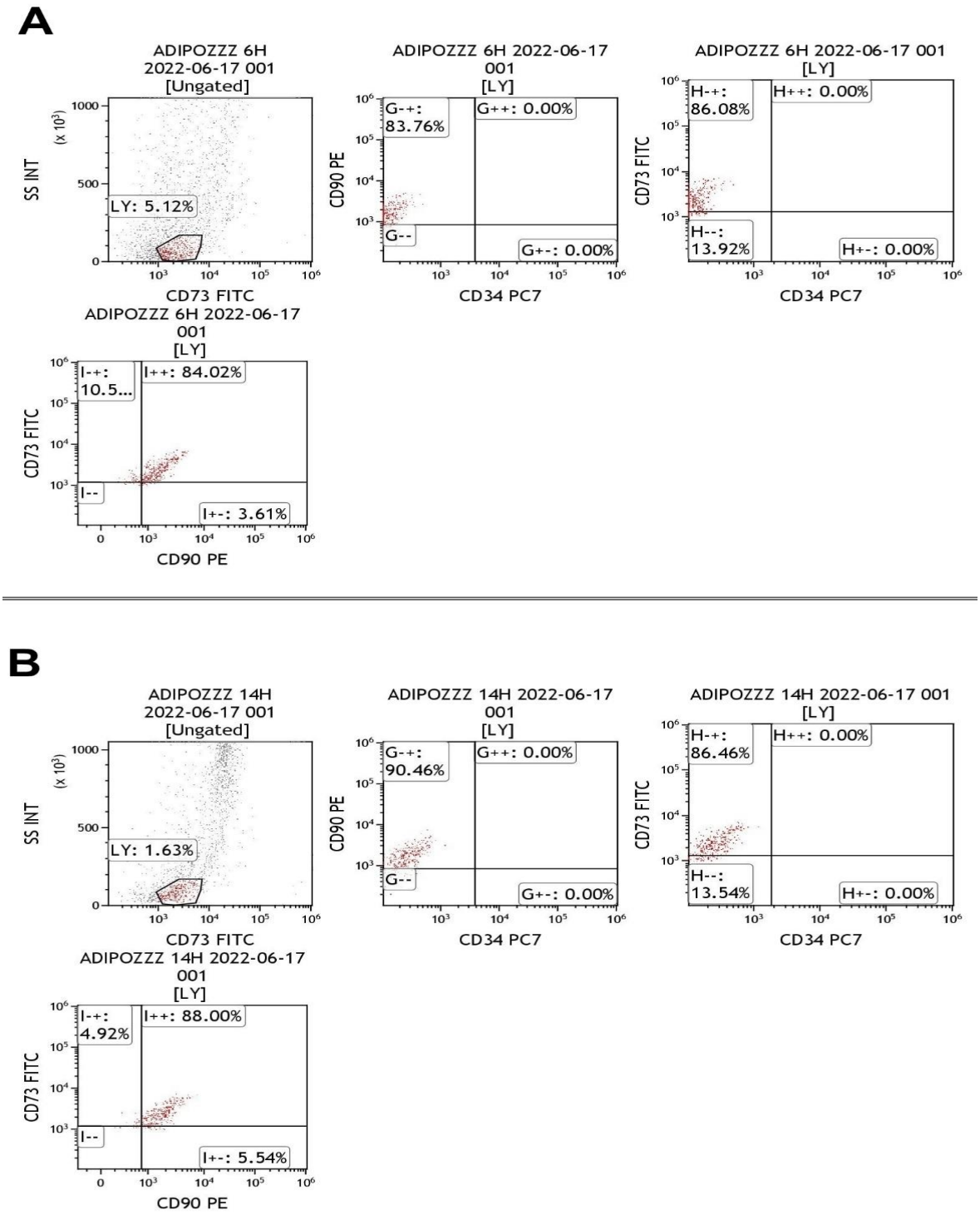

Figure 2. Expression of MSCs surface markers measured by Flow cytometry analysis in MSCs derived from adipose tissue from rat. A: In Group 1, CD73 was 86.08% CD90 83.76%. B: In Group 2, CD73 was 86.46% CD90 90.46%. CD34 was measured as negative (0%) in both groups

Differentiation experiments

As a result of differentiation experiments performed on stem cells in Group 1 and Group 2, osteogenic, adipogenic and chondrogenic differentiation was observed. Thus, mesenchymal stem cells were demonstrated by differentiation experiments (Figure 3). In Group 3, differentiation experiments could not be performed because sufficient number of cells could not be obtained.

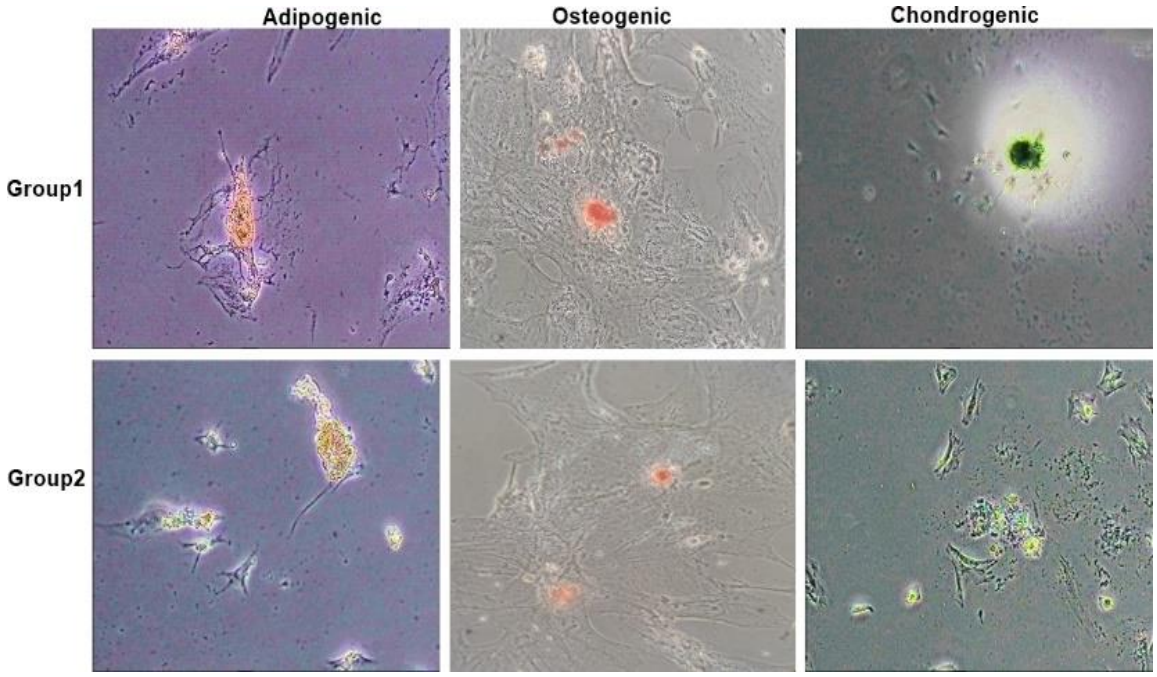

Figure 3. Differentiation of mesenchymal stem cells into adipogenic, osteogenic and chondrogenic tissue in Group 1 and Group 2. X20, Inverted microscope

qRT-PCR analysis results

As a result of qRT-PCR analysis performed on Group 3, in which flow cytometry and differentiation experiments could not be performed, the expression of CD45 was significantly lower and CD 10^6 expression was significantly higher, proving that Group 3 was also mesenchymal stem cells. Fibroblast-like morphologic images also supported this (Table 2). According to qRT-PCR analysis results, the highest expression of mTORC1 and mTORC2 was found in Group 2 and the lowest expression was found in Group 1. The expression of Group 3 was lower than in Group 2 and higher than in Group 1 and was statistically significant ($p<0.05$). Among the pro-apoptotic markers, Bax, caspase 8 and caspase 3 expression was higher in Group 1, while the lowest caspase 8 and Bax values were observed in Group 2. Caspase 9 was close to each other in Group 2 and Group 3 and higher than Group 1. Among the anti-apoptotic markers, Bcl-2 was lowest in Group 1 and highest in Group 2 (Table 2).

Table 2. The mRNA expression changes of genes in Mesenchymal Stem Cell related with groups. Data were obtained by qRT-PCR assay via ΔΔCt method in RT2 Profiles PCR array data analysis online program

Gene names	Group 1		Group 2		Group 3	
	Fold Regulation	*p* value	Fold Regulation	*p* value	Fold Regulation	*p* value
Beta Actin	1.00		1.00		1.00	
CD 34	-1.09	0.70	3.52	0.09	3.22	0.045*
CD 45	-23.59	0.34	-4.37	0.91	-103.01	0.002*
CD 73	-48.06	0.26	118.33	0.26	2.46	0.30
CD 105	1.57	0.10	1.02	0.84	1.59	0.058
CD 106	1.90	0.79	4.03	0.17	7.66	0.008*
Bcl 2	-2.87	0.37	4.39	0.37	1.53	0.95
Bax	8.75	0.34	-13.83	0.37	-1.58	0.37
mTOR	-3.72	0.37	1.29	0.54	-2.89	0.35
mTORC 1	-9.43	0.37	27.10	0.37	2.87	0.03*
mTORC 2	-1.61	0.41	3.39	0.37	2.11	0.02*
Caspase 3	1.70	0.10	-1.50	0.45	1.13	0.81
Caspase 8	4.72	0.17	-8.82	0.26	-2.09	0.34
Caspase 9	1.01	0.39	3.70	0.38	3.72	0.70

*$p<0.05$ statistically significant

Discussion

In the adult, tissue-specific stem cells are responsible for the maintenance of tissue homeostasis and the generation of progenitor cells for regeneration after tissue damage. To maintain the stem cell pool while providing the progenitor cells needed to differentiate into tissue-specific cells, stem cells must undergo a process of self-renewal. Many different factors finely regulate the balance between stem cell maintenance and tissue regeneration. These include growth factors, the extracellular environment, cell-cell signalling, inflammatory mediators and cellular metabolism. However, stem cells are exposed to harmful effects in the case of disease or during the ageing process [6].

A general decline in stem cell function and specific changes in stem cell phenotype related to local tissue niches during ageing have been reported by Bengal et al. [7]. The stem cell cycle in skeletal muscle, parts of the nervous system and hair follicles of epithelial tissues is slowed during ageing and there is a general decrease in the stem cell pool in these tissues [8, 9]. In our study, we found that cell proliferation was very low in stem cells from adipose tissue obtained from Group 3, consisting of old rats, and that proliferation was unable to progress to higher passages. Morrison et al. [9] showed that stem cells in certain tissues, e.g. haematopoietic stem cell (HSC), may retain or expand their population during ageing [9]. However, other studies have shown that although HSC numbers increase with age, cell function decreases and cell longevity differs [10, 11]. In the senescence of intestinal stem cells, an increase in the number of cells and a decrease in the function of the cells have also been observed [12]. In order to understand stem cell responses to ageing and their relevance to the stem cell niche, studies suggest that further molecular investigations are required [13].

Mesenchymal stem cells have been developed and used in preclinical and clinical applications due to their important contribution to organ formation and immune modulation. In particular, a powerful and promising approach to achieve immunomodulation and tissue regeneration has been recognised through MSC transplantation. However, the mechanisms by which MSCs exert their therapeutic effects have not been elucidated. Increasing evidence suggests that engrafted MSCs are short-lived in the recipient and subsequently apoptose in the host circulation or in the engrafted tissue [14]. In our study, we found high expression of caspase-3, caspase-8, caspase-9 and Bax in

Group 1. In Group 2, caspase-3, caspase-8 and Bax were low, whereas Bcl-2, an anti-apoptotic marker, was very high. In Group 3, caspase 3 was close to Group 1, but caspase 8, 9 and Bax were lower than Group 1 and higher than Group 2. Caspase 3 elevation in Group 3 may be age-related. However, this could not explain why caspase 3 was elevated in Group 1. It has been reported in previous studies that estrogen receptors are expressed in various stem cells, including embryonic stem cells, MSCs and cardiac stem cells [15]. It has been reported that estrogen is a regulator of embryonic stem cell differentiation and an inhibitor of cell apoptosis in mesenchymal stem cells [16]. Since the rats in Group 3 were in the premenopausal period, the rats in Group 1 were in the puberty period and estrogen levels were lower than in the reproductive period. This may result in higher apoptosis in stem cells in Group 1 and Group 3 than in Group 2. In differentiation, a role for mTORC1 was identified and rapamycin was shown to inhibit adipocyte formation [17]. Other studies have demonstrated mTOR activity is required for the function of embryonic stem cells in mammalian development and mTOR activity is important for the self-renewal and differentiation of stem cells [18, 19]. Mesenchymal stem cells are multipotent that differentiate into various cell types such as adipocyte, chondrocyte and osteoblast in response to environmental cues [20]. It has been shown that rapamycin inhibits adipogenic differentiation in human preadipocytes [21]. Several other studies have highlighted the role of mTORC1 in adipogenesis. There is strong evidence that insulin-induced mTORC1 activation enhanced adipogenesis [22]. In another study, mTORC1 and mTORC2 was investigated in cell differentiation using Raptor and Rictor knocked out MSCs. In these studies, mTORC1 in adipocyte differentiation was strengthened by the reduced capacity of Raptor-deficient MSCs to form adipocytes [23]. There are also reports that Raptor-deficient MSCs have the capacity to form a mineralizing matrix similar to bone. Rictor-deficient MSCs showed an opposite differentiation program to Raptor knockout MSCs, with increased adipocyte and decreased mineralised matrix [24]. All of the above results suggest that mTORC1 activity enhances adipogenic differentiation and suppresses osteoblastic differentiation, whereas mTORC2 suppresses adipogenic differentiation and enhances osteoblastic differentiation. However, another study suggests that mTORC1 is required for osteoblast differentiation [25]. The mTORC1 is known to regulate glutamine anaplerosis, the breakdown of glutamine to tricarboxylic acid cycle intermediates, by blocking sirtuin 4 (Sirt4) transcription [26]. Glutaminase expression, which is also involved in glutamine anaplerosis, declines with age and is associated with decreased osteogenesis [27]. It has been reported that mTORC1 promotes osteogenic differentiation by restoring glutamine anaplerosis [19]. According to our qRT-PCR results, MSCs obtained from rats in Group 2 and 3 expressed higher levels of mTORC1 and mTORC2 than those in Group 1. The mTORC1 has been shown to stimulate the differentiation of adipocytes. Therefore, a higher level of adipocyte differentiation in the stem cells of Group 2 was considered to be an expected situation. The mTORC2 acts by stimulating the differentiation of osteoblasts. It would be expected that there would be less mTORC2 in Group 3. However, the fact that there was less mTORC2 in group 1 compared to both Group 2 and Group 3 was unexpected for Group 1, where we thought there would be a high level of osteoblast activation.

The mTOR plays an important role in cell proliferation and differentiation and also regulates cellular senescence. Research into the relationship between mTOR and lifespan has shown that mTOR inhibition extends lifespan, but the mechanism by which this happens remains unknown. Some studies have suggested that the inhibition of mTORC1 does not delay ageing itself, but rather delays the onset of age-related diseases [28]. However, many researchers believe that the effects of mTOR inhibitors on longevity are directly due to a reduction in senescence [29].

Inhibition of mTORC1 has been reported to play a role in maintaining adult stem cell function in various tissues [30]. It has been reported that treatment of aged mice with rapamycin can indirectly increase the function of stem cells in the intestine by reducing mTORC1 signalling in the Paneth cell niche [31]. Similarly, caloric restriction has been reported to extend lifespan. During caloric restriction, mTORC1 is induced to allow intestinal stem cell proliferation [32].

The mTORC1 has many various functions in enhancing or limiting inflammatory or immune responses in the immune systems [33, 34]. Importantly, inhibition of mTORC1 is also used as an immunosuppressive therapy to limit the activation of T cells and to prevent graft rejection following organ transplantation. Inhibition of mTORC1, in turn, enhances the memory responses of CD8+ T cells that are critical for viral defence [35]. However, not much has been known about the role and activity of mTORC1 in immune cells during ageing. One study reported that increased mTORC1 activity in HSCs from aged mice was associated with an age-related decline in HSC function, which may contribute to anaemia, poor vaccination or increased tumour formation [36].

In our study, mTORC1 expression was highest in Group 2 and lowest in Group 1. Given the association of mTORC1 with longevity, the lowest expression in Group 1 could be explained. However, it was interesting that Group 2 was higher than 3. Indeed, mTORC1 is involved in many cellular events including protein synthesis, transcription, translation, DNA synthesis and autophagy. The high levels in this group could be due to the high number of these events or it could be because the end products and the pathways that are affected by mTORC1 and mTORC2 in the cellular events are very different and numerous.

In conclusion, our results show that mTOR is differentially expressed in MSCs in an age-dependent manner. To better understand the functional consequences of this difference, further studies are required. We believe that elucidating the molecular mechanisms in stem cells will be important for stem cells, which are widely used in both preclinical and clinical applications.

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

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Contributions of the authors to the article

G.A.M. and H.S. constructed the main idea and hypothesis of the study. H.S., E.O. and N.C. developed the theory and arranged/edited the material and method section. E.O. and G.A.M. evaluated the data of RT-PCR in the results section. E.O., G.A.M. and N.Ç. contributed to the histological evaluation of the results. Flow cytometry analysis was performed by E.M. The article written by H.S., N.C. and G.A.M. reviewed the article and made the necessary corrections and approved it. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Evaluation of risk factors for central venous line-associated bloodstream infections (CLABSIs) and the benefits of central line bundle application in reducing CLABSIs

Santral venöz kateter ilişkili kan dolaşımı enfeksiyonları için risk faktörlerinin ve santral venöz kateter paket uygulamasının yararlarının değerlendirilmesi

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Abstract

Purpose: We aimed to identify the risk factors for central line-associated bloodstream infections (CLABSIs) and the efficacy of bundle application to prevent CLABSIs. **Materials and methods:** This study was performed in the anesthesia-intensive care unit (AICU) of a tertiary hospital. A structured survey form including patients' characteristics and a central line bundle checklist was used for following of patients. Adult patients who had undergone recent central venous catheter (CVC) insertion at the AICU, those who had been transferred to ICU with the previous catheter insertion in other departments and who had received a diagnosis of CLABSI fourty-eight hours after remaining in the ICU were included in the study. The data obtained were evaluated with respect to the risk factors for CLABSIs. **Result:** The current study included 156 patients with the mean age 67.97±17.20 years (median 71.00 years), 66 were women (42.3%). Fourty-seven patients developed CLABSIs. Evaluating the results of univariate analysis, the rate of infection was lowest when catheters were inserted with the aim hemodialysis (p<0.01). The subclavian vein (p<0.01) and three-lumen catheters (p<0.01), receiving CVCs under emergency conditions (p=0.04), having been intubated (p=0.01), undergoing surgery (p=0.04) and receiving antibiotics before catheterization (p<0.01), receiving blood products through CVCs (p=0.01), repeat catheter insertions (p<0.01) were found to be associated with the development of CLABSI. **Conclusion:** In summary, multivariate analyses showed that repeat catheter insertions (p<0.01) and prolonged ICU stay (p<0.01) could raise the risk of CLABSIs. However, the risk of infection was lower (p<0.01) in patients with bundle application.

Keywords: Bundle, central line, blood stream infection, intensive care.

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Öz

Amaç: Bu çalışmada santral venöz kateter-ilişkili kan dolaşımı enfeksiyonlarının (SKİ-KDE) risk faktörlerini ve SKİ-KDE'larını önlemek için paket uygulamasının etkinliğini belirlemeyi amaçladık. **Gereç ve yöntem:** Bu çalışma üçüncü basamak bir hastanenin anestezi yoğun bakım ünitesinde (AYBÜ) yapıldı. Hastaların takibi için hasta özelliklerini içeren yapılandırılmış anket formu ve santral venöz kateter paketi kontrol listesi kullanıldı. Yakın zamanda AYBÜ'de santral venöz kateter (SVK) takılmış olan, daha önce diğer bölümlerde kateter takılarak YBÜ'ne nakledilmiş olan ve YBÜ'de 48 saat kaldıktan sonra SKİ-KDE tanısı alan erişkin hastalar çalışmaya dahil edildi. Elde edilen veriler SKİ-KDE için risk faktörleri açısından değerlendirildi.

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Bulgular: Bu çalışmaya yaş ortalaması 67,97±17,20 (medyan 71.00 yıl) olan 156 hasta alındı, hastaların 66'sı kadındı (%42,3%). Kırk yedi hastada SKİ-KDE gelişti. Tek değişkenli analizlerin sonuçları değerlendirildiğinde, hemodiyaliz amacıyla kateter takıldığında enfeksiyon oranı en düşüktü (p<0,01). Subklavian ven (p<0,01) ve üç lümenli kateterler (p<0,01), SVK'nın acil şartlarda takılması (p=0,04), entübe olmuş olmak (p=0,01), kateterizasyon öncesi operasyon geçirilmesi (p=0,04) ve antibiyotik kullanımı (p<0,01), SVK'ler yoluyla kan ürünü alınması (p=0,01), tekrarlı kateter takılması (p<0.01) SKİ-KDE gelişimi ile ilişkili bulunmuştur. **Sonuç:** Özetle, çok değişkenli analizler, tekrarlı kateter takılmasının (p<0,01) ve YBÜ'de uzun süre kalmanın (p<0,01) SKİ-KDE riskini artırabileceğini gösterdi. Ancak, paket uygulaması olan hastalarda enfeksiyon riskinin daha az olduğu (p<0,01) görüldü.

Anahtar kelimeler: Bundle, santral kateter, kan dolaşım enfeksiyonu, yoğun bakım.

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Introduction

At present, insertion of central venous catheters is an essential procedure to administer solutions that are unlikely to be given via a peripheral route, and to perform cardiovascular measurements especially in the follow-up of patients in the intensive care unit (ICU) and to perform hemodialysis [1, 2]. However, central venous catheterization may be associated with a variety of complications as well as benefits. Apart from mechanical complications, bloodstream infections (BSIs) are main crucial complications of catheterization [3] caused by microbial invasion at the time of catheter insertion or care [4]. Central-line-associated blodsteram infections (CLABSI) could lead to thousands of deaths each year and could increase mortality, hospital stay and health care costs, espacially among ICU patients [5, 6].

The National Healthcare Safety Network (NHSN) data between 2009 and 2018 from the USA reported CLABSIs decreased from 1.6 per 1000 central line-days to 0.9, except for an incraese in 2015 [7]. In contrast, the International Nosocomial Infection Control Consortium (INICC) surveillance data in 45 countries including Turkey reported a remerkably increased CLABSI rate (5.30/1,000 (CL-days) between 2013 and 2018 [8]. Since the use of central line (CL) bundles including proper antiseptic solution and adherence to protective barrier measures have been reported to prevent CLABSIs [9-11], the Centers for Disease Control and Prevention (CDC) updated the guidelines in 2011 to reduce CLABSIs and emphasized the use of chlorhexidine, taking maximal sterile barrier precautions (MBPs) [9, 10].

The insidences of CLABSIs in the ICU of the Hospital of Medical School of Pamukkale University were 7.14/1000 CL-days and 8.3/1000 CL-days in 2017 and 2018, respectively. In order to reduce the rates of CLABSIs, the use of CL bundles, including chlorhexidine as well as MBPs and hand hygiene before and after the procedure was put into practice in 2019 in the ICU. The current study sought to identify the risk factors for CLABSIs and the efficacy of bundle application to prevent CLABSIs.

Materials and methods

Study setting and population

This prospective observational study was performed in the anesthesia-intensive care unit (AICU) of a tertiary hospital with 900 beds from February 2019 to February, 2020. This study was performed in accordance with the Declaration of Helsinki, and the Pamukkale University, Non-Invasive Clinical Research Ethics Committee approved the study with the number of 60116787/020/8888 on 06/02/2019.

Study design and procedures

In line with the recommendations of the national and international guidelines, a CL bundle checklist was prepared that included the precautions (i.e., hand hygiene before and after the procedure, chlorhexidine use; which had not been used previously for cleaning the skin, and maximal sterile barrier precautions containing a cap, mask, gown, sterile gloves and drape for covering up patients and was begun to implement routinely after several months of experience. The site of cathether insertion was left to the discrition of attending physicians.

Health care workers involved in catheter insertion were informed about the procedures. Therefore, the team involved in procedures was asked to prepare the required equipment earlier, to fill out the checklist, and to adhere to the recommendations of the guidelines.

Adult patients between the ages of 18 years and older, who had undergone recent central venous catheter (CVC) insertion at the ICU, and those who had been transferred to ICU with the previous catheter insertion in departments other than ICU and who had received a diagnosis of CLABSI fourty-eight hours after remaining in the ICU were included in the study. Patients who had been transferred to the ICU having been infected were not included in the study.

Patients who were inserted CVC accompanied by bundle application in the ICU were followed up pending the development of catheter-related bloodstream infection or removal of catheters or discharge from the ICU. After catheter insertion, the procedures of catheter care were left at the discretion of ICU staff, but unlike the previous practice in which batticon had been used, clorhexidine use was required for cleaning of skin during catheter care. After insertion, catheter care was performed 72 hours apart, but when dressings had become contaminated or deformed, they were changed regardless of the time interval of care.

Data collection

Data were collected via structured survey forms. An AICU physician and a nurse from the infection control committee were assigned to collect data on patients' characteristics (age, sex, comorbidities, intubation status and APACHE-II scores, use of total parenteral nutrition via CVC at the time of catheterization, a history of surgery and use of antibiotics, etc.), as well as on the care of the catheter. During each catheterization, the physicians in charge filled out the checklist forms as to whether they adhered to the items on the checklist form. Failure to comply with even one item on the checklist was considered a total incompliance and accepted as non-compliance with CL bundle checklist.

Patients with central catheters were followed on a daily basis to identify whether any infections occurred. An infectious diseases specialist made the diagnosis of CLABSIs on the basis of the results of blood culture and the CDC criteria, which define CLABSIs as laboratory-confirmed bloodstream infection that develops in a patient who has had a central catheter for more than two days (>2 calendar days) at the date of the event in line with surveillance data [5]. The day when the catheter is placed is accepted as the first day, and the catheter that is replaced after the first two days is accepted as the new catheter. In addition, an infection developing within the first fourteen days after catheter insertion is considered to be the first episode. Furthermore, once a new infection occurs with the same catheter after the first 14 days, it is considered to be a second episode [5]. Consistent with these definitions, the study included only one procedure of catheter insertion, and one episode of each patient. Recurrent infections of the same patient were not included in the study.

During the study period, rates of infections were controlled monthly; in case of any increase in the numbers, the reasons for increases were sought, adherence to hand hygiene in the ICU was observed accordingly, training in this context was planned. All patients who met the study criteria over a 13-month period were evaluated in terms of the risk factors for infection. Furthermore, the rates of CLABSIs were compared in patients with bundle adherence and those without. The rate of CLABSI was estimated by dividing the number of CLABSIs into the number of central line-days x1000 [12, 13].

Statistical analysis

Statistical analyses were performed using IBM SPSS statistics version 22 (Nyc, USA). Shapiro-Wilks test was used for normal distribution of data. Continuous data without normal distribution were presented as median with inter quartile range (25-75 percentiles) and nonparametric Mann Whitney U test was used for between-group comparisions. Categorical variables were presented as frequency and number and compared using the chi-square test. Together with Bonferoni correction, *p* values were corrected for multiple tests. A *p* value of <0.05 was considered as significant and confidence interval (CI) was set 95.0%.

Results

General characteristics of patients and CVC insertion

The current study included 156 patients with the mean age 67.97±17.21 years (19 to 98 days; median 71.00; IQR 62.25-80.00), 66 women (42.3%), 90 men (57.7%), all of whom had CVCs and had been followed in the ICU.

The duration of catheter stays varied from zero to 163 days with a mean of 20.85±24.47 days (median 14.50; IQR 4.25-28.00), total catheter days were calculated as 3252 catheter days. Over the study period, 47 patients (30.1%) developed CLABSIs, on hospital days from three to 137 days with a mean of 24.17±24.54 days (median 17.00; IQR 9.00-27.00). The mean ICU stay was 59.11±129.11 days with a minimum zero to maximum 1007 (median: 26.00, IQR: 8.00-58.75).

Of 156 catheters, 146 (93.6%) were placed electively; the remaining 10 catheters were placed under emergency condiditions. Furthermore, 97 patients (62.2%) had new catheters for venous access, four patients (2.6%) for obtaining hemodynamic data, 49 (31.4%) recieved new catheters for hemodialysis and six (3.8%) underwent catheter reinsertion because of dysfunction of their former catheters. 136 catheters (87.2%) were inserted by residents and 20 (12.8%) by specialists with expertise in the field. The internal jugular vein (74 CVCs; 47.4%) was the site where catheters were most frequently inserted, followed by femoral vein (52 CVCs; 33.3%) and then the subclavian vein (30 CVCs; 19.2%). Of patients, 106 (67.9%) had 3-lumen CVCs and 50 (32.1%) had 2-lumen CVCs. Of 156 patients, 132 had bundle implementation accompanied by catheterization, of whom 128 (82.1%) had bundle compliance.

Time to catheter insertion from ICU admission ranged from 24 days before ICU admission to 802 days after ICU admission, with a mean of 17.51±69.31 days (median 3.00 days, IQR 0.00-15.00). Most patients received catheters within 28 hospital days, however, the maximum time was as long as 802 days because of prolonged hospital stay as well as repeat catheter insertions in one patient.

A total of 119 patients (76.3%) had been intubated at the time of CVC placement, with the APACHE II scores of 1 to 45 with a mean of 19.60±8.18 (median: 19.60, IQR 5.13-25.00). Of patients, 49.4% (n=77), 26.3% (n=41) and 0.6% (n=1) had had endotracheal, tracheal and nasotracheal intubations, respectively.

Analyzing the diseases at baseline, one patient (0.6%) had cholangitis, one (0.6%) had sepsis, one (0.6%) had liver diseases, one (0.6%) had malignant neuroleptic sendrome, three (1.9%) had benign prostatic hyperplasia, three (1.9%) had deep venous thrombosis, three (1.9%) had rheumatic diseases, three (1.9%) had mental health disorders, four (2.6%) had hypothyroidism, five (3.2%) had pulmonary diseases other than asthma and chronic obstructive pulmonary diseases (COPD), eight (5.1%) had asthma, eight (5.1%) had hematologic diseases, 13 (8.3%) had nephrological diseases, 20 (12.8%) had COPD, 25 (16.0%) had solid organ malignancies, 31 (19.9%) had cardiac diseases, 32 (20.5%) had neurologic diseases, 39 (25.0%) had diabetes mellitus, 46 (29.5%) had hypertension.

Of patients, 49 patients (38.3%) were A-Rh positive, five (3.9%) were A-Rh negative, 14 (10.9%) were B-Rh positive, four (2.3%) were B-Rh negative, 12 (9.4%) were AB-Rh positive, two (1.6%) were AB-Rh negative, 39 (30.5%) were 0-Rh positive and four (3.1%) were 0-Rh negative. Prior to catheterization, 57 patients (36.5%) had undergone surgery and 85 (54.5%) had received antibiotics over the last 10 days. After catheterization, 57 patients (36.5%) received enhanced usual care and 8 had (5.1%) excessive catheter manipulation. During the catheter stay, 72 patients (46.2%) received blood products and 24 (15.4%) received total parentheral nutrition (TPN) via CVCs. Thirty days after catheter removal, 99 patients (63.5%) had died.

Risk factors

As shown in Table 1, evaluating the results of univariate analysis, there was no significant association between the development of CLABSIs and sex ($p>0.05$), also age ($p>0.05$). However, there was a significant association between the reason for CVC insertion and the development of CLABSIs.

Table 1. Univariate analysis of the risk factors of CLABSI*

	CLABSI (+) (n=47) n (%) or median (IQR)	CLABSI (-) (n=109) n (%) or median (IQR)	*p* value
Age (years)	70 (53-78)	71 (64-81)	*p*=0.24
Time to catheter insertion from ICU admission	1 ((-1) to 26)	3 (1 to10)	*p*=0.16
Catheter day (CD)**	27 (17-40)	7 (2-20)	*p*<0.01
ICU* stay (day)**	59 (34-114)	16 (5-36)	*p*<0.01
APACHE-2	21 (16-25)	19 (14-24)	*p*=0.11
Urea (mg/dl)	45 (32-70)	94 (53-131)	*p*<0.01
Creatinine (mg/dl)	0.7 (05-1.7)	1.4 (0.8-2.8)	*p*<0.01
Procalcitonin (ng/mL)	0.3 (0.2-0.4)	0.2 (0.1-0.3)	*p*<0.01
Female	19 (29%)	47 (71%)	*p*=0.45
Reason for CVC** insertion**			
Hemodialysis	4 (8%)	45 (92%)	
Dysfonction	4 (67%)	2 (33%)	*p*<0.01
Hemodynamic data	4 (100%)	0 (0%)	
Venous acsess	35 (36%)	62 (64%)	
Site of cathether insertion			
Subclavian vein	16 (53%)	14 (47%)	*p*<0.01
Femoral vein	6 (12%)	46 (88%)	
Internal juguler vein	25 (34%)	49 (66%)	
Number of CVC lumen			
3-lumen catheter	43 (41%)	63 (59%)	*p*<0.01
2-lumen catheter	4 (8%)	46 (92%)	
Catheter insertion			
by residents	43 (32%)	93 (68%)	*p*=0.29
by specialists	4 (20%)	16 (80%)	
Emergency	6 (60%)	4 (40%)	*p*=0.04
Elective	41 (28%)	105 (72%)	
Intubation	42 (35%)	77 (65%)	*p*=0.01
Bundle adherence	24 (19%)	104 (81%)	*p*<0.01
Surgery	23 (40%)	34 (60%)	*p*=0.04
Receiving antibiotics	35 (41%)	50 (59%)	*p*<0.01
Blood transfusion	29 (40%)	43 (60%)	*p*=0.01
TPN ***	10 (42%)	14 (58%)	*p*=0.18
Unusual catheter care	14 (25%)	43 (%75)	*p*=0.24
Repeat catheter insertions	14 (70%)	6 (30%)	*p*<0.01
Mortality	24 (24%)	75 (76%)	*p*=0.04

* CLABSI: Central line-associated bloodstream infections, ** Note: Patients who had CLABSIs without bundle adherence had significantly higher catheter day then those who had CLABSIs with bundle adherence, *** ICU: Intensive care unit, **** CVC: Central venous catheter
***** TPN: Total parenteral nutrition

The rate of CLABSIs was lowest when catheters were inserted with the aim of performing hemodialysis (8.2%) (p<0.01). While the rates of infections were found to be significanlty higher when catheters were inserted due to dysfonction (66.7%) or for obtaining hemodynamic data (100%), the rates of infections were lower when catheters were inserted for hemodialysis and for obtaining venous acsess (62.2%) (p<0.01). Given the sites of catheter insertion, surprisingly, the subclavian vein was found to have the highest rate of CLABSIs (16/30 CVCs; 53.3%), but the femoral vein was observed to have the lowest infection rate (6/52 CVCs; 11.5%), which are statistically significant (p<0.01). Patients with 3-lumen catheters had statistically higher rates of CLABSIs (40.6%) as compared with those with two-lumen cathathers (8.0%) (p<0.01) (Table 1).

Considering development of CLABSIs, patients receiving CVCs under emergency condition developed significantly higher rate of CLABSIs (60.0%, p=0.04). Furthermore, patients who had been intubated prior to catheterization developed statistically higher rate of infection (35.3%, p=0.01) of whom, there was a lower rate of infection with tracheal intubation which is statistically significant (43.9%, p=0.03). Patients undergoing surgery (40.4% p=0.04) before catheterization as well as those receiving antibiotics for the last 10 days prior to catheter insertion (41.2%, p<0.01) developed significantly higher rate of CLABSIs. Given the comorbidities, only three patients with the diagnosis of mental health disorders were noted to developed infection (100% p=0.03). There was no significant association between blood type and CLABSIs (p>0.05 p=0.32). However, a higher rate of CLABSIs was found in patients receiving blood products through CVCs (40.3%, p=0.01). Repeat catheter insertions were also associated with development of CLABSI (p<0.01) (Table 1).

Patients with CLABSs had a longer period of catheter stay with a mean of 35.40±29.42 days (6 to163 days; median: 27.00; IQR 17.00-40.00; p<0.01) and also prolonged ICU stay with a mean of 114.51±169.52 days (11 to 890 days; median 59.00; IQR 34.00-113.00; p<0.01), which was statistically significant.

Patients with no CLABSIs had higher levels of urea with a mean of 99.22±54.94 mg/dl (17-288 mg/dl; median 94.00, IQR 53.00-131.00 p<0.01, normal range; 16.6-48.5 mg/dl,) and creatinine with a mean of 3.29±7.14 mg/dl (0.06-57.00 mg/dl; median 1.39; IQR 0.80-2.82 p<0.01 normal range; 0.50-0.95 mg/dl). However, patients with CLABSIs had higher levels of procalcitonin with a mean of 2.12±7.70 ng/mL (0.06-47.00 ng/mL; median 0.25; IQR 0.19-0.40; normal range 0.5<p<0.01), as was expected.

CL Bundle adherence

In our study, the group undergoing catheterization with bundle adherence had statistically a lower rate of infection (18.8%) than the group undergoing catheterization without bundle adherence (82.1%), findings consistent with the goal of the current study (p<0.00). However, when the rate of CLABSI was estimated in line with the CDC criteria by using surveillance data from our hospital, we found that rate of CLABSI was 10.09 per 1000 central line-days during the 13-month period. When the groups were evaluated seperately, the group with bundle adherence had a rate of CLABSIs of 11.36 per 1000 central line-days, but the group with no bundle adherence had a rate of CLABSIs of 9.3 per 1000 central line-days, which was not an expected rate. This might be attributed to the way in which the rate of infection is estimated (the rate of CLABSI is calculated by dividing the number of CLABSIs by the number of central line-days x1000), that is, the longer days in the denominator, the lower the rate of infection. This is consistent with the result of the group with no bundle adherence.

Multivariable logistic regression analysis was performed to identify the effect of independent factors on CLABSIs, which was found statistically significant (X^2=108.59, p<0.001). Independent variables in the model could explain 76.7% of the total variance in developing CLABSIs (p<0.01). ICU days (β=1.00, p<0.01) and repeated catheter insertions (β=0.03, p<0.01) were independent risk factors for CLABSIs, but bundle adherence (β=24.03, p<0.01) was found to be an independent protective factor.

Of 47 patients with CALBSIs, 24 had a mortality rate of 51.1% as compared with those with no CLABSIs, 75 had a mortality rate of 68.8% (p=0.04).

Causative agents of CLABSIs

Candida spp. grew in blood cultures of 16 patients [(10.25%) (*C. albicans* in four patients, *C. parapsilosis* in eleven, *C. glabrata* in one)], *Enterococcus* spp. in eleven patients (7.05%) [*E. avium* in one (0.6%); *E. faecalis* in ten patients (6.4%)], Coagulase-negative staphylococci (CoNS) in eight patients (5.13%), *K. pneumonia* in five patients (3.20%), *Acinetobacter* spp. in four (2.56%) (*A. baumannii* in three*, A. iwoffii* in one patient), *Pseudomonas* spp. in four patients (2.56%) (*P.* spp. in one patient, *P. aeruginosa* in three patients), *E. coli* in three patients (1.9%), *Aeromonas* spp. in two patients (1.28%), *Serratia marcescens* in one patient (0.6%), *Morganella morgannii* in one patient (0.6%) and *Streptococcus* spp. in one patient (0.6%).

Of the blood cultures of 8 patients growing CoNS, which are part of normal skin flora, six were without bundle applications; there was a statistically significant difference between the groups with or without bundle application (p<0.01). This emphasizes the importance of appropriate skin cleaning that decreases the risk for contamination when bundle applications are performed.

Discussion

The aim of this study is to determine the risk factors for CLABSIs, define the measures to be taken, and evaluate the outcome of bundle application during central catheter insertion as well as catheter care.

The CDC has reported that, while CLABSIs can be prevented, they cause thousands of deaths every year around the world, and they are associated with a heavy economic burden and workload on healthcare systems [2]. Multiple strategies may be necessary to prevent CLABSIs, including training health care personnel (HCP), maximum adherence to hand hygiene (HH), the use of maximum barrier precautions, and chlorhexidine for catheter and skin care. In addition, preventive strategies may also be required, including chlorhexidine patches for catheter care and antiseptic/antibiotic-impregnated catheters, an appropriate catheter site, and refining indications for the insertion and removal of catheters. Strict adherence to bundle application seems to be an advisable alternative in this context [1].

There are studies reporting reduced CLABSIs rates with bundle application and the guidelines by the CDC recommend using chlohexidine for the prevention of CALBSIs [12, 14]. Since we identified increased rates of CLABSIs at our hospital during the period between 2017 and 2018, we made a decision to reduce CLABSIs, using chlohexidine and bundle application in one pilot ICU from February, 2019 to February, 2020.

It was shown that the rate of CLABSIs was reduced with bundle implementation [15]. A study reported that the rates of CLABSI in both medical and surgical ICUs were noted to decrease by 39% and 44.4%, respectively, during periods of bundle applications [12]. In another study using the data from the hospital infection control committee, it was observed that, despite not being significant, the number of CLABSIs decreased from 23 to 13 as compared with the previous years, with a significant decrease in the rate of catheter use [16]. Similarly, another study reported that the more the compliance with CL bundle, the lower the incidence of CLABSIs, although the decreased rates of infection seemed to be statistically insignificant, which means that using bundle application alone may not yield the expected results. Additional preventive measures, including isolation, identifying indications for the insertion and removal of catheters, an appropriate catheter site, and regular and careful catheter care, should also be taken [17]. Furuya et al. [18] also stated that the incidence of CLABSIs decreased from 4.7 to 1.8 episodes per 1.000 CVC-days over a period of bundle application, despite not being statistically significant, consistent with the findings in a study by Waltz et al. [19].

Unlike aforementioned studies, an observational study examined the association between bundle application and the rates of CLABSIs in general ICU over a period of five years and identified that the rates of CLABSIs varied every three moths, without statistically significant reduction in the rates of infection [2]. In this study, the group with bundle adherence had a statistically lower rate of infection as compared to the whole group without bundle, findings consistent with the goal of the current study (p<0.01). However, when we estimated the rate of CLABSIs according to CDC criteria with the use of hospital surveillence data (which

included reinfections and patients with no bundle application who had no infection being out of the study scope), the group with bundle adherence seemed to have a higher rate of CLABSIs (11.36 per 1000 central line-days) compared to the group without bundle adherence, which can be attributed to the way in which the rate of infection was estimated: the rate of CLABSIs is calculated by dividing the number of CLABSIs into the number of central line-days x1000), the group with no bundle adherence had higher number of catheter days.

We evaluated the rates of CVC use, CLABSIs and HH adherence monthly and every three months during the study period. We noted that the rates of CLABSIs varied unexpectedly for some reasons, irrespective of the rates of HH adherence. The reason for the increased rates of CLABSIs could be attributed to the change of attending physicians among inexperienced residents. Noting that the infection rates increased, we repeated HH education and reminded new residents of the rules of bundle application, and warned them in this respect. Accordingly, the rates of infection were noted to decrease. Even if the application of CL bundle remains the key to prevent CLABSIs, other preventive interventions, including regularly checking overall adherence to the rules of HH and supporting HCP with reminder strategies, especially at the point-of-care should also be implemented.

This study also analyzed the risk factors related to the development of CLABSIs and found that they were not linked to the demographic data, including age and sex, a finding consistent with the literature [16].

Primarily, catheter placement sites should be carefully evaluated because they may be associated with the risk of infection due to the increased regional floral load of the skin and thrombophlebitis. Guidelines have emphasized that placement site and the type of catheters are important and that use of femoral catheters should be avoided, but subclavian catheters should be preferred [5]. However, in clinical practice, femoral catheters are more preferred for their easy placement and lower rate of complications. In contrast, the placement of subclavian catheters is demanding in that they require USG guidance and may lead to life-threatening complications such as pneumothorax. Regarding risk factors associated with CLABSIs, as opposed to what is usually accepted, a study found that the insertion site was not associated with an increased incidence of CLABSIs [2]. Our study surprisingly found that the femoral vein had the lowest infection rate, as did other studies [17, 20].

The reason for CVC insertion is likely to be associated with infection rates. Periodic change of CVCs is not a preferred method [5], but catheter dysfunction may occasionally occur due to causes such as thrombosis, which prompts catheter change. In a study conducted by Karapanou et al. [21], catheter placement, whether due to dysfunction or emergency, was found to increase the rate of infection.

Examining the indications for catheter placement, we found that catheterization for venous access and hemodialysis were the most common reasons and had the lowest rate of infection when catheter insertion was performed for hemodialysis.

Furthermore, the number of catheter lumens may be significantly involved in the increased rates of infection reported by several studies [5, 15]. Although a meta-analysis reported that there was no significant difference between the rate of infection and the number of catheter's lumens, the guidelines recommend using as few as possible lumens [5]. We also noted a higher rate of infection with the 3-lumen catheters than with the 2-lumen catheters.

Given all these findings, we could speculate that the reason for the unexpectedly low infection rate of femoral catheters may be related to the preference of femoral sites and 2-lumen catheters for hemodialysis, which was found to be associated with the lowest infection rate. Furthermore, difficulty in fixing dressings in subclavian and juguler regions may explain the increased rate of infection in such regions. However, as for the femoral site, dressings can be easily fixed to that region, and dressings may be covered by the diaper as well as the upper sheet of patients.

Furthermore, patients with a history of surgery, and those who received antibiotic therapy for the last 10 days, as well as those who were intubated as compared with those with no intubation had higher rate of infection.

Patients who had repeat catheter insertions also had a higher rate of infection. These invasive procedures and the use of antibiotics might make patients who have already weakened immunity more predisposed to infections. We also found that the need for emergency catheter placement elevated the rate of CLABSIs, which was considered to be probably related to inadequate preventive measures. Although there is a study showing that erythrocyte transfusion is protective in terms of infection development [20], consistent with the study by Polat et al. [16], the current study found that catheters through which blood and blood product transfusions were performed had higher rates of infection.

There are studies identifying that prolonged ICU stay as well as prolonged catheter duration are the factors associated with development of CLABSIs [16, 21]. Furthermore, such studies have also found that while APACHE II scores are associated with development of CLABSIs [2], other studies reported no association between APCHE III/IV scores and CLABSIs [12, 21]. In accordance with the literature, we also found that dwell time and prolonged ICU stay were the factors associated with infection, which could be attributed to more frequent bacterial colonization because of longer periods [2, 16].

In the current study, despite having lower rates of procalcitonin, we found that patients with no CLABSIs had higher levels of urea and creatinine. The reasons for higher levels of urine and creatinine could be that those patients had catheters with the aim of dialysis, which was performed with a two-lumen catheter. Accordingly, it can be concluded that patients with catheters for dialysis have a lower rate of CLABSIs.

When the causative agents were roughly evaluated, of the blood cultures of eight patients growing CoNS, which are part of normal skin flora, six were without bundle applications. This emphasizes the importance of appropriate skin cleaning that decreases the risk of contamination when bundle applications are performed. *Enterococcus* spp. and *Candida* spp., caused by antibiotic overdose, were also mostly isolated agents. Given *Enterococcus* spp., we could infer the importance of adherence to bundle application as well as hand hygiene, irrespective of the patient's own intestinal flora.

Of patients with CALBSIs, 51.1% developed mortality, and of those without CLABSIs, 68.8% died. The unexpectedly higher number of patients without CLABSIs who died may suggest that mortality might occur due to reasons other than infection.

In conclusion, considering risk factors in terms of CLABSIs, repeat catheterization is likely to raise the risk of infection. Patients with CLABSIs had prolonged ICU stay, which means that a longer ICU stay can raise the cost of care as well as the workload of healthcare personnel and the likelihood of developing other infections. In this context, meticulous adherence to bundle application and/or reducing the use of catheters is of vital importance to prevent CLABSIs.

Limitations

This study has several limitations. The study was carried out in only one of the ICUs of the hospital. All patients undergoing catheterization without bundle application were not included in the study. More comprehensive studies with a larger sample size may yield further data on risk factors for CLABSIs.

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

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Authors' contributions to the article

S.D. constructed the main idea and hypothesis of the study. S.D. developed the theory and arranged/edited the material and method section.S.D., I.A.S., A.K., S.K., H.S., K.O., N.A. and H.T. have done the evaluation of the data in the Results section. Discussion section of the article written by S.D., I.A.S., A.K., S.K., H.S., K.O., N.A. and H.T. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

Research Article

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Perioperative management of blood pressure in living donor kidney transplantation

Canlı donörden böbrek naklinde kan basıncının perioperatif yönetimi

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Abstract

Purpose: Delayed graft function (DGF) is a poor clinical prognostic factor in kidney transplantation (KT) which frequently occurs due to acute kidney injury (AKI) within the postoperative first week. In the present study, we researched the effect of SBP (Systolic Blood Pressure) on early graft function after reperfusion in living-donor kidney transplantation.

Materials and methods: We retrospectively obtained preoperative patient clinical data from anesthesia follow-up forms. The research data included demographic data, laboratory data, medical past and kidney-related information. SBP, central venous pressure [CVP], anesthesia duration, infusion and transfusion volumes, blood loss and urine output, surgery duration, ischemia duration and onset of graft diuresis were used as intraoperative data.

Results: There was no significant difference between 4 different systolic blood pressure categories assigned after reperfusion of the kidney in terms of the related characteristics of the recipients. There were significant differences between the 4 groups categorized according to SBP after reperfusion in terms of the related in with intraoperative anesthetic and surgucal variable (p<.001).

Conclusion: Systolic blood pressure over 140 mm Hg after reperfusion may be a safe level regarding long-term graft survival and mortality. It is needed to research the long-term prognosis of living donor kidney transplantation in larger study population to confirm the outcomes of our study.

Keywords: Blood pressure, kidney transplantation, perioperative management.

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Öz

Amaç: Gecikmiş greft fonksiyonu (DGF), sıklıkla ameliyat sonrası ilk hafta içinde akut böbrek hasarına (AKI) bağlı olarak ortaya çıkan böbrek transplantasyonunda (KT) kötü bir klinik prognostik faktördür. Bu çalışmada canlı donörden böbrek naklinde SKB'nin (sistolik kan basıncı) reperfüzyon sonrası erken greft fonksiyonu üzerine etkisini araştırdık.

Gereç ve yöntem: Hastaların ameliyat öncesi klinik verilerini retrospektif olarak anestezi takip formlarından elde ettik. Araştırma verileri demografik verileri, laboratuvar verilerini, tıbbi geçmişi ve böbrekle ilgili bilgileri içeriyordu. İntraoperatif veriler olarak SKB, santral venöz basınç (CVP), anestezi süresi, infüzyon ve transfüzyon hacimleri, kan kaybı ve idrar çıkışı, ameliyat süresi, iskemi süresi ve greft diürezinin başlangıcı kullanıldı.

Bulgular: Böbrek reperfüzyonu sonrası atanan 4 farklı sistolik kan basıncı kategorisi arasında alıcıların ilgili özellikleri açısından anlamlı bir fark yoktu. Reperfüzyon sonrası SBP'ye göre kategorize edilen 4 grup arasında intraoperatif anestezive cerrahi değişkenler açısından anlamlı fark vardı (p<.001).

Sonuç: Reperfüzyon sonrası sistolik kan basıncının 140 mm Hg'nin üzerinde olması, uzun süreli greft sağkalımı ve mortalite açısından güvenli bir seviye olabilir. Çalışmamızın sonuçlarını doğrulamak için canlı vericiden böbrek naklinin uzun vadeli prognozunun daha geniş çalışma popülasyonunda araştırılması gerekmektedir.

Anahtar kelimeler: Kan basıncı, böbrek nakli, perioperatif yönetim.

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Introduction

Delayed graft function (DGF) is a poor clinical prognostic factor in kidney transplantation (KT) which frequently occurs due to acute kidney injury (AKI) within the postoperative first week. It has been encountered in the review of available data that meticulous perioperative hemodynamic management of the patients performed KT may reduce the incidence of DGF [1]. Although there is no consensus yet, the definition of perioperative hypotension was found associated with risk for acute kidney injury in the recent studies on non-transplantation surgeries [2]. The French instructions for perioperative hemodynamic management (2013) and AKI (2016) have recommended monitoring and optimization of systolic ejection volume, and appropriate replacement of vascular volume [3]. Besides this, the guidelines for optimization of these informations and their routine use in KT patients have not been established yet [4]. Volume perfusion in the guidance of central venous pressure (CVP) is the traditional approach followed in KT [1]. However, this procedure may lead to excessive fluid load which may impair endothelial glycocalyx and cause fluid shift to the interstitial space [4]. In addition, renal hypoperfusion may occur after fluid load. As a consequence, fluid management during KT is left at the discretion of the anesthetist during the case because there is no guideline available in clinical practice which focused on optimal blood pressure targets and hemodynamic management. Kidney transplantation is the treatment method preferred in the patients with end-stage renal failure. The kidneys obtained from the living donors have longer-term and better-quality graft survival compared with the cadaveric kidneys [4]. The most important focus point of intraoperative anesthesia management in kidney transplantation is to prevent hypotensive attacks and to preserve perfusion pressure supplied to the graft at optimal level. It is important to supply optimal renal perfusion to prevent acute tubular necrosis and renal artery thrombosis. Nevertheless, there is a very small number of studies conducted on blood pressure management during kidney transplantation. It has been reported that early graft function after kidney transplantation may affect long-term graft survival [5, 6]. In the present study, we researched the effect of SBP on early graft function after reperfusion in living-donor kidney transplantation.

Material and method

The present study was approved by Non-Interventional Clinical Research Ethics Committee of Pamukkale University Medical Faculty in August 2023 (Permission Date 05.09.2023, and number 60116787-020-415588). We retrospectively obtained preoperative clinical data of the patients from anesthesia follow-up forms. The research data included demographic data (e.g. age, gender, body mass index), laboratory data (e.g. hemoglobin, albumin), medical past (e.g. complications before kidney transplantation) and kidney-related information (reason of the end-stage kidney disease, duration and type of dialysis, HLA incompatibility). SBP, central venous pressure [CVP], anesthesia duration, infusion and transfusion volumes, blood loss and urine output, surgery duration, ischemia duration and onset of graft diuresis were used as intraoperative data. The estimated glomerular filtration rate (eGFR) and creatinine level within the postoperative first 7 days were recorded as graft function. Postoperative variables (e.g. mechanical ventilation duration, postoperative intensive care unit (ICU) admission duration and total admission duration (from surgery date to discharge date)) as well as data related with postoperative complications such as acute tubular necrosis, delayed graft function, acute transplant rejection, pulmonary edema, perirenal hematoma and death were obtained from the hospital database.

Anesthesia and operation

General anesthesia induction was achieved by using propofol, remifentanil and atracurium, and following maintained by desflurane and remifentanil infusion. Together with standard monitoring, continuous arterial pressure monitoring invasive arterial monitorization though radial artery and continuous CVP monitoring through internal jugular vein were performed. In the anesthesia for renal transplantation surgery, one of the most important main targets of monitorization is probably maintenance of renal blood flow and optimal intravascular volume state. The continuous monitorization of arterial blood pressure and evaluation of reciprocal variations of pressure waveform are important for hemodynamic management. Prior to graft perfusion, optimal arterial pressure level of 70-90 mmHg and CVP level of 8-12 mmHg were maintained by preserving

adequate intravascular volume in hemodynamic management and achieving meticulous titration of anesthetic agents. The administration of 0.9% isotonic solution from the crystalloid solutions was avoided due to concerns of hyperchloremia, metabolic acidosis and renal vasoconstriction, Ringer's lactate solution was used primarily. It was administered as a crystalloid solution at a rate of 1-3 mL/kg/hour intraoperatively. The administration of hydroxyethyl starch (HES) solutions was abstained because of increasing the risk for renal failure in the critical patients. After completion of vascular anastomoses, particularly hypotension was avoided during renal perfusion. The alpha agonist agents were abstained as far as possible because of vasoconstriction effects in the patients with hypotension despite fluid resuscitation.

In addition to standard monitoring, invasive arterial pressure and central venous pressure monitoring was performed. The arterial catheter was inserted into the radial artery while the central venous catheter was placed into the internal jugular vein. Preferably lactated ringer solution was infused during the operation taking central venous pressure into consideration to prevent acidosis. Fluid therapy was planned to maintain the CVP at 10-15 mmHg before graft reperfusion. All the patients were administered 20 mg basiliximab preoperatively and 500 mg methylprednisolone during vascular anastomosis through central venous catheter. Additionally, each patient was given 20 mg furosemide just after reperfusion to improve allograft perfusion pressure and to increase diuresis. We distributed the patients into 4 groups according to systolic blood pressure (as <130 mmHg, 130-139 mmHg, 140-149 mmHg, >150 mmHg) after reperfusion to evaluate the effect of systolic blood pressure on early graft function in living donor kidney transplantation. The eGFR and creatinine values within the postoperative first 7 days were recorded as the essentially measured parameters. Urine output after reperfusion and postoperative clinical course were recorded as the secondary results.

Statistical analysis

The continuous variables were presented as mean (95% confidence interval [CI]) and compared using Kruskal-Wallis test. The recipient's urine output was distributed into 2 categories (as high and low) based on preoperative systolic blood pressure and their relationship with postoperative kidney function or postoperative complications was evaluated. The continuous variables were presented as mean (95% CI) in the analyses. All results were analyzed with a p value <0.05 considered significant.

Results

The patients who underwent living donor kidney transplantation (n=203) between January 2009 and May 2022 in the Pamukkale University Medical Faculty Hospital were screened. We excluded 17 patients in the pediatric group and 6 patients with a history of perioperative massive haemorrhage (>2000mL). We retrospectively analyzed 180 patients in the present study. Table 1 and 2 show the essential characteristics of the recipients. There was no significant difference between 4 different systolic blood pressure categories assigned after reperfusion of the kidney in terms of the related characteristics of the recipients.

Mean eGFR levels of the systolic blood pressure groups were between 9.6 mL/min/1.73 m^2 and 11.5 mL/min/1.73 m^2 in the preoperative last day. The eGFR levels were 13.6, 12.9, 14.1 and 13.1 mL/min/1.73 m^2 in the groups with SBP level of <130, 130-139, 140-149 and >150 mmHg in the postoperative 1st day, respectively. The creatinine levels were 4.5, 3.9, 4.2 and 3.1 mg/dl between systolic blood pressure groups in the postoperative 1st day, respectively. There was no significant difference between the 4 groups categorized according to systolic blood pressure level after reperfusion in terms of eGFR or creatinine values in any day of the postoperative first week. In addition, there was no significant difference between the 4 groups in terms of eGFR or creatinine levels according to a 1-year follow-up period.

Table 1. Preoperative demographic and clinical data of recipients

	Post-Reperfusion Systolic Blood Pressure (mmHg)				
	<130 (n=41)	**130-139 (n=34)**	**140-149 (n=45)**	**>150 (n=60)**	***p***
Age (year)	46.1 (42.1-50.3)	45.8 (43.0-48.7)	40.4 (39.3-43.3)	40.7 (37.8-44.1)	<.001
Men, n (%)	19 (46.3)	26 (76.4)	21 (46.6)	34 (56.6)	.70
Weight (kg)	69.9 (65.8-74.1)	60.6 (57.5-63.9)	71.3 (69.0-73.7)	62.9 (59.5-66.1)	.65
Comorbidities					
Diabetes mellitus	11 (26.8)	16 (47.0)	14 (31.1)	17 (28.3)	.77
Hypertension	27 (65.8)	21 (61.7)	29 (64.4)	36 (60.0)	.74
Serum albumin (g/dL)	3.8 (3.6-4.1)	4.0 (3.9-4.1)	3.7 (3.5-3.9)	4.1 (3.9-4.2)	.11
Preoperative Hb (g/dL)	10.1 (9.6-10.7)	11.0 (10.7-11.2)	11.8 (11.6-12.1)	10.9 (10.7-11.0)	.82
Preoperative BP (mmHg)					
SBP	125 (118-129)	134 (131-138)	146 (142-149)	156 (151-162)	<.001

BP: Blood Pressure, SBP: Systolic Blood Pressure, HB: Hemoglobin, A *p* value <0.05 is considered statistically significant

Table 2. Dialysis and Transplant Data (n=180)

	SBP After Reperfusion (mmHg)				
	<130 (n=41)	**130-139 (n=34)**	**140-149 (n=45)**	**>150 (n=60)**	***p***
Type of dialysis, n(%)					
Hemodialysis	34 (82.9)	30 (88.2)	42 (93.3)	55 (91.6)	
Peritoneal dialysis	7 (17.1)	4 (11.8)	3 (6.7)	5 (8.4)	
Duration of dialysis (mo)	26.4 (20.2-31.5)	26.7 (22.9-40.1)	35.9 (25.1-46.29)	30.3 (20.4-41.7)	.87
Etiology of kidney disease, n(%)					
Diabetes mellitus	16	9	12	11	
Glomerulonephritis	15	14	17	19	
Hypertension	6	10	11	22	
Polycystic kidney disease	3	1	4	5	
Urological	1	0	1	3	
HLA mismatches	2.6 (2.3-3.1)	2.9 (2.5-3.2)	3.0 (2.8-3.3)	2.7 (2.5-2.9)	.73

HLA: Human Leukocyte Antigen, Mo:Month, A *p* value <0.05 is considered statistically significant

Table 3 shows the relationship of systolic blood pressure after reperfusion with intraoperative anesthetic and surgical variables. There were significant differences between the 4 groups categorized according to SBP after reperfusion (*p*<.001): The relationship between SBP after reperfusion and urine output in terms of age, gender, transfusion and haemorrhage was evaluated to be similar with the results of one-variable analysis shown in Table 3.

Table 4 shows the results of the recipients after transplantation. Our patients are routinely referred to the organ transplantation ward and monitored according to the principles of intensive care unit. We encountered acute rejection clinic in none of our patients. None of our patients became exitus within the first year. The prevalence of hematoma as a postoperative complication was also found significantly different between the 4 groups (*p*=.01). Besides, the other postoperative complications were atrial fibrillation (n=1), delirium (n=3) and dental abscess (n=1). No significant difference was found between the systolic blood pressure groups regarding these complications.

Table 3. Intraoperative anesthesia and surgical data (n=180)

	SBP After Reperfusion (mmHg)				
	<130 (n=41)	**130-139 (n=34)**	**140-149 (n=45)**	**>150 (n=60)**	***p***
Surgery time (min)	181 (169-195)	189 (170-194)	175 (171-194)	183 (174-199)	.06
Anesthesia time (min)	223 (208-237)	230 (208-247)	229 (205-248)	234 (209-241)	.11
Ischemia time (min)					
Warm	2.1 (1.5-2.8)	2.2 (1.4-2.6)	1.9 (1.3-2.5)	2.5 (1.4-2.9)	.70
Cold	44 (41-49)	47 (43-51)	45 (40-54)	49 (47-58)	.27
Intravenous fluid (mL)					
Ringer lactate	1740 (1480-2090)	2080 (1950-2250)	1930 (1810-2070)	1970 (1800-2090)	.72
Blood loss (min)	110 (80-1709	145 (110-190)	130 (105-170)	160 (145-2109	.14
Postreperfusion urine utput (mL/h)	165 (119-205)	312 (265-395)	345 (296-410)	340 (289-415)	<.001
Length of postoperative hospital stay (days)	12.7 (10.1-14.6)	13.8 (12.1-15.6)	14.8 (13.7-16.1)	12.9 (10.9-13.9)	.21
Postoperative complications, n (%)					
Acute tubular necrosis	6 (14.6)	3 (8.8)	1 (2.2)	3 (5)	<.001

Min:Minute, A *p* value <0.05 is considered statistically significant

Table 4. Post-transplant results of recipients

	SBP After Reperfusion (mmHg)				
	<130 (n=41)	**130-139 (n=34)**	**140-149 (n=45)**	**>150 (n=60)**	***p***
Length of postoperative hospital stay (days)	12.7 (10.1-14.6)	13.8 (12.1-15.6)	14.8 (13.7-16.1)	12.9 (10.9-13.9)	.21
Postoperative complications, n (%)					
Acute tubular necrosis	6 (14.6)	3 (8.8)	1 (2.2)	3 (5)	.90
Delayed graft function	1 (0.02)	3 (0.09)	2 (0.04)	1 (0.01)	.72
Pulmonary edema	1 (0.02)	0 (0.0)	4 (0.09)	2 (0.03)	.14
Hematoma	2 (0.05)	0 (0.0)	1 (0.02)	2 (0.03)	.01
Kidney function eGFR					
Preoperative	10.9 (9.6-11.5)	11.5 (10.2-12.7)	9.6 (9.1-10.7)	11.1 (10.6-11.9)	<0.001
Postoperative first day	13.6 (12.5-14.4)	12.9 (12.1-14.1)	14.1 (13.1-14.7)	13.1 (12.4-14.1)	<0.001
Postoperative seventh day	39.7 (39.1-40.6)	41.2 (39.0-42.7)	40.7 (39.5-43.8)	43.7 (42.1-45.8)	<0.001
Kidney function, creatinine (mg/dL)					
Preoperative	8.3 (6.9-9.1)	7.5 (7.1-8.2)	7.7 (7.3-8.9)	6.9 (7.0-8.2)	<0.001
Postoperative first day	4.5 (4.1-4.9)	3.9 (3.4-4.5)	4.2 (3.7-4.9)	3.1 (2.8-3.7)	<0.001
Postoperative seventh day	1.1 (0.9-1.4)	1.4 (1.2-1.6)	1.5 (1.3-1.8)	1.3 (1.2-1.7)	<0.001

eGFR: Estimated Glomerular Filtration Rate, SBP:Systolic BLood Pressure, A *p* value <0.05 is considered statistically significant

Discussion

Many studies have revealed that an optimal blood pressure management is needed to protect the graft during the anesthesia. In the previous years, for instance Tiggeler et al. [7] have reported that an effort should be exerted to maintain the SBP at >120 mmHg and emphasized that 140 mmHg is an ideal target. Also we routinely achieve a sustainable blood pressure control over this value in our operations. Nevertheless, the most appropriate blood pressure level for the kidney transplant recipients has not been exactly determined despite every treatment plan and study yet. No significant difference was discovered between the 4 groups categorized according to SBP after reperfusion in terms of early graft function or major complications. However, the group with SBP <140 mm Hg after reperfusion had a tendency to show significantly lower urine output compared with the other 3 groups after releasing the renal vascular clamp. Pascual et al. [8] have reported that lower urine output values within the post-transplant first 24 hours are associated with worse 5-year graft survival rates. Besides, they have emphasized that early-term successful graft function is an important factor for long-term survival. Moreover, in our study, considering the relationship between urine output and kidney function, we found that the recovery period was more successful in the patients detected with better urine output, and fewer postoperative complications were observed. Thus, systolic blood pressure over 140 mmHg after reperfusion may be a safe level regarding long-term graft survival and mortality. Preoperatively high systolic blood pressure can be accepted as an indicator of high blood pressure after reperfusion in our recipient patients. Besides, increasing use of vasoactive inotropic agents can be associated with reduced SBP after reperfusion. In our protocol, we do not prefer to use any routine vasoactive agent, considering its potential side effects. It has been reported that maintenance of adequate intravascular volume is needed to improve early graft function to prevent acute renal failure or kidney transplantation [9]. Intraoperative volume expansion was recommended before graft reperfusion while maintaining CVP at 10-15 mmHg to protect from acute tubular necrosis secondary to inadequate intraoperative hydration [10].

It can be considered that our study has several limitations. As the first limitation, inadequate study power can be mentioned since this is the first study in our study conducted on the relationship between arterial blood pressure after reperfusion and early graft function in living donor kidney transplantation. Secondly, we researched the effect of SBP after reperfusion on early graft function in living donor kidney transplantation retrospectively. There may be uncontrollable factors in the individual recipients, such as their capability to preserve high blood pressure and the efficacy of vasoactive inotrope agents. However, it is difficult to manage the anesthesia technically in the cases of excessively low or excessively high blood pressure during kidney transplantation. The strong side of our study is obtaining the patient data by a researcher directly from the database and analysing it by two different researchers to confirm its accuracy.

In conclusion, no significant difference was observed between the 4 groups categorized according to SBP after reperfusion in terms of early graft function or major complications. However, the group with SBP <140 mm Hg showed significantly lower urine output compared with the remaining 3 groups after releasing the renal vascular clamp. Systolic blood pressure over 140 mm Hg after reperfusion may be a safe level regarding long-term graft survival and mortality. It is needed to research the long-term prognosis of living donor kidney transplantation in a larger study population to confirm the outcomes of our study.

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

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Authors' contributions to the article

I.H.A. constructed the main idea and hypothesis of the study. I.H.A. and A.M.Y. developed the theory and arranged/edited the material and method section. U.O and M.C have done the evaluation of the data in the Results section. Discussion section of the article written by I.H.A., U.O., A.M.Y and M.C reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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The effects of reoperations due to inadequate treatment in differentiated thyroid cancers on morbidity, mortality and costs

Diferansiye tiroid kanserlerinde yetersiz tedavi nedeniyle yapılan reoperasyonların morbidite, mortalite ve maliyetlere etkisi

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Abstract
Although the incidence of differentiated thyroid cancer (DTC) is high, mortality is quite low. In low and intermediate risk DTCs, reoperations due to inadequate treatment can increase morbidity, mortality, and costs in patients. In our study, current articles published on this subject were reviewed and evaluated. According to our results, morbidity, mortality and costs increase due to inadequate treatment in DTCs. Therefore, even in low and intermediate risk DTC cases, adequate surgeries such as total or near total thyroidectomy should be performed by high volume endocrine surgeons and moderate TSH suppression should be applied in all cases.

Keywords: Effects, reoperations, differentiated, thyroid, cancers.

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Öz
Diferansiye tiroid kanseri (DTK) insidansı yüksek olmakla birlikte mortalitesi oldukça düşüktür. Düşük ve orta riskli DTK'lerinde yetersiz tedavi nedeniyle yeniden yapılan ameliyatlar hastalarda morbidite, mortalite ve maliyetleri artırabilir. Çalışmamızda bu konuda yayınlanmış güncel makaleler incelenip değerlendirilmiştir. Sonuçlarımıza göre, DTK'lerinde yetersiz tedavi nedeniyle morbidite, mortalite ve maliyetler artmaktadır. Bu nedenle, düşük ve orta riskli DTK vakalarında bile, yüksek hacimli endokrin cerrahlar tarafından total veya totale yakın tiroidektomi gibi yeterli ameliyatlar yapılmalı ve tüm vakalarda orta derecede TSH supresyonu uygulanmalıdır.

Anahtar kelimeler: Etkileri, reoperasyonlar, diferensiye, tiroid, kanserleri.

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Introduction

According to GLOBACAN data, the incidence of DTC is 4 and mortality is 0.5 per hundred thousand in the world [1].

The classical approach in the treatment of DTC cases is surgery, RAI and TSH suppression. Although the primary treatment is reoperation in cases of residual or recurrent DTC, some new treatment methods such as percutaneous ablation and external radiotherapy are also applied under the guidance of ultrasonography [2].

Although there is general consensus among thyroid specialists regarding the indications for RAI treatment, there are dilemmas regarding the extent of surgical treatment and the necessity of TSH suppression. In cases of DTC that are inadequately treated, reoperation is performed due to residual cancer tissue or relapses, resulting in increased cost, morbidity and mortality, and psychological problems. For this reason, studies on the effects of reoperations due to inadequate treatment in DTCs on morbidity, mortality and costs were compiled and evaluated in our study.

According to the results obtained in a study by Scheller et al. [3], it was reported that molecular analyzes such as somatic mutations, gene expression profiles and miRNA tests should be performed while risk stratification is performed to decide on the type of surgery to be performed in DTCs.

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In DTC cases, recurrence occurs in approximately 15% of cases after the first operation. The most important risk factor leading to this is the aggressive nature of tumor cells [4].

Nieto et al. [5] detected 128 potential biomarkers for relapse in DTCs in a study they conducted, and they formed a 5-gene risk score as an independent prognostic predictive factor from these biomarkers. In a study by Harries et al. [6], it was reported that HUMARA and BRAF mutations, recurrence and lymph node metastasis rates are high in bilateral cancer (BC) and multifocal (MF) DTCs. In a single center study by Shaunak et al. [7], 478 DTC cases were analyzed and MF was reported to be an important risk factor. In a study by Kaliszevsky et al. [8], 27.1% of 177 PTC cases were found to be MF and 8.5% were BC. In a study conducted by Shen et al. [9], 33.3% of 110 patients who underwent reoperation had MF, 56.7% had BC DTC, complications of up to 32.6% occurred in these cases after reoperation, and reoperations put the patient at psychological and physical risk, therefore, it has been reported that definitive operations in DTCs should be standardized and reoperations should be avoided.

In a study conducted by Wilson et al. [10], 32 of 362 thyroidectomy cases performed by a single surgeon in a single center were reoperated for recurrence (1) or persistent cancer (31), and serious complications such as permanent hypocalcemia, NLI paralysis, and bleeding occurred in 21.8% of these cases. Due to the high complication rates in reoperations, it has been reported that resection should be adequate in primary surgery for thyroid malignancies. According to the results of Araz et al.'s [11] study in 1014 T1N0 DTC cases; MF, BC, and tumor diameter >1 cm were reported to be negative prognostic factors.

In a study, it was reported that the most appropriate treatment method in DTCs in children is total thyroidectomy (TT) and regional removal of metastasized lymph nodes, and that prognostic information can be obtained by using molecular diagnostic methods and personalized chemotherapy can be performed in these cases [12]. In a study by Sakiz et al. [13], in 1409 DTC cases, cases with and without Hashimoto's thyroiditis (HT) were compared, and they reported that lymphovascular invasion and perineural invasion were more common in cases with HT and affected prognosis poorly. Therefore, definitive operations should be performed in DTC cases with HT.

According to a study by Ullman et al. [14], the most important reason for the increase in the number of thyroid cancers in recent years is overdiagnosis. In low-risk DTCs, surgical treatment should be personalized and the extent of the resection should be adjusted according to the patient.

Cancer cells doubling time (CDT) and dwelling time (DT) in DTCs are much longer than in many other types of cancer. For example, although CDT is only 103 days in some types of breast cancers [15], in DTCs it is at least several years. Therefore, the active follow-up period should be long in all DTC cases in postoperative period to detect recurrence cases. In a study by Oh et al. [16], 273 papillary thyroid cancer (PTC) cases were followed under active observation and CDT was investigated. CDT was found to be less than 5 years in approximately 1/3 of these cases (rapid CDT cases), and 1/3 of them were found to have CDT more than 5 years (slow CDT cases). 19% of rapid CDT cases were operated within 29 months of the onset of active observation. It has been determined that the average age of these cases is younger, and that regional lymph node metastases occur within an average of 2.2 months.

In a study by Giovanella et al. [17] in 1421 DTC cases, 20% of DTCs recurred, 10% of these cases died, and investigating the Tg doubling time (TgDT) had an effect on tumor recurrence, predicting response to treatment, and overall survival (OS).

Park et al. [18] reported that Tg and Tg/TSH ratios could rise independently of the disease although there was no recurrence in the 6-year follow-up period after lobectomy (LT) surgeries performed in 208 low-risk DTC cases. Therefore, the authors stated that the monitoring of serum Tg values in DTC cases undergoing LT cannot have a predictive role.

Recurrence and mortality were investigated for an average of 18.9 years in 466 DTC cases who underwent curative treatment between 1981 and 1991 by Dong et al. [19]. Only 1.5% of these cases were treated with RAI. Cancer specific mortality was found to be 2.7, 6.2, 8.6 in the 10^{th}, 20^{th} and 30^{th} years respectively.

In DTC cases, residual cancer focus may remain after surgery due to insufficient resection. In a study conducted by Freeman, it was reported that approximately 1/3 of DTC cases left residual cancer or relapsed, and the main treatment method in these cases was reoperation [20]. In a study by Harries et al. [21], the effects of the type of surgery on mortality and morbidity were investigated in 849 DTC cases, 619 of which were unifocal and 230 (27.1%) of MF. According to the results obtained in the study, it was reported that LT did not increase mortality in selected MF cases. However, the mean follow-up period of the patients was found to be only 58 months in the study. In a study conducted by Bates et al. [22], in 69 DTC cases that underwent 92 reoperations, it was determined that 51% of the cases had MF, the mean reoperation time was 21 months, and the mean tumor diameter was 24 mm. It has been shown that the vast majority (97.1%) of the reoperated cases were not relapsed only residual.

In a study conducted by Biliomoria et al. [23] in 52,173 DTC cases, it was determined that the extent of the operation performed in >1cm DTC cases was directly parallel to the survival and did not affect cases with <1cm. However, the cases were followed only for an average of 10 years in this study. Considering the length of CDT in DTC cases, there is a possibility of increased mortality in DTC cases <1 cm when the active surveillance period is extended [18, 24].

In a study conducted in 1503 DTC cases followed with a standardized protocol, cancer-specific survival (CSS) was found to be 98.6%, 94.7%, and 87.4% at the 5^{th}, 10^{th}, and 15^{th} years, respectively. It was determined that 22.9% of the cases were MF, and tumor tissue was left behind in 24.6% of the cases after the operation, and the cancer-specific mortality (CSM) was higher in these cases. For this reason, it has been reported that the primary surgery should be exactly arranged in DTC cases [25]. In a study by Benkhaodura et al. [26], complication rates in ipsilateral and contralateral operations were compared in 73 patients, most of whom underwent reoperation due to inadequate thyroidectomy. In addition, it has been reported that complication rates are higher in ipsilateral reoperations, but the morbidity seen in contralateral reoperation cases is higher than in primary thyroidectomies, therefore, primary surgery should be performed adequately. Colombo et al. [27] compared the cases who underwent LT and TT in 370 low and intermediate risk DTC cases operated in a single center, and it was reported that 15% of the low risk DTCs who underwent LT and 50% of the cases in the intermediate risk group required additional treatment. In a study conducted by Medas et al. [28], 4420 DTC cases and 152 cases that were reoperated for recurrence after the primary operation were compared, and it was reported that LT was performed in 40.8% of the reoperated cases. It was found that the operation time, transient NLI paralysis, and permanent and transient hypoparathyroidism were significantly higher in patients who underwent reoperation. In a study by Young et al. [29], mortality was investigated in 222 patients who underwent reoperation in 11.986 >1cm DTC cases. Most of the reoperated cases have persistent disease and that the mortality due to the disease was independently statistically significantly higher in these patients. In a study conducted by Yim, recurrence occurred in 139 (10.2%) of 1357 DTC cases who underwent primary surgery by the same surgeon, within an average of 2.3 (1-10) years. It has been reported that TT was performed in only 2 of the relapsed cases, the mean tumor diameter was 2.5 cm, and 12.2% of them were T1N0 [30]. According to the results of a meta-analysis conducted by Bojoga et al. [31] in studies consisting of multiple cases, OS does not change statistically significantly compared to TT in conservative surgeries performed in selected low-risk DTC cases. However, the variables in this study show great heterogeneity and the follow-up period is less than 10 years in most of the cases.

Another dilemma among the authors in the treatment of DTCs is whether or not to use TSH suppression. One of the most important reasons for surgeons recommending conservative surgery in cases of low and intermediate DTC is that the patient does not use levothyroxine in the postoperative period. Also some authors have reported that TSH suppression does not prolong survival and leads to some complications such as osteoporosis [32]. However, some authors disagree on this respect: In a study conducted by Carhill et al. [33] in 4941 DTC cases, it was shown that moderate TSH suppression in the

early period at all stages prolongs OS. In a study conducted by Petersen et al. [34], on 1462 middle-aged women using levothyroxine for a long time, it was revealed that levothyroxine did not increase morbidity and mortality, and did not decrease the quality of life.

One of the most important reasons of the authors recommending LT as a surgical treatment method in DTCs is the higher complication rates of TT compared to LT. However, according to many authors, the most important factor affecting the complication rates in thyroid surgery is the high or low volume thyroid surgeon, rather than the extent of the operation. In a study conducted by Kandil et al. [35] in 46.261 cases, complication rates in thyroidectomy cases, regardless of the extent of the operation, are much lower in high-volume surgeons than in low-volume surgeons. When thyroidectomy operations are performed by high-volume surgeons, morbidity is low and minor complications can be easily treated [36].

Currently, surgery to remove the other lobe some time after primary LT in thyroid surgery has been simplified and defined as the second stage of an operation and called “complementary thyroidectomy” (CT). However, this application is actually a reoperation due to inadequate primary surgery.

It has been reported that CT should be performed in more than half of DTC cases [37] who underwent LT in accordance with ATA recommendations, based on the results of histopathological examinations performed during or after the operation [38, 39]. DiMarco et al. [40] reclassified 275 DTC cases who were in the low risk group and underwent LT preoperatively in accordance with ATA recommendations, according to operative and histopathological findings. Angioinvasion and local invasion or both were detected in 43.5% of these cases (117 cases), and accordingly CT was performed. In these cases, sex, age, familial anamnesis and tumor size were not found to be independent predictive factors.

Reoperations due to inadequate treatment in low and intermediate risk DTCs may have an increasing effect on total costs. In a study by Mammen and Cooper [41], it was reported that LT can be performed instead of TT in selected DTC cases, but they are not sure about the cost-effectiveness of these surgeries, and further research is needed on this subject. In a study conducted by Kim et al. [42] regarding the cost-effectiveness of treatments performed in DTC cases, TT was found to be the most cost-effective surgical method in terms of OS.

One of the most important problems in inadequate resections in DTC cases is the ineffectiveness of the treatment when RAI treatment is required, since thyroid tissue ablation is not performed. This situation also increases the total cost of treatment. In a study conducted in Germany, the cost of one session in the treatment of IUDs in thyroid diseases was found to be 1530 Euros on average [43].

According to the results we obtained in our study, performing reoperations due to inadequate treatment in low and intermediate risk DTC cases increases morbidity, mortality and costs. Therefore, operations such as TT or near TT should be preferred in all DTC cases. A second advantage of these operations is that thyroid ablation is easier when RAI treatment is required, and the treatment is more effective.

Moderate TSH suppression after the operation does not cause complications such as osteoporosis, and reduces the rates of recurrence and mortality.

Since CDT is long in low and intermediate risk DTC cases, it may take a very long time to detect residual tumor foci or recurrences. For this reason, the active follow-up period should be kept as long as 30 years, especially in cases where conservative operations were performed.

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Authors' contributions to the article

H.A. constructed the main idea and hypothesis of the study. A.A. developed the theory and arranged/edited the material and method section. H.A. has done the evaluation of the data in the Results section. H.A. reviewed, corrected and approved. In addition, all authors discussed the entire study and approved the final version.

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