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EDITORIAL

Our dear readers,

We are happy to publish the new issue of our journal. JOMPAC has completed 3 years since its establishment. When we look at these three years, it is clearly understood that our journal has come a long way in a positive way. We are getting closer to our scientific goals day by day. In near future, we want to contribute to international literature at an increasing level and to increase the success bar of our journal by entering valuable international indexes such as SCI-Exp and Pubmed. We would like to thank all authors for submitting articles contributing to both domestic and international literature with their comprehensive scientific content for publication in our journal.

Sincerely yours

Assoc. Prof. Alpaslan TANOGLU
Editor-in-Chief

EDİTÖRDEN

Sevgili okuyucularımız,

Dergimizin yeni sayısını yayımlamanın mutluluğunu yaşıyoruz. JOMPAC kuruluşundan bu yana 3 yılı tamamladı. Bu üç yıla baktığımızda dergimizin olumlu anlamda çok yol kat ettiği açıkça görülmektedir. Bilimsel hedeflerimize her geçen gün daha da yaklaşıyoruz. Yakın gelecekte SCI-Exp ve Pubmed gibi değerli uluslararası indekslere girerek uluslararası literatüre artan düzeyde katkı sağlamak ve dergimizin başarı çıtasını yükseltmek istiyoruz. Kapsamlı bilimsel içeriği ile hem yerli hem de uluslararası literatüre katkı sağlayan makalelerini dergimizde yayınlanmak üzere gönderen tüm yazarlara teşekkür ederiz.

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The utility of $ETCO_2$ value in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia

Hastanede yatan COVID-19 hastalarında hastalığın ilerlemesini ve mortalite riskini tahmin etmede $ETCO_2$ değerlerinin kullanılabilirliği

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ABSTRACT

Aim: End-tidal CO_2 ($ETCO_2$) levels are reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of his/her SpO_2 values. This study aimed to investigate the utility of $ETCO_2$values in predicting the need for intubation, ICU admission, and mortality in hospitalized patients with COVID-19 pneumonia.

Material and Method: A total of 108 hospitalized patients with COVID-19 pneumonia were included. Data on respiratory parameters (oxygen saturation, $ETCO_2$, and respiratory rate [RR]- with and without O_2 [w/wo O_2]) and laboratory parameters were recorded.

Results: The need forintensive care unit(ICU) admission was associated with significantly higher $ETCO_2$ values (wO_2:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO_2: 30.1(4.9) vs. 23.8(6.9), p=0.040). Mortality was associated with higher likelihood of higher RR (wO_2:32.4(5.8) vs. 24.6(6.8), p=0.002) and lower oxygen saturation (wO_2:92.9(3.8) vs. 95.5(4.2), p=0.025; woO_2:87.1(5.7) vs. 91.8(6.6), p=0.013). Presence vs. lack of intubation need was associated with significantly increased likelihood of saturation (wO_2:93.1(5.3) vs. 95.9(3.8), p=0.013; woO_2:87.6(8.3) vs. 92.3(5.9), p=0.007). Hospital discharge vs. ICU stay was associated with significantly higher $ETCO_2$ values (wO_2:27.9 (4.6) vs. 18.6(8.4), p=0.040; woO_2: 30.1(4.9) vs. 23.8(6.9), p=0.040)

Conclusion: Our findings revealed the association of decreased $ETCO_2$ (w/wo O_2) values with a lower likelihood of hospital discharge and increased likelihood of ICU transfer. Low oxygen saturation levels related the increased risk of both intubation need and mortality in hospitalized COVID-19 patients.

Keywords: COVID-19, intensive care unit, mortality, emergency medicine

ÖZ

Amaç: End-tidal CO_2 ($ETCO_2$) seviyeleri, SpO_2 değerlerinden bağımsız olarak hastanın solunum ve metabolik/perfüzyon durumunu yansıtır. Bu çalışma, hastanede yatan COVID-19 hastalarınıda entübasyon ihtiyacını, yoğun bakım ünitesine kabulünü ve mortaliteyi tahmin etmede $ETCO_2$ değerlerinin faydasını araştırmayı amaçladı.

Gereç ve Yöntem: COVID-19 pnömonisi olan toplam 108 hastanede yatan hasta dahil edildi. Solunum parametreleri (oksijen satürasyonu, $ETCO_2$ ve solunum hızı [RR]- O_2'li ve O_2'siz [w/wo O_2]) ve laboratuvar parametreleri ile ilgili veriler kaydedildi.

Bulgular: COVİD-19 hastalarında yoğun bakım ünitesine yatış ihtiyacı, anlamlı olarak daha yüksek $ETCO_2$ değerleri ile ilişkilendirildi. (wO_2:27,9 (4,6) vs. 18,6(8,4), p=0.040; woO_2: 30,1 (4,9) vs. 23,8 (6,9), p=0.040). Mortalite, daha yüksek RR olasılığı (wO_2:32,4 (5,8)'e karşı 24,6 (6,8), p=0.002) ve daha düşük saturasyon (wO_2:92,9 (3,8)'e karşı 95,5 (4,2), p=0.025; woO_2: 87,1 (5,7) vs. 91,8(6,6), p=0.013) ile ilişkili bulundu.

Sonuç: Bulgularımız, azalmış $ETCO_2$ (w/wo O_2) değerlerinin hastaneden taburcu olma olasılığının daha düşük ve yoğun bakım ünitesine transfer olasılığının artmasıyla ilişkisini ortaya koydu. Düşük oksijen satürasyon seviyeleri, hastanede yatan COVID-19 hastalarında hem entübasyon ihtiyacı hem de mortalite riskinin artmasıile ilişkili bulundu.

Anahtar Kelimeler: COVID-19, yoğun bakım ünitesi, mortalite, acil servis

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INTRODUCTION

Caused by a novel severe coronavirus designated as acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the coronavirus disease-2019 (COVID-19) has become a rapidly spreading pandemic since its onset in Wuhan, China, at the end of 2019 (1,2). COVID-19 has a wide clinical spectrum ranging from asymptomatic or a mild-to-moderate disease with milder symptoms to severe pneumonia with the rapid development of acute respiratory distress syndrome (ARDS) and multiple organ failure and even death (3,4). Notably, early ARDS caused by COVID-19 is considered to significantly differ from the ARDS due to different etiologies in terms of a mismatch between changes in respiratory mechanics and severity of impaired oxygenation, significantly decreased ventilation efficiency and lower lung recruitability (5-7). Hence, the lung tissue in COVID-19 patients recovering from severe ARDS is considered to reflect the typical characteristics of late-phase ARDS (reduced lung compliance, pulmonary fibrosis, and decreased end-expiratory lung volume) but also a more pronounced increase in dead space than in patients with severe ARDS due to other reasons (5,8,9).

The presence of significantly decreased ventilation efficiency and hypermetabolism even in the recovery period in COVID-19 patients is considered to explain the experience of more severe respiratory distress and CO_2 retention by these patients in the late phase of ARDS (9). The ratio of physiologic dead space to tidal volume (VD/VT) at ARDS onset was considered a strong and independent predictor of mortality risk, in addition to its demonstrated utility in detecting lung recruitment and de-recruitment as well as in assessment of the effects of pharmacologic therapies for ARDS (10). Despite its clinical value and wide access to indirect calorimetry and volumetric capnography monitors, measuring VD/VT has not been universally embraced by the larger critical care community, while bedside capnography is much more widely used to measure end-tidal CO_2 ($ETCO_2$) pressure ($PETCO_2$) (10-12). Accordingly, surrogate measures for estimating VD/VT, such as the ratio of $ETCO_2$ pressure to arterial partial pressure of CO_2 ($PETCO_2$ /$PaCO_2$) and ventilatory ratio have recently been suggested for monitoring pulmonary gas exchange in patients with ARDS (10,13), while its relevance or utility in the COVID-19 related ARDS remains unknown (10,14).

In most cases of COVID-19, adequate-to-low oxygen saturation (SpO_2) values are maintained initially, and then downturn can occur rapidly, while $ETCO_2$ levels remain accurate and reflective of the ventilatory and metabolic/perfusion status of a patient, regardless of his/her SpO_2 values (15-18). In this regard, given the great clinical significance of ascertaining a patient's condition in a timely manner and predicting the progress of the disease (3,4), measurement of $ETCO_2$ values is considered to play a critical role in detecting the CO_2 level of COVID-19 patients (18,19).

Therefore, this study was designed to investigate the utility of $ETCO_2$ values in predicting the progress of the disease and mortality risk in hospitalized patients with COVID-19 pneumonia.

MATERIAL AND METHOD

The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

A total of 108 patients (mean±SD age: years, 50% were males) hospitalized with the diagnoses of COVID-19 pneumonia were included in this prospective cross-sectional study conducted between June 2020 and December 2020 at a tertiary care hospital in Turkey.

Inclusion Criteria

- Being adult (≥18 years of age)
- Confirmed diagnosis of COVID-19 after laboratory confirmation of SARS-CoV-2 on real-time reverse transcription-polymerase chain reaction (RT-PCR) analysis

Exlusion Criteria

- Need for Intubation at the time of admission
- Patients with type 1 respiratory failure
- Patients using an oxygen concentrator at home
- Trauma
- Pregnancy
- Pulmonary embolism

Data Collection

Data on patient demographics (age, gender), presence of comorbid disease, smoking status, systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, body temperature, respiratory parameters including oxygen saturation, $ETCO_2$ and respiratory rate (RR) – with (4 lt/ and without O_2 (w/wo O_2), CT findings (Radiological Society of North America chest CT classification system used), need for intubation or intensive care (ICU) stay during hospitalization and and laboratory parameters including hemoglobin (Hb, g/dL) and lymphocyte (cells/μL) counts, ferritin (ng/ml), troponin (ng/L), D-Dimer and potassium

(mEq/lt) levels were recorded in each patient. $ETCO_2$ measurements were performed on a sidestream capnometry monitor (Vital Sign Monitor VS2000). Immediately after the initial evaluation of the patient was completed, $EtCO_2$ measurement was performed by the sidestream method by an emergency medicine specialist or an emergency medicine resident. All emergency residents and physicians had in-service training about the standard usage of the sidestream capnography and were informed about the study protocol.

All patients diagnosed with COVID-19 were treated in accordance with the official COVID-19 Adult Treatment Algorithm guidance established by Republic of Turkey Ministry of Health [20]. Patient demographics, comorbid disease, pulmonary involvement, vital signs, respiratory parameters and laboratory parameters were evaluated with respect to ICU admission, intubation need and in hospital mortality.

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Pearson Chi-square ($\chi 2$) test, Fisher's exact test and Continuity correction were used for the comparison of categorical data. Mann-Whitney U test and independent sample t-test and ANOVA were used for the parametric variables. Data were expressed as "mean (standard deviation, SD), median (min-max) and percent (%) where appropriate. $p<0.05$ was considered statistically significant.

RESULTS

Overall, males composed 50% of the study population. Comorbidity was noted in 62.0% of patients and pulmonary involvement was evident in 97.2% (type 1 in 68.5%) of patients. The initial hospitalization unit was general ward in 24 (27.3%) patients and ICU in 84 (72.4%) patients and intubation need was evident in 20 (18.5%) patients (**Table 1**).

ICU admission, the primary outcome of this study, was associated with low $ETCO_2$ measured both with and without oxygen therapy (p=0.006, p=0.015 respectively). Low oxygen saturation, high respiratory rate measured while under oxygen therapy, advanced age, presence of comorbidity and high ferritin were found to be significant in terms of need for intensive care admission (p=0.001, p=0.001, p=0.013, p=0.01 and p=0.001 respectively). The relationship between other factors and the need for ICU hospitalization is presented in **Table 2**.

Table 1. Baseline characteristics of the patients (n=108)

Gender, n (%)	
Female	54 (50)
Male	54 (50)
Comorbidity, n (%)	
Present	67 (62)
Absent	41 (38)
CT findings, n (%)	
Type 1	74 (68.5)
Type 2	10 (9.3)
Type 3	15 (13.9)
Type 4	9 (8.3)
Pulmonary involvement, n (%)	
Yes	105 (97.2)
No	3 (2.8)
Initial hospitalization unit, n (%)	
ICU	84 (72.4)
General ward	24 (27.3)
Intubation need, n (%)	
No	88 (81.5)
Yes	20 (18.5)
Mortality	
No	100 (92.6%)
Yes	8 (7.4%)

CT: Computed tomography ICU: Intensive care unit

Another primary outcome, the presence of comorbidity, advanced age, low oxygen saturation with and without oxygen therapy, high oxygen-free respiratory rate, low hemoglobin, high ferritin and high D-dimer were found to be significant in terms of increased intubation risk, which is the other primary outcome (p=0.01, p=0.002, p=0.013, p=0.007, p=0.041, p=0.011,p=0.012, p=0.023 respectively). The relationship between intubation risk and other parameters is presented in **Table 3**.

Mortality, the secondary outcome of this study, was not associated with $ETCO_2$ measured both with and without oxygen therapy and comorbid disease presence (p=0.190, p=0.322 and p=0.15 respectively). Oxygen saturation with oxygen therapy and respiratory rate were found to be associated with mortality (p=0.025, p=0.007 respectively). The relationship between other factors and mortality was presented in **Table 4**.

DISCUSSION

Our findings in a prospective cohort of patients hospitalized with COVID-19 pneumonia revealed higher likelihood of hospital discharge than ICU stay in patients without comorbidities and those with higher $ETCO_2$ (w/wo O_2) values. Presence of comorbidity, older age, high ferritin and D-dimer levels and low hemoglobin levels increased the likelihood of intubation need during hospitalization. High RR with O_2 but low oxygen saturation levels (w/wo O_2) were the factors associated with increased risk of both intubation need and mortality in hospitalized COVID-19 patients. Intubation need was also associated with increased risk of mortality.

Table 2. Study parameters with respect to ICU admission need

	Ward (n=88)	ICU (n=20)	p value
Gender, n (%)			
Female	43 (51)	11 (46)	0.64
Male	41 (49)	13 (54)	
Comorbidity, n (%)			
Present	45 (54)	22 (92)	0.01
Absent	39 (46)	2 (8)	
CT findings, n (%)			
Type 1	59 (70)	15 (62)	0.12
Type 2	7 (8)	3 (13)	
Type 3	9 (11)	6 (25)	
Type 4	9 (11)	0 (0)	
Pulmonary involvement, n (%)			
Yes	81 (96)	24 (100)	1.00
No	3 (4)	0 (0)	
	mean(SD;min-max)	**Mean (SD; min-max)**	
Age (year)	61.6 (18.9; 19-92)	72.3 (12.5; 38-90)	0.013
Vital signs			
Systolic blood pressure (mmHg)	130.1 (18.8; 90-185)	132.8 (23.8 ;87-183)	0.545
Diastolic blood pressure (mmHg)	75.1 (13.5; 11-102)	73.5 (10.7; 53-88)	0.616
Pulse (bpm)	87.1 (18.9; 21-140)	86.2 (15.6; 68-132)	0.834
Respiratory rate (/min)	26.8 (5.9; 15-48)	28.2 (9.4;12-48)	0.382
Body temperature (°C)	36.6 (0.6;35-38)	36.4 (0.5;35-38)	0.065
Pulmonary gas exchange			
Saturation – without O_2	92.4 (5.4; 66.0-100.0)	88 (9.1; 66.0-98.0)	0.001
$ETCO_2$ without O_2	30.1 (4.9; 20.0-39.0)	27.3 (6.9; 15.0-40.0)	0.015
RR without O_2	27.7 (9.8; 10.0-95.0)	28.4 (9.6; 12.0-48.0)	0.345
$ETCO_2$ with O_2	27.9 (4.6; 17.0-39.0)	22.9 (7.3; 8.0-38.0)	0.006
RR with O_2	24.8 (6.7; 10.0-46.0)	26.7 (8.0; 9.0-42.0)	0.001
Saturation with O_2	95.9 (3.8; 82.0-100.0)	93.1 (5.3; 80.0-99.0)	0.013
Laboratory parameters			
Lymphocyte (10^3/µL)	1.8 (1.6; 0.3-9.6)	2.8 (5.1; 0.3-22.5)	0.746
Hemoglobin (g/dL)	16.1 (19.5; 6.8-123.0)	11.4 (2.1; 7.8-14.6)	0.271
Ferritin (ng/ml)	407 (431; 12-1650)	770 (683; 66-2457)	0.001
Troponin (ng/L)	0.96 (3.6; 0.0-17.6)	0.2 (0.3; 0.0-1.2)	0.368
D-Dimer (ng/ml)	906 (1183; 108-5881)	1056 (944; 156-3014)	0.439
Potassium (mEq/L)	4.1 (0.6;2.4-6.0)	4.4 (1.1; 2.8-6)	0.484

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

A remarkably increased physiological dead space is considered likely to be a prominent pathophysiological feature in mechanically ventilated COVID-19 patients recovering from severe ARDS (9). Although the underlying mechanism remains unclear, the proposed mechanisms involve a regional ventilation/perfusion heterogeneity due to loss of lung perfusion regulation and hypoxic vasoconstriction and the pulmonary micro-thrombosis (5,9,21,22). Our findings indicate that average $ETCO_2$ in hospitalized COVID-19 patients to be 29.5 mmHg (ranged, 15 to 40 mmHg), while a decrease in $ETCO_2$ value was associated with increased likelihood of a patient to be transferred to ICU. In addition, both high RR and low saturation (w/wo O_2) were associated with increased likelihood of intubation need and increased mortality risk among hospitalized COVID-19 patients. Accordingly, our findings support that derangement in gas exchange during ARDS related to COVID-19 is caused by an elevated regional ventilation/perfusion mismatch, which is mainly due to non-perfused but ventilated units (dead space fraction) (23).

Indeed, the presence of increased intrapulmonary shunt in ARDS has been associated with rising $PaCO_2$ that coincides with decreasing $PETCO_2$ (24), while alveolar and shunt-associated dead space was reported to account for over half of the measured physiologic dead space as $PETCO_2/PaCO_2$ fell to < 0.60 in ARDS not related to COVID-19 (10). Hence, the ratio of $PETCO_2/PaCO_2$, an easily calculated measure with readily available technology at the bedside, has been considered to be beneficial in evaluating pulmonary gas exchange dysfunction in ARDS (10), while $PETCO_2/PaCO_2 < 1$ is considered to suggest the presence of elevated intrapulmonary shunt fraction and VD/V also in the COVID-19 setting (14).

Similarly, a decrease in the $PETCO_2$ /$PaCO_2$ ratio in early ARDS was reported to be associated with increased VD/VT ratio, oxygenation dysfunction, illness severity scores and increased risk of hospital mortality in ARDS patients (10). Similar to elevated VD/VT in early ARDS, decreasing $PETCO_2/PaCO_2$ ratio is also associated with increasing illness severity and mortality risk and thus is

considered likely to be used specifically for monitoring patients with ARDS associated with COVID-19 (10,14). In another study among COVID-19 patients, decreased CO_2 levels, possibly caused by hyperventilation during mechanical ventilation (MV), were reported to increase the mortality risk but had no significant impact on the severity of pneumonia (19). The authors also reported that after adjustment for age, history of cardiovascular disease, WBC, platelet, oxygen support, and lymphocyte count, decreased CO_2 levels remained to be predictor of higher mortality risk in COVID-19 patients (19).

Moreover, the poor prognostic impact of decreased CO_2 levels in COVID-19 patients was also reported to be stronger in case of cardiovascular comorbidity, older age and high D-dimer levels (19). Notably, our findings revealed that older age, presence of comorbidity and high D-dimer levels were associated with higher risk of intubation need, which was found to be an independent predictor of in-hospital mortality.

In fact, the association of high D-dimer levels with increased the likelihood of intubation need in hospitalized COVID-19 patients in the current study seems also notable given that inflammatory diffuse micro-thrombosis leading to elevated D-dimers, higher pulmonary vascular resistance and larger dead space fraction are considered the key pathophysiological trait of ARDS from COVID-19, while the elevated D-dimers are also considered an independent predictor of mortality and enlarged pulmonary vessels in COVID-19 patients with ARDS (23,25,26).

Table 3. Study parameters with respect to intubation need

	Intubation need		p value
	No (n=88)	Yes (n=20)	
Gender, n (%)			
Female	44 (50.0)	10 (50.0)	1.00
Male	44 (50.0)	10 (50.0)	
Comorbidity, n (%)			
Present	49 (55.7)	18 (90.0)	0.01
Absent	39 (44.3)	2 (10.0)	
CT findings, n(%)			
Type 1	63 (71.6)	11 (55.0)	0.26
Type 2	7 (8.0)	3 (15.0)	
Type 3	10 (11.4)	5 (25.0)	
Type 4	8 (9.1)	1 (5.0)	
Pulmonary involvement, n(%)			
Yes	86 (97.7)	19 (95.0)	0.38
No	2 (2.3)	1 (5.0)	
	Mean (SD;min-max)	**Mean (SD;min-max)**	
Age (year)	61.5 (18.6;19.0-92.0)	75.1 (10.2;52.0-90.0)	0.002
Vital signs			
Systolic blood pressure (mmHg)	130.7 (18.6;90.0-185.0)	130.7 (24.7;87.0-183.0)	0.997
Diastolic blood pressure (mmHg)	75.5 (13.5;11.0-102.0)	71.2 (9.4;53.0-88.0)	0.182
Pulse (bpm)	87.2 (18.7;21.0-140.0)	85.5 (15.9;68.0-132.0)	0.334
Respiratory rate (/min)	26.8 (6.4;15.0-48.0)	28.8 (8.4;12.0-48.0)	0.241
Body temperature (°C)	36.6 (0.6;35.8-38.8)	36.4 (0.5;35.9-38.0)	0.147
Pulmonary gas exchange			
Saturation – without O_2	92.3 (5.9;66.0-100.0)	87.6 (8.3;66.0-98.0)	0.007
$ETCO_2$ without O_2	29.7 (5.3;20.0-39.0)	28.6 (6.3;15.0-40.0)	0.429
RR without O_2	27.6 (10.0;10.0-95.0)	29.0 (8.6;12.0-48.0)	0.041
$ETCO_2$ with O_2	27.3 (5.4;7.6-39.2)	24.5 (6.3;14.0-38.0)	0.570
RR with O_2	24.9 (6.8;10.0-46.0)	26.6 (8.0;9.0-42.0)	0.329
Saturation with O_2	95.9 (3.8;80.0-100.0)	93.1 (5.3;81.0-99.0)	0.013
Laboratory parameters			
Lymphocyte (10^3/μL)	3.8 (19.4;0.3-183.0)	2.7 (5.0;0.3-22.5)	0.277
Hemoglobin (g/dL)	15.0 (16.3;6.8-123.0)	11.0 (2.3;7.8-14.6)	0.011
Ferritin (ng/ml)	417.8 (481.7;9.0-2457.0)	700.4 (546.4;115.0-1650.0)	0.012
Troponin (ng/L)	0.8 (3.3;0.0-17.6)	0.2 (0.3;0.0-1.2)	0.157
D-Dimer (ng/ml)	856.0 (1093.1;85.0-5881.0)	1245.1 (1006.5;156-3014)	0.023
Potassium (mEq/L)	4.1 (0.6;2.4-6.0)	4.2 (0.9;2.9-5.8)	0.893

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

Table 4. Study parameters with respect to survival

	Survival status				p value
	Survivor (n=100)		Non-survivor (n=8)		
Gender, n (%)					0.72
Female	51 (51)		3 (38)		
Male	49 (49)		5 (63)		
Comorbidity, n (%)					0.15
Present	60 (60)		7 (87)		
Absent	40 (40)		1 (12)		
CT findings, n (%)					0.40
Type 1	70 (70)		4 (50)		
Type 2	8 (8)		2 (25)		
Type 3	14 (14)		1 (12)		
Type 4	8 (8)		1 (12)		
Pulmonary involvement, n (%)					0.53
Yes	98 (98)		7 (88)		
No	2 (2)		1 (12)		
	n	**Mean (SD; min-max)**	**n**	**Mean (SD; min-max)**	**p value**
Age (year)	100	63.5 (18.6;19-92)	8	70.5 (7.6; 58-78)	0.435
Vital signs					
Systolic blood pressure (mmHg)	100	130.8 (19.6; 90-185)	8	128.8 (23.7; 87-155)	0.777
Diastolic blood pressure (mmHg)	100	74.9 (13.0; 11-102)	8	71.6 (11.5; 53-88)	0.489
Pulse (bpm)	100	86.2 (18.0; 21-140)	8	95.1 (18.7; 77-132)	0.231
Respiratory rate (/min)	100	26.6 (6.6; 12-48)	8	33.4 (6.9; 26-48)	0.007
Body temperature (°C)	100	36.6 (0.6; 35.8-38.8)	8	36.5 (0.3; 36-36)	0.795
Pulmonary gas exchange					
Saturation – without O_2	100	91.8 (6.6; 66-100)	8	87.1 (5.7; 79-95)	0.013
$ETCO_2$ without O_2	100	29.7 (5.4; 20-40)	8	27.7 (6.5; 15-35)	0.322
RR without O_2	100	27.4 (9.8; 10-95)	8	34.3 (6.5; 26-48)	0.053
$ETCO_2$ with O_2	100	27.0 (5.7; 7.6-39.2)	8	24.3 (5.8; 14-32)	0.190
RR with O_2	100	24.6 (6.8; 9-46)	8	32.4 (5.8; 26-42)	0.002
Saturation with O_2	100	95.5 (4.2; 80-100)	8	92.9 (3.8; 87-98)	0.025
Laboratory parameters					
Lymphocyte (10^3/μL)	100	3.5 (18.2; 0.3-183)	8	4.7 (7.6; 0.6-22.5)	0.819
Hemoglobin (g/dL)	100	14.4 (15.4; 6.8-123)	8	12.2 (2.1; 9.1-14.4)	0.925
Ferritin (ng/ml)	87	471 (516; 9-2457)	7	442 (317; 115-967)	0.522
Troponin (ng/L)	82	0.8 (3.1; 0-17.6)	7	0.(0; 0-0)	0.375
D-Dimer (ng/ml)	92	909 (1087; 85-5881)	7	1163.1 (1083.7; 218-3014)	0.319
Potassium (mEq/L)	99	4.2 (0.6; 2.4-6)	7	4.2 (1.1; 2.9-5.8)	0.745

CT: Computed tomography; $ETCO_2$: End-tidal CO_2; RR: respiratory rate; ICU: Intensive care unit, Pearson Chi-Square, Fisher's Exact test, Continuity Correction, Mann-Whitney U test, Independent t test

Our findings are consistent with previous data on the association of decreased $ETCO_2$ levels with poor prognosis in COVID-19 patients, supporting the likelihood of elevated ventilation-perfusion mismatch due to high dead space fraction to be a specific characteristic of this syndrome that may provide important insights for clinical treatment recommendations (9,19,23). Notably, potential for lung recruitment in patients with ARDS from COVID-19 is considered highly variable and use of simple bedside estimates of recruitability is recommended to guide personalized MV settings (23). Although, shortness of breath, reduction of pulmonary perfusion and increased alveolar dead space and MV hyperventilation have been considered amongst the reasons for decreased CO_2 levels (17,19,27), since most COVID-19 patients require various forms of oxygen support, among other treatment, clinicians are recommended to focus on MV hyperventilation to prevent a decrease in the CO_2 levels due to hyperventilation as an effective and practical measure to improve patients' survival and to adjust oxygen flow in accordance with patients' requirements to treat pneumonia (19,28).

Certain limitations to this study should be considered. First, potential lack of generalizability is an important limitation due to single-center study design with relatively small sample size. Second, lack of data on other surrogate measures for estimating VD/VT, such as $PETCO_2$ /$PaCO_2$ ratio or ventilatory ratio seems to be another limitation of the present study.

CONCLUSION

Our findings in a prospective cohort of hospitalized patients with COVID-19 pneumonia revealed the association of decreased $ETCO_2$ (w/wo O_2) values with lower likelihood of hospital discharge and increased likelihood of ICU transfer. Although $ETCO_2$ values per se had no significant impact on survival status, presence of comorbidity, older age, high D-dimer levels increased the likelihood of intubation need during hospitalization, while initial general ward hospitalization, high RR (wO_2) but low oxygen saturation levels (w/woO_2) predicted the increased risk of both intubation need and mortality in hospitalized COVID-19 patients. In this regard, our findings emphasize the clinical significance of $ETCO_2$-based dynamic monitoring of pulmonary gas exchange as combined with patient age, comorbidity status and peripheral blood parameters in patients with COVID-19 related ARDS, in assisting clinicians to identify patients at an increased risk of worse outcomes and thus to provide timely tailored treatment in those with potentially dismal prognosis.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Katip Çelebi University Training and Research Hospital Noninvasive Clinical Researches Ethics Committee (Date: 02.07.2020, Decision No: 2020-GOKAEK-816).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Özgün Makale

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Holistic analysis of hepatosteatosis literature: a scientometric study of global hepatosteatosis publications between 1980 and 2019

Hepatosteatoz literatürün bütünsel analizi: 1980 ve 2019 arasındaki küresel hepatosteatoz yayınlarının scientometrik çalışması

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ABSTRACT

Aim: Hepatosteatosis is a subtype of Non-Alcoholic Fatty Liver Disease (NAFLD) with an increased significance and prevalence in recent years, progressing to chronic liver disease and even hepatocellular carcinoma. It has become the new focus of hepatology instead of viral hepatitis in the last 5 years because of its increasing prevalence and close association with metabolic diseases such as obesity, diabetes and hyperlipidemia. The present study aimed to make a holistic scientometric analysis of scientific studies conducted on hepatosteatosis.

Material and Method: We analyzed scientometric analysis of "hepatosteatosis" publications that were indexed in Web of Science databases between 1980 and 2019 and found a total of 996 articles.

Results: The most published documents were original articles (80.924%). The most investigated areas in the hepatosteatosis literature were found to be gastroenterology, biochemistry and endocrinology (n=751, 687 and 575 documents, respectively). The USA was the leading country with 371 articles, followed by Turkey, China, Japan, Italy and Germany (n=146, 145, 81 and 58 articles, respectively). Zhang Yen was found to be the most productive author from Yanbian University (China) and California University was the most productive institution. The hepatosteatosis literature H-index was measured as 76, with an average of 24.8 citations per item and a total of 24.705 citations. The most indexed keywords were found to be "hepatosteatosis", "fatty liver", "obesity" and "insulin resistance". The USA, China, UK, Germany and Italy were found to be the most cooperating countries.

Conclusion: Hepatosteatosis is an issue with increased importance and popularity with the intense interest of researchers in the past few years. The data of the present study, in which the scientometric analysis of the studies on hepatosteatosis was performed, emphasized the importance of the subject once again and will guide researchers for new researches to be conducted on many subjects such as which countries, institutions, individuals and journals are more interested in hepatosteatosis, and in which areas the studies are concentrated. To the best of our knowledge, it is the first scientometric study evaluating hepatosteatosis.

Keywords: Hepatosteatosis, holistik analisis, metabolic disorders, scientometric

ÖZ

Amaç: Hepatosteatoz, son yıllarda önemi ve prevalansı artan, kronik karaciğer hastalığına ve hatta hepatosellüler karsinomaya ilerleyen Alkolsüz Yağlı Karaciğer Hastalığı'nın (NAFLD) bir alt tipidir. Artan prevalansı ve obezite, diyabet, hiperlipidemi gibi metabolik hastalıklarla yakın ilişkisi nedeniyle son 5 yılda viral hepatit yerine hepatolojinin yeni odağı haline gelmiştir. Bu çalışma, hepatosteatoz ile ilgili yapılan bilimsel çalışmaların bütüncül bir scientometrik analizini yapmayı amaçlamıştır.

Gereç ve Yöntem: 1980 ile 2019 yılları arasında Web of Science veri tabanlarında indekslenen "hepatosteatoz" yayınlarının scientometrik analizini inceledik ve toplam 996 makale bulduk.

Bulgular: En çok yayınlanan dökümanlar orijinal makalelerdi (%80,924). Hepatosteatoz literatüründe en çok araştırılan alanların gastroenteroloji, biyokimya ve endokrinoloji olduğu bulundu (sırasıyla n=751, 687 ve 575 döküman). ABD 371 makale ile lider ülke olurken, onu Türkiye, Çin, Japonya, İtalya ve Almanya takip etti (sırasıyla n=146, 145, 81 ve 58 makale). Zhang Yen'in Yanbian Üniversitesi'nden (Çin) en üretken yazar olduğu ve California Üniversitesi'nin en üretken kurum olduğu tespit edildi. Hepatosteatoz literatür H-indeksi madde başına ortalama 24,8 ve toplam 24.705 atıf ile 76 olarak ölçüldü. En çok indekslenen anahtar kelimelerin "hepatosteatoz", "yağlı karaciğer", "obezite" ve "insülin direnci" olduğu bulundu. ABD, Çin, İngiltere, Almanya ve İtalya en çok işbirliği yapılan ülkeler olarak belirlendi.

Sonuç: Hepatosteatoz, son birkaç yıldır araştırmacıların yoğun ilgi göstermesi ile birlikte önemi ve popülaritesi artmış bir konudur. Hepatosteatoz üzerine yapılan araştırmaların scientometrik analizinin yapıldığı bu çalışmanın verileri, konunun önemini bir kez daha vurgulamış ve hepatosteatoz ile hangi ülke, kurum, kişi ve dergilerin daha çok ilgilendikleri ve araştırmaların hangi alanlarda yoğunlaştığı gibi pek çok konuda araştırmacılara yapılacak yeni araştırmalar için yol gösterici olacaktır. Bildiğimiz kadarıyla da hepatosteatozu değerlendiren ilk scientometric çalışmadır.

Anahtar Kelimeler: Hepatosteatozis, bütünsel analiz, metabolik bozukluklar, scientometrik

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INTRODUCTION

Hepatosteatosis is a pathological condition in which there is an accumulation of triglycerides in hepatocytes (1-3). When it occurs in the absence of excessive alcohol consumption, it is called non-alcoholic fatty liver disease (NAFLD). It is known that hepatosteatosis is extremely common in obese and diabetic patients (4-6). The prevalence of hepatosteatosis is increasing rapidly worldwide due to the rapid increase in obesity and obesity-related comorbidities. The worldwide prevalence of hepatosteatosis is estimated to be as high as 1 billion and is the most common cause of chronic liver disease in the United States. Hepatosteatosis is usually asymptomatic but is the most common cause of elevated liver enzymes (4,7-9). Generally, the clinical history of the patients includes alcohol use, drugs, diabetes mellitus (DM), obesity, pregnancy and elevated liver enzymes. Liver ultrasound is an easy way to detect hepatosteatosis (4,10). The most important approach for the treatment of hepatosteatosis is treatments for the causes of hepatosteatosis.

Until 5 years ago, viral hepatitis (B and C) constituted an important part of clinical research in the field of hepatology. Thanks to the development of therapies that suppress hepatitis B virus replication and highly effective antivirals, almost all patients are cured of hepatitis C virus infection and their complete eradication is expected in the very near future (11). Therefore, the focus of hepatology has recently changed to hepatosteatosis and non-alcoholic steatohepatitis (NASH).

Scientometrics is a statistical field investigating academic literature in a certain area (12). Although it has been a popular and trending scientific method of analyzing academic publications, the medical corpus lacks a holistic scientometric study evaluating hepatosteatosis literature.

In this study, we aimed to evaluate the scientometric features of the hepatosteatosis literature covering the 1980-2019 period.

MATERIAL AND METHOD

Ethics committee approval was not required for the preparation of the article.

All data analyzed in our study were collected by using Web of Science (WoS, Clarivate Analytics) databases. The keyword of "hepatosteatosis" was used for our basic search. All documents produced between 1980 and 2019 were included in the scientometric assessment. GunnMap 2 free web source was used for creating an info-map revealing country distribution of the global production of the hepatosteatosis literature (13). We created scientometric networks for keywords and institutions in VoSviewer software (14). Ethics committee approval was not required for the preparation of the article. Institutional approval was obtained for the preparation of the article. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

RESULTS

General Features of Hepatosteatosis Literature

A total of 996 indexed articles were found between 1980 and 2019 in WoS databases. Original articles covered 80.924% of all literature followed by proceeding papers, reviews, and case reports (339, 74, and 22 items, respectively; **Table 1**). The most studied areas in hepatosteatosis literature were Gastroenterology, Biochemistry, and Endocrinology (n=751, 687, and 575 documents, respectively; **Table 1**).

Productivity of Countries, Authors, Source Titles, and Institutions

The USA was the leading country with 371 articles followed by Turkey, China, Japan, Italy, and Germany (n=146, 145, 81, and 58 papers, respectively; **Figure 1**). The global distribution map of productivity revealed irregularity and most countries in Africa and Central Asia had no contribution to the literature (**Figure 2**). Zhang Y from Yanbian University (China) was found as the most prolific author and the University of California was the most productive institution (**Table 1**). Six of the top ten foundations were from the USA and China was the only developing country according to the most contributor institutions (**Table 1**). The most productive source titles in the literature were Diabetes, PLOS One, and Hepatology (4.317, 3.715, and 3.614%, respectively; **Table 1**).

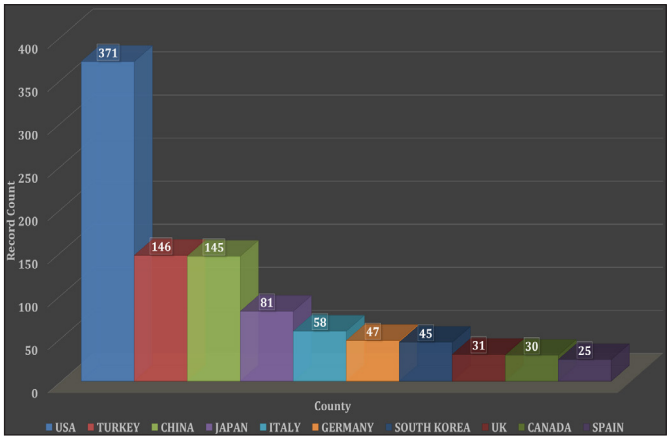

Figure 1. Top ten countries producing documents in hepatosteatosis area by total record count

Table 1. Top ten document types, research areas, source titles, authors, and organizations in hepatosteatosis literature [a]

			Record count	% a
Document Type				
Original Article			806	80.924
Meeting Document (Abstract)			180	18.072
Meeting Document (Full Text)			159	15.964
Review			74	7.430
Case Report			22	2.209
Letter			13	1.305
Editorial Material			12	1.205
Correction			5	0.502
Book			3	0.301
Others			460	46.185
Research Area				
Gastroenterology			751	75.402
Biochemistry			687	68.976
Endocrinology			575	57.731
Genetics			510	51.205
Nutrition			497	49.900
Pathology			337	33.835
Cell Biology			336	33.735
Pharmacology			312	31.325
Physiology			203	20.382
Immunology			192	19.277
Journal Name				
Diabetes			43	4.317
PLOS One			37	3.715
Hepatology			36	3.614
FASEB Journal			29	2.912
Journal of Hepatology			23	2.309
Journal of Lipid Research			21	2.108
Journal of Biological Chemistry			19	1.908
Diabetologia			15	1.506
Endocrinology			15	1.506
Cell Metabolism			14	1.406
Author	**Institution**	**Country**		
Zhang Y	Yanbian University	China	13	1.305
Gonzalez FJ	National Institutes of Health	USA	12	1.205
Hines IN	East Carolina University	USA	11	1.104
Li Y	Guangxi University	China	10	1.004
Kahn CR	Harvard Medical School	USA	9	0.904
Sajan MP	University of South Florida	USA	9	0.904
Shimano H	University of Tsukuba	Japan	9	0.904
Wheeler MD	East Carolina University	USA	9	0.904
Farese RV	University of South Florida	USA	8	0.803
Hussain MM	Winthrop University	USA	8	0.803
Organizations		**Country**		
University of California System		USA	36	3.614
Harvard University		USA	30	3.012
National Institutes of Health		USA	26	2.610
University of Texas System		USA	23	2.309
University of North Carolina		USA	20	2.008
Chinese Academy of Sciences		China	17	1.707
Centro de Investigación Biomédica en Red		Spain	17	1.707
Institut National de la Santé et de la Recherche Médicale		France	17	1.707
Shanghai Jiao Tong University		China	15	1.506
University Of North Carolina		USA	15	1.506
Total			996	100

[a]Total percentage may exceed 100% because certain items were included in more than one category.

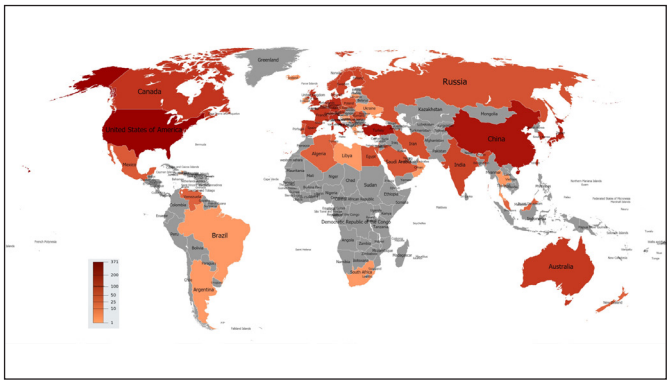

Figure 2. Global distribution of the productivity in hepatosteatosis literature

Citation Analysis

The h-index of hepatosteatosis literature was measured as 76. Average citations per item were 24.8 and the total number of citations was 24,705 (24,184 without self-citations). Starting year of citations was 1986 with one record. The peak year was 2019 with 4003 citations. The most cited document was an original article titled "Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism" by Cao et al. published in 2008 in the journal Cell.

Scientometric Networks Analyses

A scientometric network map of the most indexed keywords revealed a flower pattern in which the keywords of "hepatosteatosis", "fatty liver", "obesity" and "insulin resistance" were centered (**Figure 3**). The most used keywords were detected to be "hepatosteatosis", "obesity", "insulin resistance", "non-alcoholic fatty liver disease" and "fatty liver" (**Table 3**). The most collaborative institutions were the Chinese Academy of Sciences, Shanghai Jiao Tong University, and Harvard University (total link strength= 20, 17, and 15, respectively, **Figure 4**). The USA, China, the UK, Germany, and Italy were the most cooperative countries according to the scientometrics network (total link strength= 202, 96, 55, 47, and 43, respectively; **Figure 5**).

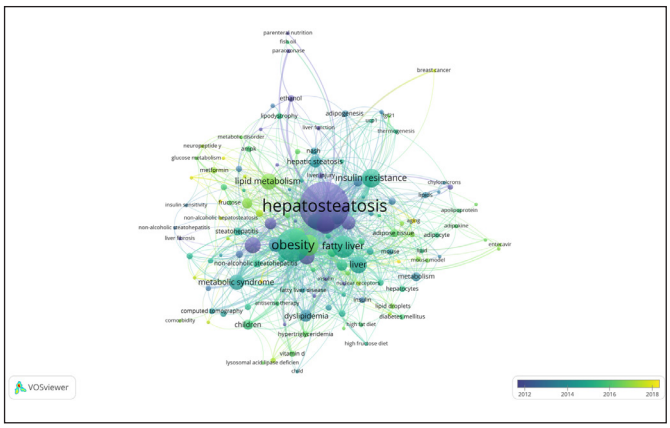

Figure 3. Scientometric network of the most used keywords in hepatosteatosis literature

Table 2. The ten most-cited manuscripts by time periods on hepatosteatosis

Article	Author	Journal name/published	Total citation	Average citations per year
Identification of a lipokine, a lipid hormone linking adipose tissue to systemic metabolism	Cao, Haiming; Gerhold, Kristin; Mayers, Jared R.; et al.	Cell	677	52.08
Fibroblast Growth Factor 21 Corrects Obesity in Mice	Coskun, Tamer; Bina, Holly A.; Schneider, Michael A.; et al.	Endocrinology	667	51.31
Endoplasmic reticulum stress in liver disease	Malhi, Harmeet; Kaufman, Randal J.	Journal of Hepatology	655	65.50
Essential metabolic, anti-inflammatory, and anti-tumorigenic functions of miR-122 in liver	Hsu, Shu-hao; Wang, Bo; Kota, Janaiah; et al.	Journal of Clinical Investigation	475	52.78
Adipocyte-derived Th2 cytokines and myeloid PPAR delta regulate macrophage polarization and insulin sensitivity	Kang, Kihwa; Reilly, Shannon M.; Karabacak, Volkan; et al.	Cell Metabolism	466	35.85
Impaired regulation of hepatic glucose production in mice lacking the forkhead transcription factor foxo1 in liver	Matsumoto, Michihiro; Pocai, Alessandro; Rossetti, Luciano; et al.	Cell Metabolism	376	26.86
Crucial role of a long-chain fatty acid elongase, Elovl6, in obesity-induced insulin resistance	Matsuzaka, Takashi; Shimano, Hitoshi; Yahagi, Naoya; et al.	Obesity	330	23.57
Cafeteria Diet Is a Robust Model of Human Metabolic Syndrome with Liver and Adipose Inflammation: Comparison to High-Fat Diet	Sampey, Brante P.; Vanhoose, Amanda M.; Winfield, Helena M.; et al.	Obesity	296	29.60
Dephosphorylation of translation initiation factor 2 alpha enhances glucose tolerance and attenuates hepatosteatosis in mice	Oyadomari, Seiichi; Harding, Heather P.; Zhang, Yuhong; et al.	Cell Metabolism	291	22.38
Adipocytokines in obesity and metabolic disease	Cao, Haiming	Journal of Endocrinology	282	40.29

Table 3. Most used 20 keywords by decades in the literature related to hepatosteatosis literature

Keyword (Total link strength)
1. Hepatosteatosis (279)
2. Obesity (191)
3. Insulin resistance (92)
4. Non-alcoholic fatty liver disease (81)
5. Fatty liver (71)
6. Oxidative stress (71)
7. Metabolic syndrome (66)
8. Liver (65)
9. Diabetes (64)
10. Lipid metabolism (56)
11. Inflammation (52)
12. Type 2 diabetes (50)
13. Steatosis (49)
14. Dyslipidemia (47)
15. Fibrosis (43)
16. Lipogenesis (36)
17. Adiponectin (34)
18. Hepatic steatosis (33)
19. Mitochondria (32)
20. Atherosclerosis (29)

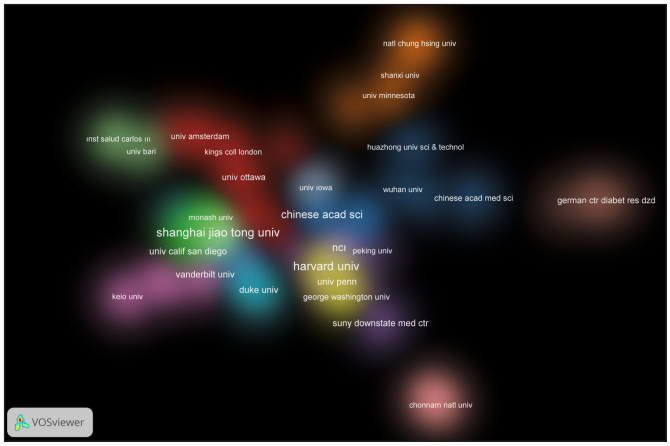

Figure 4. Scientometric network of the most collaborative countries in hepatosteatosis literature

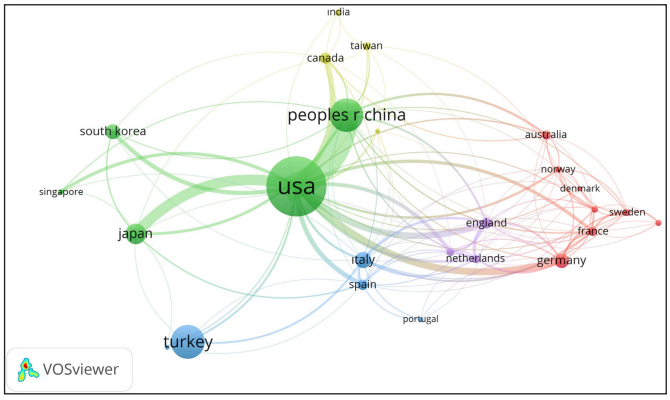

Figure 5. Scientometric network of the most collaborative institutions in hepatosteatosis literature

DISCUSSION

Although fatty liver had been known for many years, it has not been considered as a separate disease until 1980. An increasing number of studies have been conducted on hepatosteatosis since this date and the importance of hepatosteatosis was emphasized in these studies. Hepatosteatosis is among the subtypes of NAFLD. NAFLD is the fastest growing chronic liver disease with a worldwide prevalence of approximately 25%. Nearly 30% of NAFLD can lead to fibrosis, cirrhosis, liver failure and even hepatocellular carcinoma (15). Hepatosteatosis, which is a subtype of NAFLD, is known to be extremely common in obese patients and patients with diabetes. There is a significant increase in hepatosteatosis because of the significant increase in the prevalence of obesity and diabetes all over the world (4). It can be argued that the prevalence of hepatosteatosis will also increase in the future with the addition of sedentary lifestyles, which is among the important problems of our age, to these metabolic disorders. Although the main focus of hepatology was viral hepatitis (especially hepatitis B and C) until recent times, today, significant increases are reported in studies conducted on hepatosteatosis and NAFLD (16). According to the literature review conducted in the present study, it was found that only one scientometric study was conducted regarding NAFLD and NASH, but no scientometric studies have yet been conducted for hepatosteatosis. To the best of our knowledge, the present study will make a significant contribution to the literature and scientists because it is the first scientometric analysis to evaluate hepatosteatosis. This scientometric analysis can save researchers time by evaluating hepatosteatosis studies in the literature accurately and quickly, and guide researchers in future hepatosteatosis studies. The results of this study can help scientists on many issues, such as which keywords researchers will commonly use, which journals, institutions and countries will be most interested in hepatosteatosis studies.

The interest of researchers in hepatosteatosis studies began in the early 1980s and has continued to increase until our present day. Obesity and diabetes, which are major public health problems all over the world, are the leading causes of death and disability and are closely related to hepatosteatosis (4,17). The fact that hepatosteatosis is both significantly increased in prevalence and associated with important metabolic diseases may explain why researchers have recently been more interested in hepatosteatosis and the increase in the literature in this area. In the analysis in the present study, it was found that the United States of America (18), the country that has the highest obesity prevalence in the world, is by far the country with the highest contribution to the hepatosteatosis literature with 371 articles. No African country was in the top 10. The prominent country in Europe was Turkey, but it was China in Asia. When the keyword network was examined, it was seen that hepatosteatosis is associated with many metabolic disorders, especially "obesity", "fatty liver", "insulin resistance", and "lipid metabolism". These data emphasize the importance of hepatosteatosis. For hepatosteatosis, gastroenterology, biochemistry and endocrinology were the three most investigated fields and original articles constituted 80.92% of the studies. Diabetes was the journal that contributed the most to the literature with 43 articles. Although 7 out of the top 10 most prolific authors were from the United States, Zhang Y from Yanbian University (China) was found to be the most prolific author. Regarding the hepatosteatosis literature, the top 5 most productive institutions were also from the USA, with California System University being the most productive institution with 36 studies. Among the top 10 contributing institutions were 2 from China and 1 from Spain and France.

The most important limitation of the present study was that all analyzed data were collected by using only the Web of Science database. We think that there is a need for scientometric analysis of hepatosteatosis by scanning other databases along with Web of Science.

CONCLUSION

The results of the study clearly showed the relationship of hepatosteatosis with metabolic disorders such as obesity, diabetes and dyslipidemia, and the importance that scientists attached to this issue recently. The importance given to hepatosteatosis by scientists in the USA, which is one of the countries where obesity and diabetes are big problems, was among the prominent characteristics. We think that the data of the present study will guide other studies to be conducted on subjects such as which countries, institutions, individuals and journals are more interested in hepatosteatosis and in which areas the studies are concentrated.

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethics committee approval was not required for the preparation of the article. Institutional approval was obtained for the preparation of the article.

Informed Consent: Since this study used an immortal cell line, infomed consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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İmmünglobülin G4 ilişkili hastalıkta nüksü etkileyen faktörler: retrospektif bir analiz

Factors affecting relapse in immunoglobulin G4-related disease: a retrospective analysis

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ÖZ

Amaç: Bu çalışmada immünglobülin G4 ilişkili hastalıkta (IgG4-İH) klinik tutulum özelliklerinin, nüks oranlarının ve nüks ile ilişkili faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmamıza IgG4-İH tanısıyla 36 hasta dahil edildi. Bu hastaların demografik, klinik, laboratuvar, radyolojik bulguları, steroid, immünsüpresif tedavi rejimleri ve nüks oranları retrospektif olarak kaydedildi.

Bulgular: Hastaların %36'sı kadındı ve ortalama yaş 58,5±13,2 yıldı. Remisyon oranı %56, nüks oranı ise %19 olarak tespit edildi. İlk tanı anında pankreatit ve retroperitoneal fibrozisi olan hastalarda nüks oranı daha yüksekti (p=0.001). Tek değişkenli analize göre, nüks ile ilişkili bulunan faktörler şu şekildeydi: Hastalık süresi (p=0.001), alerji öyküsü (p=0.018), sigara kullanımı (p=0.027), eozinofili (p=0.001), total IgE (p=0.005) ve kreatinin yüksekliği (p=0.001). Çok değişkenli analizde ise hastalık süresi (Odds oranı (OO) [%95 güven aralığı (GA)]=1.1. [1.01-1.20]; p=0.016) nüks ile ilişkili bağımsız risk faktörü olarak bulundu.

Sonuç: IgG4-İH'li hastalıkta nüks riski, tanı anında pankreas ve retroperitoneal tutulumu olması, alerji öyküsü, sigara kullanımı, eozinofili, total IgE ve kreatinin yüksekliği ile ilişkiliydi. Bu risk faktörlerini taşıyan hastalarda kombine immünsüpresif tedavilerin tercihi ve steroid dozunun kontrollü azaltılması nüksü engellemekte yararlı olabilir.

Anahtar Kelimeler: IgG4 ilişkili hastalık, nüks, retroperitoneal fibrozis

ABSTRACT

Introduction: In this study, it was aimed to determine the clinical features of involvement, relapse rates and relapse-related factors in immunoglobulin-G4-related disease (IgG4-RD).

Materials and Method: Thirty-six patients with IgG4-RD were included in our study. Demographic, clinical, laboratory, radiological findings, immunosuppressive treatment regimens and recurrence rates of these patients were recorded retrospectively.

Results: 36% of the patients were female and the mean age was 58.5±13.2 years. The remission rate and relapse rate were 56% and 19%, respectively. Recurrence was detected more frequently in the coexistence of pancreatitis and retroperitoneal fibrosis at the time of diagnosis (p=0.001). Based on univariate analysis, factors associated with relapse were attributed as follows: disease duration (p=0.001), history of allergy (p=0.018), smoking (p=0.027), eosinophilia (p=0.001), total IgE (p=0.005) and elevated creatinine (p=0.001). In multivariate analysis, disease duration (odds ratio (OR) [95% confidence interval (CI)]=1.1. [1.01-1.20]; p=0.016) was found to be an independent risk factor for relapse.

Conclusion: The risk of recurrence in disease with IgG4-RD was associated with pancreatic and retroperitoneal involvement at the time of diagnosis, history of allergy, smoking, eosinophilia, high total IgE and creatinine. Combined immunosuppressive therapy and slow steroid dose reduction are important to prevent relapse in high-risk patients.

Keywords: IgG4-related disease, relapse, retroperitoneal fibrosis

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GİRİŞ

İmmünglobulin G4 ile ilişkili hastalık (IgG4-İH), birden fazla organ sistemini etkileyebilen immün aracılı fibroinflamatuar bir hastalıktır (1). Klinik bulguları, tutulan organ ve tutulum şiddetine göre değişkenlik gösterir. Sıklıkla birden fazla organ sisteminin tutulumu görülür (2). Gözyaşı ve tükrük bezleri, hipofiz, pankreas, safra yolları, retroperitoneal doku, akciğerler, böbrekler, aorta, meninksler, prostat ve tiroid bezi tutulabilir (3,4). En sık etkilenen organlar tükrük bezi, lakrimal bez ve pankreastır (2). Organomegali nedeniyle tıkanıklık veya bası bulguları görülebileceği gibi organın hücresel infiltrasyonu veya fibrozisine bağlı organ disfonksiyonu ve yetmezlik bulguları da görülebilir (5). Aort diseksiyonu ve ani kardiyak ölüm, morbidite ve mortalite riskinde artışla ilişkilidir (1).

Tanı için klinik, serolojik, radyolojik ve patolojik verilerin korelasyonu gereklidir (5). Patolojik örneklerde, lenfoplazmasitik hücre infiltratları, storiform fibrozis, obliteratif flebit ve IgG4+ plazma hücre infiltratları karakteristiktir (1). Klinik, serolojik ve radyolojik bulguların kombinasyonu ile biyopsi yapılmadan da tanı konulabilir (5). IgG4-İH'da alerji öyküsü, serum Ig E düzeylerinde artış vardır (6). Hastalık kortikosteroid tedavisine iyi yanıt verir. Kortikosteroidler IgG4-İH tedavisinde remisyon indüksiyonu için ilk basamakta önerilmektedir (7). Ancak, yüksek riskli hastalarda kortikosteroid dozunun azaltılması veya kesilmesini takiben nüks sıktır (3,4). Bu nedenle, aktivitesi ve nüks riski yüksek hastalarda başlangıçtan itibaren rituksimab gibi B-hücresi azaltıcı veya diğer immünsüpresif tedaviler kullanılması akılcı bir yaklaşım olabilir (3,4,7,8,9). Yakın geçmişte tanımlanmış bir hastalık olması, heterojen bir klinik göstermesi nedeniyle halen standart bir tedavi yaklaşımı yoktur. Steroid tedavisinin monoterapi veya diğer immünsüpresif ajanlarla kombine şekilde kullanımı halen tartışma konusudur (9,10,11).

Günümüzde, IgG4-İH'da uzun vadeli prognostik sonuçlar, farklı organ tutulumlarında tedavi şekli ve nükssüz sağkalım ile ilgili veriler belirsizdir. Literatürde nüksü öngörücü faktörler ile ilgili sınırlı sayıda çalışma mevcuttur (10,12). Bu çalışmada IgG4-İH'da nüks ile ilişkili prediktif faktörlerin belirlemesi amaçlanmaktadır.

GEREÇ VE YÖNTEM

Katılımcılar

Çalışma Başkent Üniversitesi Girişimsel Olmayan Araştırmalar Etik Kurulu tarafından onaylandı (Tarih: 07.09.2022, Karar No: KA22/314) ve Başkent Üniversitesi Araştırma Fonu tarafından desteklendi. İnsan katılımcıları içeren tüm prosedürler, Kurumsal Araştırma Komitesinin etik standartlarına ve 1975 Helsinki İlkeler Deklarasyonuna ve sonraki değişiklikleri veya karşılaştırılabilir etik standartlarına uygun olarak gerçekleştirildi.

Başkent Üniversite Hastanesi Romatoloji Bölümü'nde Ocak 2012 ile Temmuz 2022 tarihleri arasında IgG4-İH tanısı konulan 18 yaş üstü toplam 36 erişkin hastanın tıbbi kayıtları geriye dönük olarak incelendi. 2011 klinik tanı kriterleri (13) ve 2019 klasifikasyon kriterlerini (14) karşılayan, IgG4 düzeyi ≥135 mg/dl ve 3 aydan uzun takip süresi olan hastalar çalışmaya dahil edildi. Eş zamanlı kanser, enfeksiyon, hematolojik hastalık veya diğer romatizmal hastalığı olanlar ve anti-nötrofil sitoplazmik antikor (c ANCA ve p ANCA) serolojisi pozitif hastalar çalışma dışı bırakıldı. Analiz için toplanan değişkenler; hastalık başlangıç yaşı, cinsiyet, takip süresi, organ tutulumu, tutulan organ sayısı (tek veya birden fazla organ), serum IgG4 seviyeleri, Eritrosit sedimantasyon hızı (ESR), C-reaktif protein (CRP), serum kreatinin seviyesi, hemoglobin, eozinofil sayısı, anti-nükleer antikor (ANA), c ANCA ve p ANCA serolojisi (ELISA yöntemi ile), Ig E düzeyi, proteinüri ve hematüri varlığı idi. Radyoloji bulguları ve biyopsi sonuçları, tedavide kullanılan ilaçlar, remisyon ve nüks oranları kaydedildi. Verilerin istatistiksel analizi planlandı. Alerji öyküsü ve sigara kullanımı kaydedildi. 2 veya üstü organ tutulumu çoklu organ tutulumu olarak kabul edildi.

Tedavi Yanıtı ve Nüks Tanımı

Remisyon; klinik semptomlarda düzelme ve görüntüleme yöntemlerinde iyileşme olarak tanımlandı (8). Nüks ise remisyon sağlandıktan sonra serum IgG4 seviyelerinde yükselme olsun veya olmasın klinik ve radyolojik bulgularda tekrar kötüleşme, organ fonksiyon bozukluklarının ortaya çıkması veya ilerlemesi, kitle lezyonlarının tespit edilmesi olarak tanımlandı (8).

İstatistik Yöntemi

Verilerin istatistiksel analizinde SPSS 25.0 paket programı kullanıldı. Kategorik ölçümler sayı ve yüzde olarak, sürekli ölçümlerde ortalama ve standart sapma (gerekli yerlerde ortanca ve minimum-maksimum) olarak özetlendi. Kategorik değişkenlerin karşılaştırılmasında Ki Kare test ya da Fisher test istatistiği kullanıldı. Gruplar arasında sürekli ölçümlerin karşılaştırılmasında dağılımlar kontrol edildi, değişkenler nonparametrik dağılım göstermediğinden Mann Whitney U testi kullanıldı. Çok değişkenli analiz yöntemi olarak Logistik Regresyon analizi Back-Wald metodu kullanıldı. Tek değişkenli analiz sonucu $p<0.10$ olanlar logistik regresyon modeline eklendi. Tüm testlerde istatistiksel önem düzeyi 0.05 olarak alındı.

BULGULAR

Hasta Profili

Çalışmamız, yaş ortalaması 58,5±13,2 yıl ve katılımcı-

ların %36'sının kadın olduğu toplam 36 hasta ile yapıldı. Ortalama takip süresi 47 (3-180) aydı. Hastaların %11'inde alerji öyküsü mevcuttu. Ortalama serum IgG4 düzeyi 267mg/dl (min 141-maks 1450) olarak hesaplandı. IgG4 düzeyinin 2 katından yüksek olduğu hasta sayısı %50 (n=18) idi. Hastaların temel demografik, klinik ve laboratuvar verileri **Tablo 1**'de gösterilmiştir. %19 hastada total IgE yüksekliği (>100 IU/mL) tespit edildi. Tanı %39 hastada biyopsi ile doğrulandı.

Tablo 1. Hastaların Demografik, Klinik ve Laboratuvar verileri

Parametreler	Değerler
Cinsiyet (Kadın)	13 (%36)
Yaş (Yıl)	58,5±13,2
Hastalık süresi (Ay)	61 (6-143)
Alerji öyküsü	4 (%11)
Sigara kullanımı	21 (%58)
IgG4 düzeyi, mg/dL	267 (141-1450)
ESH, mm/sa	47 (5 -103)
C-Reaktif Protein, mg/dl	24 (1 -231)
Kreatinin, mg/dl	0,8 (0,5-7,5)
Hemoglobin, gr/dl	10.6 ±1.9
Ig E düzeyi, IU/mL	66 (12-680)
Ig E yüksekliği	7 (19)
Eozinofil sayısı, hücre/µl	210 (10-2000)
ANA pozitifliği	7 (19)
Tek organ tutulumu	13 (36)
Çoklu organ tutulumu (≥2)	23 (64)
Remisyon oranı	20 (56)
Nüks sıklığı	7 (19)
Tedavi kesilen hasta sayısı	15 (42)
Ölüm	2 (6)

Aritmetik Ortalama ±Standart Sapma, ortanca (minimum- maksimum), n (%), İmmünglobülin G4: IgG4, ESH: Eritrosit sedimentasyon hızı, İmmünglobülin E: Ig E, ANA: Anti-nükleer antikor

Klinik Tutulum Şekilleri

En sık tutulan organlar lakrimal ve tükrük bezleriydi (%25). Hastaların %64'ünde tanı anında çoklu organ tutulumu mevcuttu. Hastalarımızın tutulum şekilleri **Tablo 2**'de gösterilmiştir. Çoklu organ tutulumu olarak en sıklıkla retroperitoneal doku ve aorta %17 (n=6), ikinci sıklıkla ise retroperitoneal doku ve pankreas %14 (n=5) birlikteliği saptandı.

Tablo 2. Tutulan Organ Sistemleri, n (%)

	n (%)
Lakrimal veya tükürük bezi	9 (25)
Retroperitoneum- aorta	6 (17)
Retroperitoneum- pankreas	5 (14)
Pankreas – lenf nodu	4 (11)
Tükrük bezi- pankreas	4 (11)
Akciğer- nörolojik	4 (11)
Nörolojik	2 (6)
Akciğer	2 (6)

Nüks

Remisyon oranı %56 (n=20) ve nüks oranı ise %19 (n=7) idi. Hastaların %42'sinde ise tam remisyon sağlandı ve takipte nüks ile karşılaşılmadı. Hastaların %89 (n=32)'u kombine immünsüpresif tedavi aldı. Nüks grubunda (n=7); 2 hasta prednizolon ve siklofosfamid, 2 hasta prednizolon ve metotreksat, 3 hasta ise prednizolon ve azatiyoprin tedavisi aldı. Nüks olmayan grupta (n=29) ise 1 hasta prednizolon ve azatiyoprin, 2 hasta prednizolon ve mikofenolat mofetil, 4 hasta sadece prednizolon, 6 hasta prednizolon ve metotreksat, 16 hasta prednizolon, rituksimab ve siklofosfamid tedavisi kullandı. Nüks gelişen hastalarda; alerji öyküsü varlığı (p=0.018), sigara kullanımı (p=0.027), Ig E yüksekliği (p=0.005), eozinofili ve kreatinin yüksekliği (p=0.001) ve hastalık süresinin uzunluğu (p=0.001) nüks ile ilişkili tespit edildi. Çoklu organ tutulumunda nüks daha sık gözlense de istatistiksel anlamlı değildi (p=0.382). Tek değişkenli analizlerde anlamlı çıkan değişkenler için çok değişkenli lojistik regresyon analizi yapıldı. Çok değişkenli analizde, hastalık süresi (Odds oranı (OO) [%95 güven aralığı (GA)]=1.1. [1.01-1.20]; p=0.016) nüks ile ilişkili bağımsız risk faktörü olarak bulundu (**Tablo 3**). Nüks gelişen ve nüks gelişmemiş IgG4-İH hastaların kıyaslanması **Tablo 4**'te gösterilmiştir.

Tablo 3: İmmünglobülin G4 ilişkili hastalıkta nüks ile ilişkili faktörlerin regresyon analizi

Parametreler	Çok değişkenli analiz	P değerleri OO (%95 GA)
Hastalık süresi (Ay)	0,016	1,1 [1,01-1,20]
Alerji öyküsü	0,947	0,8 [0,0-358,8]
Sigara kullanımı	1,000	0,0 [0,0-]
Eozinofili	0,565	1,0 [0,99-1,01]
Total IgE	0,084	1,1 [0,9-1,10]
Kreatinin	0,137	3,5 [0,7-18,8]

OO: Odds oranı, GA: güven aralığı, p<0.05 anlamlı

Tablo 4. Nüks gelişen IgG4 ilişkili hastaların kıyaslanması

	Nüks gelişen grup (n=7)	Nüks gelişmeyen grup (n=29)	p
Yaş (Yıl)	59,8±10,9	58,1±13,9	0.845
Cinsiyet (Kadın)	2 (29)	11 (38)	1.000
Hastalık süresi (Ay)	120 (62-143)	48 (6-134)	0.001
Alerji öyküsü	3 (42,9)	1 (3,4)	0.018
Sigara kullanımı	7 (100)	14 (48)	0.027
Tek organ tutulumu	1 (14)	12 (41)	0.382
Çoklu organ tutulumu	6 (86)	17 (59)	0.382
IgG4	316 (194-352)	124 (119-139)	0.754
IgE düzeyi, IU/mL	236 (40-640)	60 (12-680)	0.005
C-Reaktif Protein, mg/dl	63 (12-124)	20 (1-123)	0.131
ESH, mm/sa	53 (30-87)	40 (5-103)	0.366
Eozinofil sayısı	1180 (79-1950)	200 (10-2000)	0.001
Kreatinin, mg/dl	1,9 (0,7-14)	0,7 (0,5-3,7)	0.001
Tedavi kesilen hasta sayısı	2 (29)	13 (45)	0.676

Retroperiteneum, pankreas	5 (71)	0 (0)	0.001

n (%), p<0.05 anlamlı, İmmünglobülin G4: IgG4, ESH: Eritrosit sedimentasyon hızı, İmmünglobülin E: Ig E

Bir hastada 5. yıldan sonra mesane kanseri gelişti. 2 hasta kaybedildi. Bu hastaların ölüm nedenleri hepatit B re-aktivasyonuna bağlı fulminan hepatit ve sepsisti.

TARTIŞMA

IgG4-İH son yıllarda daha iyi tanımlanmış ancak seyri ve prognozu ile ilgili verilerin halen sınırlı olduğu bir hastalıktır. IgG4-İH'da tanı anındaki mevcut klinik bulgular ile nüks arasındaki ilişkinin ortaya konması, bu hastaların prognozu, ideal tedavi stratejileri, morbidite ve mortalite riskini belirlemek açısından önemlidir. IgG4-İH'da steroid tedavisinin kesilmesinden veya azaltılmasından sonra nüks oranları %24-63 arasında bildirilmektedir (8,15,16). Çoğu çalışmada nüks hızı %30'un üzerinde rapor edilmektedir (12).

Bizim çalışmamızda ise nüks oranı %19 olarak saptandı. Literatüre göre nüks oranı çalışmamızda daha düşüktü. Culver ve ark. (17) çalışmasında nüks oranı %57,7'idi. Bu çalışmada hastaların %79'u steroid monoterapisi almıştı. Yine remisyon indüksiyonda sadece steroid kullanan başka bir çalışmada nüks oranı %37 olarak tespit edildi (7). Hastaların %68'nin sadece rituksimab aldığı başka bir çalışmada ise nüks oranı %37'di (18). Bizim çalışmamızda ise nüks oranının düşük olma sebebinin, çoklu organ tutulumu olan ve IgG4 düzeyi eşik düzeyin 2 katından yüksek olan hastaların tanıdan itibaren kombine immünsüpresif tedavi alması ve steroid tedavisine en az 6 ay süreyle devam edilmesi ile ilişkili olduğunu düşünmekteyiz.

Hastalarımızın ortalama serum IgG4 düzeyi 267 mg/dl idi. Hastaların %50' sinden fazlasında ise serum IgG4 düzeyinde 2 katından daha yüksek tespit edildi. Culver ve ark. (17) çalışmasında serum IgG4 düzeyinin 280 mg/dl ve üzerinde olması IgG4-İH teşhisi için faydalı olduğu tespit edilmiştir. Bu çalışmada ayrıca IgG4 düzeyi ve çoklu organ tutulumu ile nüks arasında ilişkili de ortaya koyulmuştur (17). Literatürde serum IgG4 düzeyi, seri ölçümleri ve nüks arasında, farklı çalışmalarda farklı sonuçlar elde edilmiştir (12,17,18). Çalışmamızda da IgG4 düzeyi, takip ölçümleri ve nüks arasında ilişki saptanmadı. Nüks ile çoklu organ tutulumu arasında da ilişki tespit edilmedi. Çoklu organ tutulumu olan hastalarda nüks daha sık görülmekle beraber bu oran istatistiksel anlamlı değildi. Bunun da çalışmaya dahil edilen hasta sayısının az olmasıyla ilişkili olabileceğini düşünüyoruz.

IgG4-İH'da, serum Ig E düzeyleri %34-86 oranında yüksek saptanmaktadır (19). Yine periferal kan ve doku eozinofilisi ve alerji öyküsü de bu hastalarda yüksek tespit edilebilir (18-20). Eozinofilisi ve alerji öyküsü de bazı çalışmalarda nüksle ilişkili bulunmuştur (12,17-19). Literatürde IgE'nin 380 IU/L düzeyinden yüksek olması ile nüks arasında korelasyon gösterilmiş ve bu hastalarda yakın takip önerilmiştir (18,19). Çalışmamızda hastaların %19'unda IgE yüksekliği tespit edildi. Ortalama IgE düzeyi ise 236 IU/ml idi. Serum eozinofil ve IgE yüksekliği ile nüks arasında bizim hasta grubumuzda da literatürle uyumlu olarak istatistiksel anlamlı ilişki tespit edildi. Alerji oranımız çalışmamızda nispeten düşüktü (%11). Bunun da çalışmanın retrospektif olması, öykü alma sırasında alerjinin yeterince sorgulanmaması ile ilişkili olabileceğini düşünüyoruz. 277 hastayla Çin'de yapılan bir Kohort çalışmasında, tanı anında genç olmak, erkek cinsiyet, tanı ve tedavi arasında geçen süre, alerji öyküsü nüks ile ilişkili bulunmuştur (12). Çalışmamızda hastaların %64'ü erkekti. Ancak cinsiyet ve yaşla nüks arasında ilişki saptanmadı. Sigara kullanımı ve hastalık süresinin uzunluğu nüks ile ilişkili saptandı. Sigara, seropozitif romatoid artrit başta olmak üzere otoimmünite üzerine tetikleyici olduğu bilinmektedir (21). IgG4-İH ile ilgili yapılan bir çalışmada hastalığın ortaya çıkması için ilk değiştirilebilir risk faktörü olarak sigara bildirilmiştir (21). IgG4-İH, nüks ve sigara kullanımıyla ilgili literatürde veri yoktur. Çalışmamızda sigara kullanan hastalarda nüks oranı daha yüksek saptandı.

IgG4-İH, steroid tedavisine iyi yanıt verir, ancak steroid dozunun azaltılması veya idame tedavi sırasında hastaların üçte birinden fazlasında nüks gelişir (12). Steroid tedavisinin kesilmesi hastalık nüksü için bağımsız bir risk faktörü olarak gösterilmiştir. İdame aşamasında literatürde monoterapide >6,25 mg/gün steroid tedavisi önerilmektedir (15). Nüks riskini azaltma için tedaviye immünsüpresif ajanların eklenmesi önerilmektedir (15). Başka bir çalışmada ise steroid dozunun <0,4mg/gün' den yavaş azaltılması azalmış nüks ile ilişkili gösterilmiş (22). Çalışmamızda idame tedavide 4 mg'ın altında steroid kullanan hastalarda nüks sıklığında artış tespit edilmedi. Bunun da hastaların düşük doz steroid tedavisin yanı sıra ek immünsüpresif tedavi kullanmasıyla ilişkili olduğunu düşünüyoruz.

Literatürde lakrimal bez, tükürük bezleri, akciğer, lenf nodu, pankreas ve safra yollarında tutulumu olan hastalarda nüks oranı daha yüksek bulunan çalışmalar vardır (15). Bizim çalışmamızda ise tanı anında retroperitoneal ve pankreas tutulum birlikteliği olan hastalarda, nüks riski daha yüksek oranda tespit edildi. Çalışmamızda kreatinin yüksekliği de nüks ile ilişkili bulunmuştur. Kreatinin artışı retroperitoneal tutulumu olan hastalarda tespit edildi. Literatürde kreatinin yüksekliği ile nüks arasında ilişki gösteren bir çalışma yoktur.

Çalışmamızın kısıtlılıkları, sınırlı sayıda hasta ile yürütülen tek merkezli ve retrospektif bir çalışma olmasıdır. Çalışmamızın gücü, hastaların aynı hekim tarafından düzenli takip edilmesidir.

IgG4-İH'da nüks için risk faktörlerinin belirlenmesini sağlayacak, ideal tedavi için yol gösterici olacak, daha fazla sayıda hasta içeren, prospektif ve çok merkezli çalışmalara ihtiyaç vardır.

SONUÇ

IgG4-İH'da tanı anındaki klinik bulgular ile nüks arasındaki ilişkinin ortaya konulması, bu hastaların prognozu ve mortalite risklerinin belirlenmesi ve tedavi planlamasında önemlidir. Çalışmamızda tanıda serum IgE, eozinofil ve kreatinin yüksekliği, alerji öyküsü, hastalık süresi ve sigara kullanımı nüks ile ilişkili faktörler olarak tespit edildi. Hastalık süresi nüks ile ilişkili bağımsız risk faktörü olarak bulundu. Retroperitoneal doku ve pankreas tutulumu olması nüks için risk taşıyordu. Bu risk faktörlerine sahip hastaların nüks açısından daha dikkatli ve yakından takip edilmesi gerektiği kanaatindeyiz. Bu hastalarda uzun süreli kombine immünsüpresif tedavi kullanımı nüks, mortalite ve morbidite oranlarında azalmaya yol açabileceğini düşünüyoruz.

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Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

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Radyoterapi uygulanan meme kanserli hastalarda pandemi etkileri

Pandemic effects in breast cancer patients treated with radiotherapy

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ÖZ

Amaç: Pandemide kanser hastalarının immünsupresif olmaları nedeniyle COVID-19 enfeksiyonuna yakalanma riskinin arttığını ve enfeksiyona bağlı mortalite oranlarının genel popülasyondan daha yüksek olduğunu biliyoruz. Çalışmamızda meme kanseri nedeniyle radyoterapi yapılan hastalarda pandemi etkilerini gözlemlemek, COVID-19 enfeksiyonunu ağır geçirmelerini etkileyen faktörleri analiz etmek amaçlanmıştır.

Gereç ve Yöntem: Çalışmada 01/05/2019-31/12/21 tarihleri arasında tedavi uyguladığımız ve takipteki 122 hasta, onamları alınarak tarafımızca oluşturulan 20 soruluk bir form ile poliklinik kontrolleri sırasında değerlendirildi.

Bulgular: Medyan yaş 50 (aralık 25-84) olup, 62 (%50,8) hasta COVID-19 hastalığını geçirmişti. Hastaların tamamında halsizlik yorgunluk görülmüştü. Hastaların %86'sı aşı yaptırmıştı. %63,1'i önlem için maske kullanmaktaydı. Vitamin kullanımı oranı %21,3'tü. Hastalığı ağır geçirenlerin hiçbiri vitamin kullanmamıştı (p:0,61). Erken evre hastalarda ileri evre hastalara göre vitamin kullanımı daha azdı (p:0,005). Yaş, performans, evre, hastalığı tedavi öncesi veya sonrasında geçirmiş olmak, aşının yapılış zamanı hastalığın ağır geçirilmesi üzerinde istatistiksel olarak anlamlı bulunmamıştır.

Sonuç: Onkoloji hastalarının radyoterapi sürecinde COVID-19 enfeksiyonundan korunmada aşı, maske ve mesafenin en etkili yöntemler olduğu görülmüştür. Vitamin kullanımı ve kullanılan vitamin türünün COVID-19 enfeksiyonunun şiddetine etkisini değerlendirebilmek için daha fazla hasta sayısına ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, meme kanseri, onkoloji, pandemi

ASBTRACT

Objective: We know that the risk of contracting COVID-19 infection increases due to the immunosuppression of cancer patients in the pandemic and the mortality rates due to infection are higher than the general population. In our study, it was aimed to observe the effects of the pandemic in patients who received radiotherapy for breast cancer, and to analyze the factors affecting their severe COVID-19 infection.

Materials and Method: In this study122 patients who were treated and followed up between 01/05/2019-31/12/21 were evaluated during their outpatient clinic controls with a 20-question form created by us after taking their consent.

Results: The median age was 50 (range 25-84), and 62 (50.8%) patients had COVID-19 disease. Fatigue was observed in all patients. 86% of the patients had been vaccinated. 63.1% of them were using masks for precaution. The rate of vitamin use was 21.3%. None of the patients with severe disease used vitamins (p:0.61). Vitamin use was less in early-stage patients than in advanced-stage patients (p:0.005). Age, performance, stage, having the disease before or after treatment, time of vaccination were not found statistically significant on severe disease.

Conclusion: It has been seen that vaccination, mask and distance are the most effective methods in the prevention of COVID-19 infection in the radiotherapy process of oncology patients. A larger number of patients is needed to evaluate the effect of vitamin use and the type of vitamin used on the severity of COVID-19 infection.

Keywords: COVID-19, breast cancer, oncology, pandemic

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GİRİŞ

İlk olarak Çin'in Vuhan Eyaleti'nde saptanan koronavirüs hastalığı (COVID-19), Mart 2020'de Dünya Sağlık Örgütü (DSÖ) tarafınca küresel bir salgın olarak kabul edilmiştir. Ateş, öksürük, nefes darlığı, halsizlik ve yorgunluk sıklıkla karşılaşılan semptomlarıdır (1).

Kanser, kardiyovasküler hastalıklar, akciğer hastalıkları, diyabet gibi kronik sağlık sorunları olan kişilerde COVID-19 enfeksiyon riski daha fazladır (2). Mevcut hastalıkları ve tedavileri nedeniyle immünsupresif olan kanser hastalarının COVID-19 hastalığına yakalanma olasılıkları yüksek olup, çalışmalarda kanser hastalarında bu hastalığa bağlı mortalite oranları normal popülasyondan daha yüksek olarak bulunmuştur. Zhang ve arkadaşlarının (3) yayınladığı metaanalizde kanser tanısı olan COVID-19'a bağlı mortalite oranı (%22,4) normal popülasyona göre daha yüksek bulunmuştur. Ayrıca Çin verilerine göre kanser olmayan hastalara kıyasla mekanik ventilasyon veya yoğun bakım ünitesine kabul edilme veya ölüm riskinin 3,5 kat daha yüksek bulunmuştur (4).

Hastalığı iyileştirebilecek kesin bir tedavinin olmaması, virüsün bulaşıcılığının yüksek olması, tüm dünya ülkelerinin sağlık sistemleri üzerinde olumsuz etkileri nedeniyle, aşı geliştirilmesi yoluna gidilmiştir. Zayıflatılmış canlı virüs, inaktif virüs, viral vektör, nükleik asit (RNA, DNA), protein subunit ve virüs benzeri partikül (VLP) içeren aşılar geliştirilmiş ve bir kısım aşı acil kullanım onayı ile uygulanmaya başlamıştır (5).

COVID-19'un onkoloji hastalarında saptanan şiddetli seyri nedeni ile onkoloji hastaları aşılama için yüksek öncelikli bir alt grup olarak kabul edildi. Ulusal Kapsamlı Kanser Ağı (NCCN), aktif kanser tedavisi gören ve tedavisi görmek üzere olan ve son altı ay içinde kanser tedavisi gören kişilerin mümkün olan en kısa sürede aşı yaptırmaya öncelik vermelerini öneri olarak yayınladı. Amerikan Kanser Araştırmaları Derneği (AACR), Amerikan Kanser Enstitüleri Birliği (AACI) ve Hastalık Kontrol ve Önleme Merkezleri (CDC) dahil olmak üzere birçok kuruluş, COVID-19 aşısı için kanserli hastalara öncelik verilmesini tavsiye etti. Analizlerde, aşılamanın kanser hastalarında COVID-19 bulaşını önleme ve COVID-19'a bağlı mortaliteyi azaltmada etkili olduğu gösterilmiştir (6,7).

Sağlık Bakanlığı verilerine göre bugüne kadar COVID-19 aşılarına yönelik gerek yürütülen klinik çalışmalarda gerekse mevcut aşı uygulamalarında ciddi yan etkilere rastlanmamıştır. Aşılama sonrasında görülen yan etkiler sıklıkla hafif olup yorgunluk, baş ağrısı, ateş, titreme, kas/eklem ağrısı, kusma, ishal, aşı uygulanan bölgede ağrı, kızarıklık, şişlik gibi hafif yan etkiler bildirilmiştir (8).

COVID-19 pandemisi sürecinde birçok ülke sağlık sisteminin çoğu alanında değişiklikler yapma yoluna gitmiştir. Özellikle riskli olan onkoloji hastaları için günlük onkolojik pratikte değişik modifikasyonlar yapılmıştır. Rutin kanser taramaları geçici olarak durdurulmuş, rutin takiplerde bazı koşullarda takip aralıkları uzatılmıştır. Pandemi süresince immünoterapi, hedefe yönelik ilaçlar ve hormonal ilaçlar COVID-19 bulaş ve mortalite riskini arttırmadığından bu ilaçların kullanımı devam ettirilmiştir. Kemoterapi alan hastalarda immünsupresyon ve enfeksiyon riski nedeni ile uluslararası kılavuzlar çerçevesinde bazı değişikliklere gidilmiş, küratif tedavi düşünülen ve kemoterapiye iyi yanıt alınabilecek tümörlerin tedavileri standart olarak devam etmiştir. Metastatik evre hastalarda ise hastayla birlikte tedaviye karar verilmesi önerilmiştir. Onkolojik tedavi alan hastaların %50'sinden fazlası tedavi sürecinin bir aşamasında multidisipliner ayağın önemli bir parçası olan radyoterapi tedavisine ihtiyaç duymaktadır. Meme kanserli hastalarda da adjuvan veya palyasyon radyoterapi tedavisi uygulanır. Ortalama 5-6 hafta radyoterapi planlanan bir hasta hafta içi her gün genellikle ayaktan kontrolsüz bir ortamdan hastaneye gelmekte ve tedavi cihazında yaklaşık 15-20 dakika süren tedaviden sonra günlük hayatına devam etmektedir. Tedavi süresince hastalara diğer hastalardan, hasta refakatçileri ve departmandaki sağlık personelinden veya toplu taşımada insanlarla temastan kaynaklanabilecek bulaş riski fazladır. Riskin çok olduğu meme kanserinde Sağlık Bakanlığının COVID-19 Rehberi, 14 Nisan 2020 tarihli "Kanser Hastalarına Bakım Veren Merkezlerde Enfeksiyon Kontrol Önlemleri" başlıklı yönergesi ve Türk Radyasyon Onkolojisi Derneği'nin önerilerine göre hasta ve hasta yakınları, sağlık çalışanları, bekleme/tedavi alanları ve takip ve tedavi sırasında alınması gereken önlemler belirtilmiştir (8).

Sağlık sisteminin aşırı yüklendiği bu kriz döneminde hastaların sağkalımını olumsuz etkilemeyecek şekilde tedavi zamanlaması, sıralaması ve dozlarında birtakım değişiklikler yapıldı. Rutin radyoterapi pratiğinde İngiltere ve İskandinav ülkelerinde hipofraksiyone tedaviler sıklıkla kullanılmakla birlikte ülkemizde, ABD ve birçok Avrupa ülkesinde konvansiyonel fraksiyone rejimleri kullanılmaktadır. COVID-19 salgını ile birlikte yapılan önerilerde bazı tümörlerde olduğu gibi meme kanserinde de hipofraksiyone radyoterapi rejimler kullanılmıştır (9,10).

Kanser hastalarında COVID-19 maruziyetini gidermek ve hastalığa yakalanma oranlarını azaltmak için bazı önlemler almak gereklidir. Hastalık Kontrol ve Önleme Merkezi (CDC), COVID-19 salgınını yavaşlatmanın ve sonuçta hayat kurtarmanın en etkili yolunun yeni enfeksiyonların önüne geçerek "salgın eğrisini düzleştirmek" olduğunu bildirmiştir (11). COVID-19 enfeksiyonu başlıca damlacık ve temas yoluyla bulaşır. Hem asemptomatik hem de hastalık belirtileri gösteren bireyler hastalığı başkalarına bulaştırabileceği için herkesin korunma önlemlerine uygun davranması çok önemlidir. Korunmada en etkili yöntemler; el hijyeni, maske kullanımı, sosyal mesafe, hastaların izolasyonu ve temaslı takibi, sağlık çalışanlarının korunması ve çevre temizliğidir (12).

Tedavide kesin etkili olduğu bilinen antiviral bir ilaç bulunmadığından, hedef bağışıklık sistemini ve antioksidan savunma mekanizmalarını güçlendirmek olmuştur (13).

COVID-19 pandemisiyle birlikte vitaminlerin hastalıktan korunma ve tedavideki yararlarıyla ilgili araştırmalar artmış olup etkin olduğunu bildiren yayınlar olduğu kadar, bu sonucu desteklemeyen çalışmaların olduğu da gözlenmektedir. Çalışmalarda, COVID-19 da dahil çeşitli viral hastalıklarda vitaminlerin konak bağışıklık sistemini güçlendirme üzerine etkili olduğu gösterildiğinden bu süreçte vitaminlere olan ilgi artmıştır. Vitaminlerin hastalıktan korunma ve tedavideki etkin olduğunu bildiren yayınlar olduğu kadar, bu sonucu desteklemeyen çalışmalarda vardır.

Virüslere karşı fiziksel bariyerin güçlendirilmesinde, antimikrobiyal peptitlerin üretiminin uyarılmasında ve inflamatuvar sitokin üretiminin azalmasını sağlayarak sitokin fırtınalarının önlenmesinde önemli rolü olduğu bilinen, immünomodulatör bir ajan olan Vitamin D'nin COVID-19 enfeksiyonu ile ilişkisini değerlendiren meta-analizde vitamin D eksikliğiyle hastalık şiddeti, hastaneye yatış ve mortalite oranları arasında anlamlı ilişki olduğu saptanmıştır (14-16)

Bağışıklık hücrelerinin etkinliğini arttırarak, anti-enflamatuar ve antioksidan etkisi ile bağışıklık sistemini modüle ettiği bilinen C vitamininin de COVID-19 hastalarında immün yanıtın güçlendirilmesine katkıda bulunarak sağkalım oranlarını arttırabileceği ifade edilmektedir. Vitamin C ayrıca enfeksiyonlar sırasında üretilen reaktif oksijen türlerinin zararlı etkilerini nötralize etmektedir (17).

Vitamin B12 (Vit B12), hematopoetik, sinir ve bağışıklık sistemi için destekleyici olduğu bilinen önemli bir immünomodülatördür ve konak hücrede viral replikasyonu baskılayabilir. Vit B12 eksikliğinde lenfopeni, CD8 hücrelerinin sayısı ve doğal öldürücü hücrelerin işlev bozukluğu gözlemlenebilir. Vit B12 düzeyi eksikliği olan COVID-19 hastalarının klinik progresyonunun Vit B12 eksikliği olmayanlardan daha kötü olduğunun belirlendiği ve bu nedenle COVID-19 hastalarında Vit B12 takviyesinin olumlu etkisi olabileceği Vit B12 ile bağışıklığı arttırdığı tahmin edilmektedir. COVID-19 hastalarında Vit B12 takviyesinin olumlu etkisi olabileceğini çalışmalarda gösterilse de bu konuda bir netlik yoktur (18-20).

Çalışmamızda amacımız meme kanseri tanısı alan hastalarımızın pandemiden ne ölçüde etkilendiklerini, hastalığı ağır geçirmelerine etkili olan faktörleri analiz etmektir.

GEREÇ VE YÖNTEM

Bu çalışma, üniversite/yerel insan araştırmaları etik kurulu tarafından onaylanmış ve insan katılımcıları içeren çalışmalarda gerçekleştirilen tüm prosedürler, kurumsal ve/veya ulusal araştırma komitesinin etik standartlarına, 1964 Helsinki Bildirgesi ve daha sonra yapılan değişikliklere veya karşılaştırılabilir etik standartlara uygun olarak yapılmıştır. Çalışma için Kartal Lütfü Kırdar Şehir Hastanesi Klinik Araştırmalar Etik Kurulu'ndan etik kurul onayı alınmıştır (Tarih: 28.09.2022, Karar No: 2022/514/234/16).

Çalışma için 01/05/2019-31/12/2021 tarihleri arasında tedavi uyguladığımız ve takipteki 122 hasta, onamları alınarak tarafımızca oluşturulan 20 soruluk bir form ile poliklinik kontrolleri sırasında değerlendirildi. Hastaların verileri SPSS ver. 17 (SPSS Inc.,IBM, Chicago, IL, USA) istatistik yöntemi kullanılarak analiz edildi. Verilerin dağılım uygunluğu kontrol edilmiş ve korelasyon analizleri, Pearson testi kullanılarak yapıldı. İstatistiksel anlamlılık sınırı olarak p değerinin 0,05'in altında olması anlamlı kabul edildi.

BULGULAR

Medyan yaş 50 (aralık 25-84) olup, hastalık evreleri ve aldıkları tedaviler **Tablo 1**'de gösterilmiştir. COVID-19 testi pozitif olarak saptanmış olan 62 (%50,8) hasta mevcuttu ve bu hastaların %27,9'u COVID-19 enfeksiyonunu hafif olarak geçirmişti. Hastaların tamamında semptom olarak halsizlik yorgunluk görülmüştü. Hastaların yatış oranları, aşı yapılma oranı, hangi aşıyı oldukları, aşı yan etkileri, hastalığı ne zaman geçirdikleri ve diğer hasta ve hastalık özellikleri **Tablo 2** ve **3**'de özetlenmiştir. Hastaların %4,9'unda hastaneye yatış ihtiyacı olmuş ve 1 hastada yoğun bakıma yatmıştı. Radyoterapi tedavisine 17 (%13,9) hastada ara verilmişti. Medyan tedavi arası 14 gün (aralık 3-90 gün) idi. Hastaların %86'sı aşılanmış, 20'si ölü, 54'ü mRNA, 32'si her iki aşıyı yaptırmışlardı. 27 hasta aşı yaptırmadan önce hastalığı geçirmişti. Altı hasta (%4,9) pandemide bulaş korkusu nedeni ile takiplerini aksatmıştır (**Tablo 4,5**).

Tablo 1. Meme kanserli hastaların performans, evre ve tedavi özellikleri

	n	%
ECOG		
0	77	63,1
1	13	27
2	12	11,9
Evre		
Erken	51	41,8
İleri	56	45,9
Metastatik	15	12,3
Metastaz Bölgesi		
Beyin	1	0,8
Karaciğer	2	1,6
Kemik	8	6,6
Kemik-Viseral	1	0,8
Hangi Tedavileri Aldı?		
NAK+C+RT+HRT	41	33,6
C+KT+RT+HRT	42	34,4
C+RT	7	5,7
C+RT+HRT	21	17,2
KT+RT	8	6,6
HRT+RT	3	2,4

NAK: Neoadjuvan kemoterapi, C: Cerrahi, RT: Radyoterapi, KT: Kemoterapi, HRT: Hormonoterapi

Tablo 2. Meme kanserli hastaların COVID-19 enfeksiyonu özellikleri

	n	%
COVID-19 pozitifliği		
Evet	61	50
Hayır	61	50
Şiddeti		
Hafif	33	27
Orta	16	13,1
Ağır	12	9,8
Kaç kez geçirdi?		
1	55	44,3
2	6	4,9
4	1	0,8
Ne zaman geçirdi?		
Tedavi öncesi	21	17,2
Tedavi esnasında	10	8,2
Tedavi sonrası	29	23,8
Tedavi öncesi ve sonrası	2	1,6
Bulgular		
Grip benzeri		63,1
Ateş		5,7
Halsizlik		5,7
Dispne		1,6
Tat duyu kaybı		2,5
Hepsi		13,9

Tablo 3. Meme kanserli hastaların COVID-19 enfeksiyonu yönetimi

Hastanede yatış gerekli oldu mu? n (%)	Evet 6 (%4,9)	Hayır 55 (%45,1)
Yoğun bakım ihtiyacı oldu mu? n (%)	Evet 1 (%0,8)	Hayır 60 (%49,2)
COVID-19 ilaç tedavisi aldı mı? n (%)	Evet 23 (%18,9)	Hayır 38 (%31,1)
Tedaviye ara verildi mi? n(%)	Evet 17 (%13,9)	Hayır 44 (%36,1)

Tablo 4. Meme kanserli hastaların aşılanma durumu

	n	(%)
Aşı oldunuz mu?		
Evet	104	(%85,2)
Hayır	17	(%13,9)
Hangi aşı?		
Sinovac	20	(%16,4)
Biontech	54	(%44,3)
Sinovac-Biontech	32	(%26,2)
Kaç doz?		
1	8	(%6,6)
2	29	(%23,8)
3	40	(%32,8)
4	21	(%17,2)
5	7	(%5,7)
6	1	(%0,8)
Aşı zamanı		
Tedavi öncesi	20	(%16,4)
Tedavi sırasında	62	(%50,8)
Tedavi sonrası	14	(%11,5)
Tedavi öncesi ve sonrası	10	(%8,2)

Tablo 5. Meme kanserli hastaların tedavi seyri

Ağır grip geçirdiniz mi? n (%)	Evet 17 (%13,9)	Hayır 105 (%86,1)
Aile içinde hastalığı geçiren oldu mu? n (%)	Evet 64 (%47,5)	Hayır 58 (%52,5)
Takiplerinde aksama yaşadınız mı? n (%)	Evet 6 (%4,9)	Hayır 115 (%94,3)

Aşı yan etkisi olarak en sık kol ağrısı (%21,3) ve halsizlik (%7,4) görülmüştü. Kol ağrısı anlamlı olarak canlı aşı uygulananlarda fazlaydı (p:0,002). Bu süreçte 17 hasta çok ağır grip geçirmiş fakat testleri negatifti.

Hastaların %63,1'i önlem için maske kullanmaktaydı. Vitamin kullanımı oranı %21,3'tü. Erken evre hasta grubunda vitamin kullanımoranı %8,7 iken ileri evre hasta grubunda %12,6 idi. Hastalar vitamin olarak D, C, B12 tercih etmişlerdi. %9,8'i maske dahil hiçbir önlem almamıştı.

Hastaların COVID-19 enfeksiyon şiddeti subjektif olarak değerlendirilmiştir. Hafif şiddetli hastalık grubunda, semptomsuz veya ilaç tedavisine gerek olmayan; orta şiddetli hastalık grubunda, hastalığı semptomatik geçiren ve ilaç kullanma gereksinimi olan ve ağır şiddetli hastalık grubunda hospitalizasyon gereken hastalar yer almakta idi. Hastalığı ağır geçirenlerin hiçbiri vitamin kullanmamıştı (p:0,61). Erken evre hastalarda ileri evre hastalara göre vitamin kullanımı daha azdı (p:0,005). Hastaların evre ve vitamin tercihi arasında anlamlı bir ilişki bulunmadı.

Yaş (p:0,82), performans (p:0,34), evre (p:0,14), hastalığı tedavi öncesi veya sonrasında geçirmiş olmak (p:0,91), aşının yapılış zamanı hastalığın ağır geçirilmesi (p:0,92) üzerinde istatistiksel olarak anlamlı bulunmamıştır.

TARTIŞMA

Kanser hastaları mevcut hastalıkları ve almakta oldukları tedavilere bağlı olarak bağışıklık sistemleri sağlıklı insanlara göre daha zayıftır ve enfeksiyonlara karşı daha hassastırlar. Ayrıca onkoloji hastalarında COVID-19'a bağlı ölüm riskinin de oldukça yüksek olduğu bildirilmiştir. Meme kanseri tanı yöntemlerinin artması ile erken dönemde saptanmakta ve insidansı giderek artmaktadır. Meme kanserli hastalar uzun sağkalım beklediğimiz grubu oluşturur. Tedavi multidisipliner olup cerrahi, kemoterapi, radyoterapi, hormonoterapi ve uygun hastalarda immünoterapiden oluşmaktadır. Erkeklerde meme kanseri kadınlara oranla görülme sıklığı çok düşük olup çalışmamızda tüm hastalar kadındı (22-24).

Çalışmalarda özellikle kanser gibi ciddi sağlık sorunları olan bireylerde, SARS-CoV-2 enfeksiyon riski daha fazla olarak saptanmıştır. Wuhan Üniversitesi Kanser Tedavi Merkezi'ne başvuran 1524 kanser hastasının verisinin incelendiği çalışmada, kanser hastalarında COVID-19'a yakalanma riskinin genel populasyondan iki kat daha

fazla olduğu bildirilmiştir. Çalışmamızda da 62 (%50,8) hasta COVID-19 hastalığını geçirmiştir(2,25).

Kanser hastalarında diğer olgulara göre invaziv solunum desteği, yoğun bakım ihtiyacı ve ölüm oranlarının daha yüksek olduğu (%39 vs. %8, p=0,0003) ve hastaların daha hızlı olarak kaybedildiği (13 gün vs. 43 gün, p <0,0001) gözlenmiştir. Meme kanserli hastalarımızda COVID-19 enfeksiyonu %27,9 hafif, %13,1 orta, %9,8 ağır olarak seyretmişti. Yapılan diğer çalışmalarda akciğer kanserli hastalar daha çok sayıda olup hastalık bu hastalarda daha kötü seyretmiştir ve bu hastalarda daha çok yatış ve yoğun bakım ihtiyacı olmuştur. Hastalarımızın sadece 1 tanesi yoğun bakıma yatmıştı (4,26).

Ateş, öksürük, nefes darlığı, halsizlik ve yorgunluk sıklıkla karşılaşılan semptomlarıdır (1). Bizim hastalarımızda da semptomlar benzer olup, tüm hastalarda halsizlik ve yorgunluk görülmüştür. Tüm hastalarda halsizlik yorgunluk görülmesinin altında yatan sebep kanser hastalığının kendisinin yarattığı ve/veya tedavilerin yan etkisi olarak beklenen halsizlik yorgunluk üzerine enfeksiyon yükünün eklenmesi olabilir diye yorumlanmıştır.

Radyoterapi birçok kanser tedavisinde lokal kontrol ve sağkalımı anlamlı olarak arttırmakta, metastatik hastalıkta palyasyon sağlayarak hastaların yaşam kalitesini iyileştirmektedir. Radyobiyolojik esaslar gereği radyoterapi mümkün olduğunca planlandığı şekilde ara vermeden uygulanmalıdır. Tedavi başladıktan sonra verilen uzun aralar bazı kanser türlerinde tedavi etkinliğini azaltmakta ve hatta tümör repopulasyonunu arttırarak sonuçları olumsuz yönde etkilemektedir(27). Çalışmamızda 17 (%13,9) hastada tedaviye ara verildi. Bu hastaların 10 tanesi tedavi sırasında COVID-19 enfeksiyonu geçirmesi, 7 hasta da testleri negatif olmasına rağmen çok ağır grip geçirmeleri nedeni ile ara verilmişti. Onkoloji servislerimiz pandemi boyunca çalışmaya devam etti bu nedenle hastaların radyoterapi ayağında bir aksama yaşanmadı(%94,3) .

COVID-19 salgını ile birlikte yapılan önerilerde bazı tümörlerde olduğu gibi meme kanserinde de hipofraksiyone radyoterapi rejimler kullanılmıştır. Kliniğimizde de hastaların hastaneye geliş ve insanlarla temasını en aza indirmek amacı ile küratif tedavilerin tümü hipofraksiyone fraksiyon şeması kullanılarak uygulanmıştır (9,28).

2020 yılının sonlarından itibaren birçok ülkede uygulanmaya başlanmıştır. Bugüne kadar dünya nüfusunun %31,2'sine en az bir doz COVID-19 aşısı uygulanmıştır. Aşılama için yüksek öncelikli alt grup olarak kabul edilen onkoloji hastaları için ülkemizde aşılamada öncelik verildi. Dünya nüfusunun %23,5'i tam aşılıdır. Dünya çapında toplam 4,7 milyar doz aşı uygulanmıştı. Hastalarımızda da aşılanma oranı yüksekti (%85,2) (28).

Çalışmamızda Sağlık Bakanlığının verilerine benzer olarak aşı yan etkisi olarak en sık kol ağrısı (%21,3) ve halsizlik (%7,4) görülmüştü. Kol ağrısı anlamlı olarak canlı aşı uygulananlarda fazlaydı.

Başlıca damlacık ve temas yoluyla bulaşan COVID-19 enfeksiyonundan korunmada en etkili yöntemler; el hijyeni, maske kullanımı, sosyal mesafe, hastaların izolasyonu ve temaslı takibi, sağlık çalışanlarının korunması ve çevre temizliğidir (29). %70,4 oranda hastalarımız önlem için maske kullanmaktaydı. Önlem almayanların hepsi COVID-19 enfeksiyonu geçirmişti.

Vitamin C ve D ve B12 vitamininin bağışıklık sistemi üzerinde çok sayıda yararlı etkisi olduğu birçok çalışmada gösterilmiştir. Vitamin kullanımının COVID-19 hastalarında yararlı olabileceğini bildiren çalışmalar olduğu gibi etkisiz olduğunu bildiren yayınlar da bulunmaktadır. Pandemi döneminde immün sistemi güçlendireceği düşünülerek vitamin kullanımında bir artış olmuştur. Çalışmamızda vitamin kullanımı oranı %21,3'tü. Hastalar vitamin olarak C, D, B12 tercih etmişlerdi. Hastalığı ağır geçirenlerin hiçbiri vitamin kullanmamıştı (p:0,61) ve istatistiksel olarak anlamlılığa yakındı. Erken evre hastalarda ileri evre hastalara göre vitamin kullanımı daha azdı (p:0,005).

SONUÇ

Onkoloji hastalarının tedavilerinin aralıksız, aksamadan devam etmesi uzun bir sağkalım için gereklidir. Bu nedenle salgın sürecinde kanser hastalarının sosyal izolasyon ve kişisel hijyen kurallarına uyması halen önemini korumaktadır. Onkoloji hastalarının radyoterapi sürecinde COVID-19 enfeksiyonundan korunmada aşı, maske ve mesafenin en etkili yöntemler olduğu gösterilmiştir. Vitamin kullanımı ve kullanılan vitamin türünün COVID-19 enfeksiyonunun şiddetine etkisini değerlendirebilmek için daha fazla hasta sayısına ve kanıt düzeyi yüksek çalışmalara ihtiyaç vardır.

ETİK BEYANLAR

Etik Kurul Onay: Çalışma için Kartal Dr. Lütfi Kırdar Şehir Hastanesi Klinik Araştırmalar Etik Kurulu'ndan etik kurul onayı alınmıştır (Tarih:28/9/2022, Karar No:2022/514/234/16).

Aydınlatılmış Onam: Çalışma anket çalışması olarak tasarlandığından hastalardan yazılı bilgilendirilmiş onam formu alınmıştır.

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışmada herhangi bir finansal destek almadıklarını beyan etmektedirler.

Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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Evaluation of laparoscopy results for the patients with chronic pelvic pain

Kronik pelvik ağrılı hastalarda laparoskopi sonuçlarının değerlendirilmesi

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ABSTRACT

Aim: The study aims to retrospectively evaluate the laparoscopy results of patients who underwent laparoscopy with chronic pelvic pain (CPPS) diagnosis in two groups of fertile and infertile patients.

Material and Method: This retrospective study examined the electronic records of 170 patients who underwent laparoscopy due to CPPS were included in the study. The patients were divided into two groups: the CPPS and unexplained infertility group (n: 87) as the case group and the CPPS fertile group (n: 83) as the control group. Women aged 25-40 years with unexplained infertility and CPPS were included in the study.

Results: Results found a statistically significant association between infertility in women and laparoscopy results ($p<0.001$). There was no statistically significant association between infertility in women and symptoms ($p>0.05$). There was no statistically significant association between women's infertility and smoking status ($p>0.05$). Mann-Whitney test did not find a statistically significant association between case and control regarding age and body mass index (BMI) ($p>0.05$). There was a statistically significant difference between groups in terms of the duration of pain ($p<0.05$). The duration of pain in the case group ($M=5.34$; $SD=1.67$) was higher than the duration of pain in controls ($M=4.8$; $SD=1.72$).

Conclusion: Results showed that the duration of pain in the infertile group was significantly higher than in the fertile group, which could mainly be attributed to endometriosis.

Keywords: Laparoscopy, chronic pelvic pain, infertility

ÖZ

Amaç: Çalışmamız, kronik pelvik ağrı (KPAS) tanısı ile laparoskopi yapılan hastaların laparoskopi sonuçlarını fertil ve infertil olmak üzere iki grupta retrospektif olarak değerlendirmeyi amaçlamaktadır.

Gereç ve Yöntem: Bu retrospektif çalışmada, KPAS nedeniyle laparoskopi yapılan 170 hastanın elektronik kayıtları incelendi. Hastalar vaka grubu olarak KPAS ve açıklanamayan infertilite grubu (n: 87) ve kontrol grubu olarak KPAS fertil grubu (n: 83) olmak üzere iki gruba ayrıldı. 25-40 yaş arası açıklanamayan infertilite ve KPAS olan kadınlar çalışmaya dahil edildi.

Bulgular: Kadınlarda infertilite ile laparoskopi sonuçları arasında istatistiksel olarak anlamlı bir ilişki buldu ($p<0,001$). Kadınlarda infertilite ile semptomlar arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p>0,05$). Kadınların infertilitesi ile sigara içme durumu arasında istatistiksel olarak anlamlı bir ilişki yoktu ($p>0,05$). Mann-Whitney testi, yaş ve vücut kitle indeksi (VKİ) açısından olgu ve kontrol arasında istatistiksel olarak anlamlı bir ilişki bulmadı ($p>0,05$). Ağrı süresi açısından gruplar arasında istatistiksel olarak anlamlı fark vardı ($p<0,05$). Olgu grubundaki ağrı süresi ($Ort=5,34$; $SD=1,67$), kontrol grubundaki ağrı süresinden ($Ort=4,8$; $SD=1,72$) daha uzundu.

Sonuç: Sonuçlar, infertil grupta ağrı süresinin fertil gruptan anlamlı olarak daha yüksek olduğunu gösterdi ve bu durum esas olarak endometriozise atfedilebilir.

Anahtar Kelimeler: Laparoskopi, kronik pelvik ağrı, kısırlık

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INTRODUCTION

Chronic pelvic pain (CPPS) is any pain in the pelvic area unrelated to pregnancy, menstruation, and sexual intercourse, which has lasted at least six months or more and has no known organic cause (1-3). Gynecological, urological, digestive, and musculoskeletal factors and psychological issues have been proposed as effective causes of this complication (3-5). The complexity of the variety of pelvic pain causes these patients not to receive a definitive diagnosis in more than 60% of cases, and this point is especially evident in the case of musculoskeletal factors (5-7). The prevalence of this pain in different societies, according to the characteristics of the studied society and the method of conducting the study, has been reported to be between 8.3-39% (7,8). Diagnosing and treating CPPS accounts for 10% of visits to obstetricians and gynecologists, 20% of all laparoscopies, and 12-16 hysterectomies, which in the United States cost over $2.8 billion per year (5). According to an estimate (8), 158 million pounds are spent annually on diagnosing and treating this condition in the British National Health Service. This pain affects women's daily activities and quality of life and negatively affects their mental and physical health (8,9).

Mak et al. (10) reported the prevalence of CPPS as 39% in a hospital-based study of 559 people. A study by Faul et al. (11) on 581 women showed that 39% had pelvic pain, 46 had painful intercourse, 9% had painful menstruation, and 12 had irritable bowel syndrome. Horne et al. (9) reported an annual incidence of CPPS in the UK of 38 cases per 1,000 women aged 15-73. In another study, among 3916 women aged 18-49 years, the prevalence of CPPS in the form of recurring pain with a fixed duration and at least six months unrelated to sexual intercourse, pregnancy and dysmenorrhea were reported as 24% (6). Argentino et al. (3) reported a study in New Zealand on 2,261 women aged 18-50 years that among the participants, the three-month prevalence of chronic pelvic pain was 25.4%, and about half of these women (47.7%) were undiagnosed. Singh et al. (12) showed that until that date, only 18 epidemiological studies were conducted on the frequency of non-periodic pelvic pain, which was reported as 1.2-24%. The studies conducted on the frequency of CPPS while expressing the importance and extent of the issue and the need to address it, indicate that there is still no consensus among researchers, even on the basic concepts and definition of CPPS, which causes dispersion in the findings of epidemiological studies. Therefore, the necessity of further investigations considering the diversity of demographic indicators in terms of the living environment, especially in developing societies, is raised.

Patients with unknown pelvic pain are a typical case of visiting the emergency room, which has always been a problem. These patients are hospitalized for several days without a diagnosis or by taking various radiographs, tests, sonography, and computed tomography scan, or even surgery without pathology, suffer a lot of cost and waste of time. Laparoscopy, a relatively less invasive new method, allows access to the entire abdominal and pelvic cavity except for the kidneys with multiple magnifications (5-7). This is a diagnostic and therapeutic method with a high percentage and can be an alternative to diagnostic laparotomy (13). The study aims to retrospectively evaluate the laparoscopy results of patients who underwent laparoscopy with the diagnosis of CPPS.

MATERIAL AND METHOD

The study was carried out with the permission of Bezmialem Vakıf University Non-interventional Clinical Research Ethics Committee (Date: 6/9/2022, Decision No: 2022/261). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. With the ethics committee approval, the data were scanned retrospectively using the hospital ınformation management system between December 2017-March 2022.

A total of 170 patients who underwent laparoscopy due to CPPS were included in the study. The patients were divided into two groups: the CPPS and unexplained infertility group (n: 83) as the case group and the chronic pelvic pain fertile group (n: 87) as the control group. Women aged 25-40 years with unexplained infertility and chronic pelvic pain were included in the study. Those with a previous history of laparoscopy, diagnosed with endometriosis, male infertility, tubal factor, or ovulatory dysfunction were excluded from the study.

The Visual Analogue Scale (VAS) measures pain intensity. The VAS consists of a 10cm line, with two endpoints representing 0 ('no pain') and 10 ('pain as bad as it could possibly be'). VAS scores were found in patient files and recorded.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality, and the nonparametric tests were performed given the groups' non-normality before the statistical analyses. Mean and standard deviations (SD) were measured to check each continuous variable, including age, body mass index (BMI), the duration of pain, CA-125, VAS. The Mann-Whitney U test was performed to study the difference between the two groups. SPSS v22 was used for statistical analyses. A value of $p<0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two groups' total mean was measured based on the Mann-Whitney test with the power of 95%, effect size of 50%, and 0.05 type 1 error for at least 92 patients (11).

RESULTS

This study included one hundred seventy age-matched (32.46 ± 3.43) and BMI-matched (24.65±2.08) women. **Table 1** shows descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters (n=170).

Study parameters	median (range)	mean ± SD
Age	32 (25-40)	32.46±3.43
BMI	25 (18.2-34)	24.65±2.08
The duration of pain (y)	5 (1-9)	5.06±1.71
CA-125 (U/mL)	25 (5-75)	27.91±13.69
Visual Analog Scale of pain	6 (4-9)	6.3±1.34

SD, standard deviation

The average pain duration in women was 5.06±1.71. The average CA-125 score in women was 27.91±13.69). The average women's VAS of pain score was 6.3±1.34). **Table 2** shows the comparison of laboratory findings of the nominal study parameters.

As stated in **Table 2**, the highest frequency of laparoscopy results in total was endometriosis (31.8%), adeomyosis(14.7%), adhesion (16.5%), ovarian cyst (12.9%), no pathology detected (7.1%), pelvic inflammatory disease (PID) (5.3%), hydrosalpenx (4.7%), myoma (3.5%), polycystic ovary syndrome (PCOS) (1.2%), tuboovarian abscess (1.2%), and tuberculosis (1.2%). As can be seen from **Table 2**, the highest frequency of symptoms in total was dysmenorrhea (35.3%), dyspareunia (32.9%), fever, weight loss, anorexia (9.4%), irregular cycles (8.2%), gastrointestinal (GIS) symptoms (5.9%), vaginal discharge (5.3%), and heavy menstrual bleeding (2.4%).

As stated in **Table 2**, a chi-square test found a statistically significant association between infertility in women and laparoscopy results (p<0.001). The Pairwise Z-Tests found that the ovarian cyst in women in the control group was significantly higher than in the case group. The Pairwise Z-Tests found that the Adhesion in women in the control group was significantly higher than in the case group. The Pairwise Z-Tests found that the hydrosalpenx in women in the case group was significantly higher than in the control group. The Pairwise Z-Tests found that the endometriosis in women in the case group was significantly higher than in the control group. The Pairwise Z-Tests found that the no pathology detected in patients in the control group was significantly higher than in the case group.

Table 2. Comparison of laparoscopy results of the nominal study parameters

Variables	Categories	Total	Case(n=83) n(%)	Control(n=87) n(%)	p
Laparoscopy result					<0.001*
	Ovarian Cyst	22(12.9)	2(9.09)	20(90.91)†	
	Adhesion	28(16.5)	8(28.57)	20(71.43) †	
	Hydrosalpinx	8(4.7)	7(87.5) †	1(12.5)	
	Adenomyosis	25(14.7)	14(56)	11(44)	
	Endometriosis	54(31.8)	41(75.93) †	13(24.07)	
	PCOS	2(1.2)	1(50)	1(50)	
	PID	9(5.3)	4(44.44)	5(55.56)	
	Myoma	6(3.5)	4(66.67)	2(33.33)	
	Tuboovarian abscess	2(1.2)	1(50)	1(50)	
	Tuberculosis	2(1.2)	0(0)	2(100)	
	No pathology detected	12(7.1)	1(8.33)	11(91.67) †	
History of previous surgery					0.032*
	Yes	81(47.6)	26(63.4)	15(36.6) †	
	No	89(52.4)	57(44.2) †	72(55.8)	
Cigarette					0.655*
	Yes	41(24.1)	41(50.6)	40(49.4)	
	No	129(75.9)	42(47.2)	47(52.8)	
Symptoms					0.428*
	Dyspareunia	56(32.9)	27(48.2)	29(51.8)	
	Dysmenorrhea	60(35.3)	33(55)	27(45)	
	Vaginal discharge	9(5.3)	2(22.2)	7(77.8)	
	Fever, weight loss, anorexia	16(9.4)	5(31.3)	11(68.8)	
	Irregular cycles	14(8.2)	7(50)	7(50)	
	GIS symptoms	10(5.9)	6(60)	4(40)	
	Heavy menstrual bleeding	4(2.4)	2(50)	2(50)	

*Pearson Chi-Square Test, † The Pairwise Z-Tests, PCOS: Polycystic ovary syndrome , PID: Pelvic inflammatory disease , GIS: Gastrointestinal symptoms

Table 2 shows that the history of previous surgery was significantly higher in the case group($p<0.05$). There was no statistically significant association between infertility in women and symptoms ($p> 0.05$). There was no statistically significant association between women's infertility and smoking status ($p> 0.05$). **Table 3** shows the comparison of laparoscopy results case and control groups on the numeric study parameters.

Table 3. Comparison of laparoscopy results of the numeric study parameters

Study parameters	Case (n=83) M±SD	Control (n=87) M±SD	p
Age	32.35±3.37	32.57±3.5	0.833
BMI	24.64±2.03	24.66±2.14	0.906
The duration of pain	5.34±1.67	4.8±1.72	0.037
CA-125	28.77±13.41	27.09±13.98	0.523
Visual Analog Scale of pain	6.05±1.3	6.54±1.34	0.019

M, Mean; N, number of subjects; BMI, body mass index; All variables were tested by a Mann-Whitney U test.

As stated in **Table 3**, a Mann-Whitney test did not find a statistically significant association between case and control regarding age and BMI ($p>0.05$). There was a statistically significant difference between groups in terms of the duration of pain ($p<0.05$). The duration of pain in the case group 5.34±1.67 was higher than the duration of pain in controls 4.8±1.72.

There was a statistically significant difference between groups regarding the CA-125 ($p>0.05$). The mean CA-125 score in case group 28.77±13.41 was comparable to controls 27.09±13.98. There was a statistically significant difference between the case group and controls regarding the VAS ($p<0.05$). The VAS in the case group 6.05±1.3) was lower than controls 6.54±1.34.

DISCUSSION

The present study investigated the laparoscopy results of two fertile and infertile groups with CPPS. The results showed that the duration of pain in the infertile group was significantly higher than in the fertile group. The findings of this study are consistent with previous studies (7-9, 13-16). Sallis et al. (17), in a similar study, pointed out the positive relationship between infertility and CPPS. Also, the studies in this field generally prefer laparoscopy over the laparotomy method due to fewer complications and injuries (13-16).

Since endometriosis was a known pathology in more than 75% of the participants in the infertile group, endometriosis can be introduced as one of the leading causes of CPPS in infertile patients. Pain is a serious concern for women with endometriosis and may affect the quality of life in various ways. More than 50% of women with endometriosis suffer from pain during intercourse (dyspareunia) (10,18). In our study, 32.9% of the participants suffered from dyspareunia. Several studies show a correlation between dyspareunia and uterosacral or rectovaginal endometriosis (10,13-16,18-20).

According to studies, psychological factors, along with physical causes, which cause chronic pelvic pain, affect the differential diagnosis of this disease. The psychological factors, such as the quality of sleep, the existence of stressful factors, anxiety, and depression, and the physical factors, such as sexual abuse experience and sexual complications, such as decreased sexual desire, painful intercourse, and orgasm problems, are the mentioned causes of CPPS (19,20). According to the studies, psychological factors sometimes make a person prone to CPPS or are involved in accelerating the illness and pushing the illness towards its chronicity (21,22).

The present study showed a significant relationship between infertility, endometriosis, and dyspareunia. Painful intercourse can cause anxiety and fear of pain, aggravate spasms of pelvic floor muscles, and as a result, cause CPPS (22). Also, endometriosis, similar to pain, has an effect on people's mental states and personalities (21). Previous studies have shown that endometriosis negatively affects a person's self-image and causes loss of physical strength and fertility (17,22,23). Mothers who have daughters are concerned that their daughters may develop endometriosis in the future and suffer from pain and infertility (17). It should be noted that not only the pain caused by endometriosis but also the emotional problems associated with this disease, such as feelings of guilt and distress at work, are effective on the quality of life, and all these cases can be effective in aggravating CPPS (12,24).

Although, according to the general definition, CPPS is defined as pain with no structural cause (13), in some sources, endometriosis, adhesions, irritable bowel syndrome, and interstitial cysts have been proposed as four common causes of this complication (12). In the present study, 35.3% of the studied women suffered from dysmenorrhea, which was significantly higher in the infertile group. These findings were consistent with the findings of previous studies (8,12,16-18, 21). Also, there was a significant correlation between the history of surgery between the two groups with CPPS, which is consistent with previous studies (24,25).

Since all the people participating in this study were selected retrospective, the above findings can be limited to the study community's scope. Comparative and community-based studies with more samples are recommended for more accurate conclusions about the findings based on geographical differences.

CONCLUSION

The present study results showed that the duration of pain in the infertile group was significantly higher than in the fertile group, which could mainly be attributed to endometriosis. In order to reach a definitive diagnosis and plan the treatment, laparoscopy is necessary to investigate the etiology of CPPS in cases where no pathology is detected by pelvic examination and ultrasonography.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem Vakıf University Non-interventional Clinical Researches Ethics Committee (Date: 6/9/2022, Decision No: 2022/261).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Diyabetik maküla ödeminde arka vitreus dekolmanının rolü

The role of the posterior vitreous detachment in diabetic macular edema

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ÖZ

Giriş: Bu çalışmada diyabetik retinopatisi olan olgularda total arka vitreus dekolmanı (PVD) varlığının maküla ödemi oluşumu üzerine olan etkisini diğer risk faktörleriyle birlikte değerlendirmeyi amaçladık

Gereç ve Yöntem: Diyabetik retinopatili 103 hastanın 166 gözü prospektif olarak çalışma kapsamına alındı. Maküla ödemi olan 58 hastanın 96 gözü (grup 1) ve maküla ödemi olmayan 45 hastanın 70 gözü (grup2) PVD varlığı ve diğer risk faktörleri açısından karşılaştırıldı.

Bulgular: Yaş ortalamaları 1.grupta 61,8 ±5,5, 2.grupta 63,6±7,2 idi (p>0,05). İki grupta kadın/erkek oranı ve diyabet süreleri açısından anlamlı fark yoktu. Maküla ödemi olan 96 gözün 11'inde (%11,45), maküla ödemi olmayan 70 gözün 8'inde (%11,42) PVD bulundu. Her iki grupta PVD oranları açısından istatistiksel olarak anlamlı bir fark saptanmadı ($\chi2$=0,9953, p>0,05). İki grupta proliferatif diyabetik retinopati oranları, hipertansiyon ve proteinüri varlığı, açlık kan şekeri, üre, kreatinin ve HbA1c oranları karşılaştırıldı. İki grup arasında anlamlı fark saptanmadı (p>0,05). İnsülin kullanma oranı 2.grupta fazla bulundu (p<0,001).

Sonuç: Çalışmamızda, maküla ödemi olan ve maküla ödemi olmayan gruplarda PVD oranları arasında anlamlı fark saptanmadı. Bu nedenle PVD varlığının maküla ödemine karşı koruyucu bir faktör olmadığı kanısına vardık. Diyabetik maküla ödeminin patogenezi multifaktöriyeldir. Arka vitreus dekolmanının maküla ödemi üzerindeki rolünü anlamak için daha geniş çaplı ve maküla ödemini uzun süre takibe alan çalışmalar yapılmalıdır

Anahtar Kelimeler: Diyabetik retinopati, maküla ödemi, arka vitreus dekolmanı

Bu çalışmanın, tezden türetilen poster olarak TOD. XXXVI Ulusal Kongresi, 2002;S.179.' de kısa özeti sunulmuştur.

ABSTRACT

Introduction: In this study, we aimed to evaluate the effect of the presence of total posterior vitreous detachment (PVD) on the formation of macular edema in patients with diabetic retinopathy together with other risk factors.

Material and Method: 166 eyes of 103 patients with diabetic retinopathy were prospectively included in the study. 96 eyes of 58 patients with macular edema (group 1) and 70 eyes of 45 patients without macular edema (group 2) were compared in terms of the presence of PVD and other risk factors.

Results: The mean age was 61.8±5.5 in the first group and 63.6±7.2 in the second group (p> 0.05). There was no significant difference between the two groups in terms of female/male ratio and duration of diabetes. PVD was found in 11 (11.45%) of 96 eyes with macular edema and 8 (11.42%) of 70 eyes without macular edema. There was no statistically significant difference in terms of PVD rates in both groups ($\chi2$ = 0.9953, p> 0.05). Proliferative diabetic retinopathy rates, presence of hypertension and proteinuria, fasting blood glucose, urea, creatinine and HbA1c rates were compared in the two groups. Insulin use rate was higher in the second group (p <0.001).

Conclusion: In our study, there was no significant difference between PVD rates in the groups with and without macular edema. Therefore, we concluded that the presence of PVD is not a protective factor against macular edema. Pathogenesis of diabetic macular edema is multifactorial. In order to understand the role of posterior vitreous detachment on macular edema, larger-scale studies that follow macular edema for a long time should be done.

Keywords: Diabetic retinopathy, macular edema, posterior vitreous detachment

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GİRİŞ

Maküla ödemi, retina damarlarının permeabilite artışı sonucu primer olarak iç ve dış pleksiform tabakalarda olmak üzere intraretinal sıvı birikimi sonucu oluşan retinal kalınlaşmadır. Maküla ödemi, nonproliferatif diyabetik retinopatide (NPDR) en önemli görme kaybı nedeni iken, tüm diyabetik retinopatililerde (DR) vitreus homorajisi ile birlikte en sık görme kaybı nedenidir. Diyabetik maküla ödeminin patogenezi multifaktöriyel olabilir. Potansiyel faktörler arasında diyabetin süresi, yüksek kan basıncı, insülin kullanımı, yüksek glikolize hemoglobin (HbA1c), proteinüri ve panretinal fotokoagülasyon vardır (1,2). Kardiyak ve renal yetmezlik de maküla ödemi ile ilşkilidir. Tüm bu faktörler kan-retina bariyerinin bozulmasına sebep olabilir (3). Vitreusun diğer tip maküla ödemlerinin patogenezinde rolü olduğu bazı çalışmalarda gösterilmişti. Schepens ve ark. (4) periferal üveit, retinitis pigmentosa ve afakiye sekonder maküla ödemi olan hastaların makülası üzerinde vitreusun traksiyonunu göstermişlerdir. Bazı otörler vitreusun diyabetik maküla ödemi oluşumunda veya şiddetlenmesinde rolü olduğunu, kalınlaşmış, gergin ve yapışık premaküler arka hiyaloidin oluşturduğu tanjansiyel traksiyonun makülada fokal veya grid fotokoagülasyona cevap vermeyen diffüz vasküler sızıntı oluşturabildiğini iddia etmişlerdir (5,6,7). Arka hiyaloidin soyulması ile birlikte yapılan vitrektomi, retinovasküler sızıntıyı azaltmak ve vizyonu düzeltmek için bu hastalarda başarıyla kullanılmıştır (8,9).

Diyabetik hastalarda maküla ödemi oluşumuna ve şiddetlenmesine neden olan pekçok faktör vardır. Bu çalışmamızda maküla ödemi olan ve maküla ödemi olmayan diyabetik retinopatili olgularda total arka vitreus dekolmanı (PVD) varlığının maküla ödemi oluşumu üzerine olan etkisini diğer risk faktörleri ile birlikte değerlendirmeyi amaçladık.

GEREÇ VE YÖNTEM

Eylül 2001-Mayıs 2002 tarihlerinde Sağlık Bakanlığı Ankara Eğitim ve Araştırma Hastanesi Göz Kliniği'ne başvuran 55 yaşın üzerinde, diyabetik maküla ödemi olan ve maküla ödemi olmayan nonproliferatif ve proliferatif diyabetik retinopatili 103 hastanın 166 gözü prospektif olarak çalışma kapsamına alındı. Elli sekiz hastanın 96 gözünde maküla ödemi mevcuttu. Maküla ödemi olmayan 45 hastanın 70 gözü kontrol grubu olarak alındı. Hastalardan sözlü ve yazılı onam alındı. Bu çalışma, Ankara Eğitim ve Araştırma Hastanesi'nde 2001 yılında (2020 yılı öncesi) kurum onayı alınarak uzmanlık tezi çalışması olarak yapılmıştır. Tüm işlemler etik kurallara ve Helsinki Bildirgesi ilkelerine uygun olarak gerçekleştirildi.

Maküla merkezinden 500µ mesafeye kadar olan alanda retina kalınlaşması veya komşuluğunda retinal kalınlaşma olan sert eksuda varlığı ya da bir disk çapı alanda bir disk çapı veya daha fazla retinal kalınlaşma varlığı klinik önemli maküla ödemi olarak çalışmaya alındı. Hastalarda maküla ödeminin varlığı; 90 dioptri lens yardımı ile biyomikroskobik olarak binoküler muayene, renkli fundus fotoğrafı ve fundus floresein anjiografi (FFA) ile değerlendirildi. Arka vitreus dekolmanı varlığı 90 dioptri lens yardımı ile ve X10 büyütme yapılarak binoküler muayene ile değerlendirildi. Disk üzerinden belirgin olarak vitreusun ayrıldığı veya belirgin Weiss halkasının var olduğu gözler total PVD'si var olarak kabul edildi. Maküla ödemi olan ve olmayan gözlerdeki PVD oranları değerlendirildi.

Çalışmamızda dışlanma kriterleri şunlardı: vitreus bantları nedeniyle makülası değerlendirilemeyen ciddi proliferatif diyabetik retinopati (PDR), vitreus hemorajisi, maküler dejenerasyon, preretinal membranlar, santral retinal ven ve retinal ven dal tıkanıklığı, kistoid maküler ödem ve diğer maküler anormaliteler, yoğun katarakt, afaki.

Çalışmamızda hastaların şu kriterleri de değerlendirildi: yaş, cinsiyet, diyabet süresi, diyabetin ne ile regüle edildiği, sistemik hipertansiyon varlığı, en iyi düzeltilmiş görme keskinliği (EİDGK), diyabetik retinopatinin cinsi, katarakt varlığı, daha önceki lazer tedavileri, açlık kan şekeri, üre, kreatinin, HbA1c düzeyi, tam idrar analizi.

Çalışmamızda PVD varlığının iki gruptaki oranları ki-kare testi ile karşılaştırıldı. Ayrıca iki grubun diğer özellikleri karşılaştırılırken ki-kare ve student t testleri kullanıldı.

BULGULAR

Maküla ödemi olan hastaların (grup I) 38'inin her iki gözünde, 20'sinin tek gözünde ödem mevcuttu. Birinci grupta 38 gözde diffüz, 58 gözde fokal ödem tespit edildi. Maküla ödemi olmayan hastaların (grup II) 25'inin her iki gözü, 20'sinin tek gözü çalışmaya dahil edildi.

Hastaların demografik verileri **Tablo 1**'de gösterilmiştir. Buna göre gruplar arasında yaş ortalamaları, cinsiyetleri ve diyabet süreleri açısından anlamlı bir fark yoktu. En iyi düzeltilmiş görme keskinliği (EİDGK) açısından bakıldığında, kontrol grubunda EİDGK 0,5 ve üzerinde olan göz sayısı anlamlı olarak daha fazla idi.

Tablo1. Demografik veriler

	Grup I, n= 96	Grup II, n=70	P*
Yaş (ort±SD) (aralık)	61,89±5,54 (55-75)	63,60±7,21 (55-83)	>0,05[a]
Cins (%) (kadın/erkek)	36/22 (%62,1/ %37,9)	26/19 (%57,8/%42,2)	χ2=0,659 p>0,05[b]
Diyabet süresi (yıl) (ort±SD)	13,96±6,9	15,46±7,9	>0,05[a]
EİDGK (%)			χ2=0,0132 p<0,05[b]
<0,1	17 (%17,7)	6 (%8,6)	
0,1-0,4	48 (%50)	26 (%37,1)	
>0,5	31 (%32,3)	38 (%54,3)	

SD=standart deviasyon, EİDGK=en iyi düzeltilmiş görme keskinliği, astudent t testi, b Ki-kare testi, P* için <0,05 anlamlı kabul edildi

İki grup arasındaki PVD oranları açısından anlamlı bir fark yoktu. Diğer risk faktörlerinden PDR oranları, hipertansiyon ve proteinüri varlığı açısından da gruplar arasında anlamlı fark saptanmadı. Bu risk faktörlerinin karşılaştırılması **Tablo 2**'de detaylı gösterilmiştir.

Tablo 2. Hastaların PVD ve diğer risk faktörleri

	Grup I, n=96	Grup II, n=70	Toplam, n=166	χ^2	p*
PVD n (%)	11 (%11,45)	8 (%11,42)	19 (%11,44)	0, 9953	>0,05[a]
Diyabetik retinopati				0,363	>0,05[a]
PDR (%)	28 (%29,2)	16 (%22,9)	44 (%26,5)		
NPDR (%)	68 (%70,8)	54 (%77,1)	122 (%73,5)	0,363	>0,05[a]
Hipertansiyon var (%)	28 (%48,3)	24 (%53,3)	52 (% 50,5)	0,610	>0,05[a]
Proteinüri var (%)	26 (%44,8)	22 (%48,9)	48 (%46,6)	0,681	>0,05[a]

PVD: arka vitreus dekolmanı; PDR:proliferatif diyabetik retinopati; NPDR: nonproliferatif diyabetik retinopati; aKi-kare testi, P* için <0,05 anlamlı kabul edildi

Ki-kare testi ile karşılaştırıldığında II. grupta insülin kullanım oranı anlamlı olarak daha fazla bulundu (**Tablo 3**). Ayrıca hastaların açlık kan şekeri, üre, kreatinin ve HbA1c oranları da karşılaştırıldı ve her iki grupta anlamlı bir fark saptanmadı (p>0,05) (**Tablo 4**).

Tablo 3. İlaç kullanımı

	OAD	İnsülin	OAD+İNS	İlaçsız
Grup I	39 (%67,2)	16 (%27,6)		3 (%5,2)
Grup II	19 (%42,2)	15 (%33,3)	10 (%22,2)	1 (%2,2)

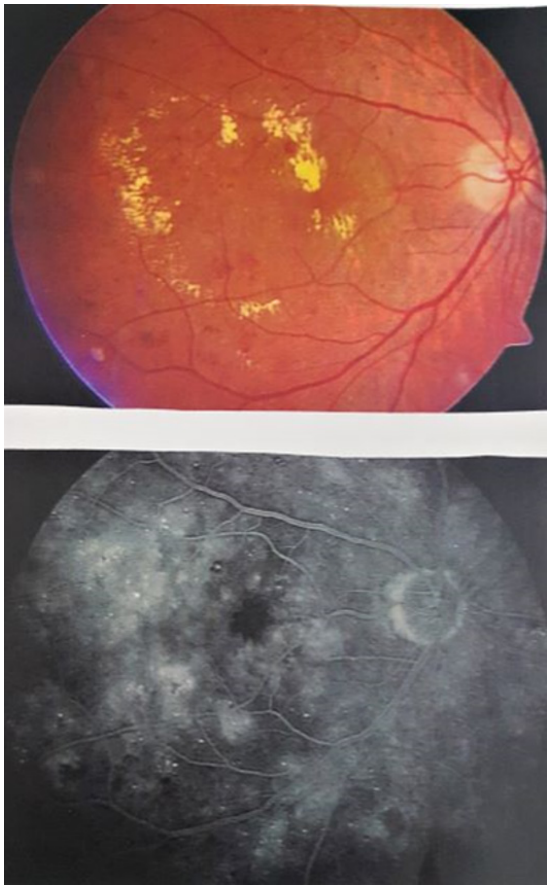
χ^2=0,00035,P<0,001

Tablo 4. Laboratuvar bulguları

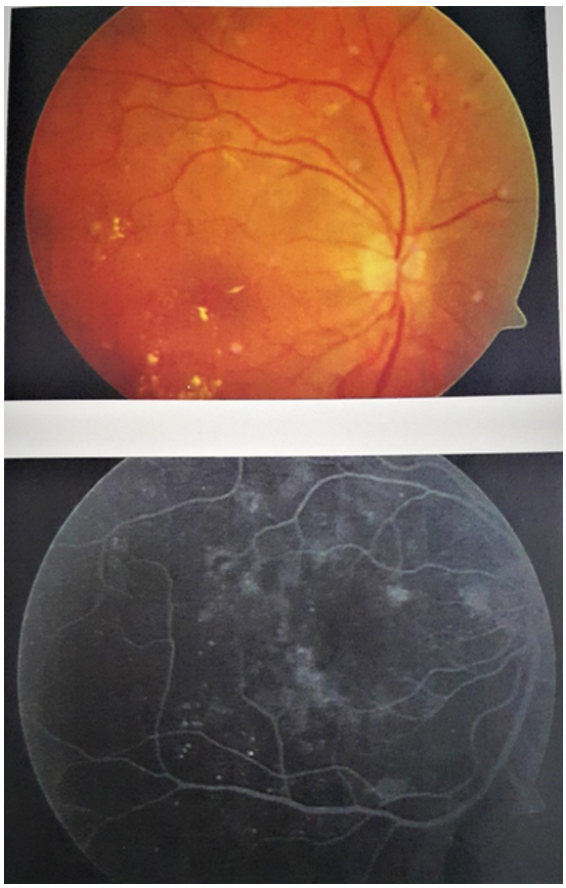
	Grup I, n =96	Grup II, n =70	P*
AKŞ (mg/dl)	210,15±69,37	195,48±62,14	>0,05
Üre (mg/dl)	41,06±15,10	39,44±16,79	>0,05
Kreatinin (mg/dl)	1,11±0,27	1,12±0,40	>0,05
HbA1c (%)	8,75±1,9	8,53±1,4	>0,05

AKŞ:Açlık kan şekeri; P* için <0,05 anlamlı kabul edildi

Birinci grupta 35 hastaya, II. grupta ise 25 hastaya FFA çekildi (**Resim 1**, **Resim 2**). Maküla ödemi olan 16 göze daha önceden fokal maküler lazer, 4 göze grid lazer, 9 göze panretinal fotokoagülasyon (PRP) yapılmıştı. İkinci grupta ise 8 göze fokal lazer, 9 göze PRP yapılmıştı. Birinci grupta 14 gözde, II. grupta 5 gözde başlangıç düzeyde veya orta düzeyde katarakt tespit edildi. Birinci grupta 4 göz, II. grupta 1 göz psödofak idi. Afak hastalar çalışma dışında tutuldu.



Resim 1. Diffüz maküla ödemli bir olgumuzun fundus fotoğrafı ve FFA'sı



Resim 2. Fokal maküla ödemli bir olgumuzun fundus fotoğrafı ve FFA'sı

SONUÇ

Diyabetik olgularda maküla ödemi, birçok nedene bağlı olarak oluşur. Son yıllarda bu faktörlerin yanında vitreusun da maküla ödemi oluşumunda önemli rolü olduğu gösterilmiştir. Yaşa bağlı spontan olarak oluşan PVD'nin maküla ödemi üzerindeki etkisi ve PVD'nin maküla ödemi için koruyucu bir faktör olup olmadığı araştırılmıştır (10). Daha sonraki çalışmalarda ise cerrahi yolla ve enzimatik vitreolizis yoluyla vitreusun maküladan ayrılmasının maküla ödeminin seyrine olan etkileri incelenmiştir (11). Vitreomaküler yapışıklığı olan, santral retinal ven tıkanıklığı gelişen gözlerde maküla ödeminin belirgin olarak kronisite gösterdiği saptanmıştır. Ven tıkanıklığı sonrası vitreus kontraksiyonu meydana geldiğinde sentripedal traksiyonun maküler bölgede yer alan vitreus lifleri yoluyla Müller hücrelerine iletildiği, traksiyonun Müller hücrelerinde şişmeye neden olduğu ve maküla ödemi geliştiği savunulmuştur (12).

Mevcut çalışmada vitreusun diyabetik maküla ödemindeki rolünü değerlendirmek için maküla ödemi olan ve olmayan gözlerdeki PVD oranlarını karşılaştıran prospektif bir çalışma yapıldı. Daha önce kliniğimizde yapılan bir çalışmada PVD'nin tanısında biyomikroskobik muayene ve ultrasonografi (USG) karşılaştırılmış, her iki muayene yöntemi ile PVD oranları aynı tespit edilmişti (13). Bu nedenle bu çalışmada, PVD varlığı 90 dioptri lens yardımıyla biyomikroskobik muayene ile saptandı. Oküler USG ile PVD varlığı tekrar değerlendirildi. Çalışmada 55 yaş ve üzerindeki hastalar seçildi. Çünkü yaşlanmaya bağlı PVD sıklığı bu yaş grubunda artmaktadır. Bu seçim normalde meydana gelen PVD'nin diyabetik maküla ödemi üzerindeki etkisinin incelenmesine imkan sağladı.

Prospektif olarak yapılan mevcut çalışmada, her iki grupta PVD oranları açısından istatistiksel olarak anlamlı fark saptanmadı. Nasrallah ve ark. (5) yaptıkları bir çalışmada retrospektif olarak 60 yaş ve üzerinde diyabetik retinopatisi olan 125 gözü incelemiş, maküla ödemi olan 105 gözün 21'inde (%20), maküla ödemi olmayan 20 gözün 11'inde (%55) PVD bulmuşlardır. Bunun sonucunda jel vitreusdaki dejeneratif değişiklikler sonucu yapışık arka hiyaloidin makülada yarattığı tanjansiyel traksiyona bağlı olarak diffüz karakterde maküla ödemi oluşturabileceğini ileri sürmüşlerdir. Yine başka bir çalışmalarında 50 yaşın altında diyabetik retinopatisi olan gözlerde PVD oranı değerlendirilmiş, maküla ödemi olanlarda PVD oranının daha yüksek olduğu gösterilmiştir (6). Bu iki çalışmanın sonucunda genç diyabetiklerde PVD'nin diyabete bağlı vitreus kontraksiyonundan kaynaklandığı ve makülada traksiyon oluşturarak maküla ödemine yol açtığı, yaşlı hastalarda ise PVD'nin syneresisden kaynaklandığı ve makülada hiç traksiyon oluşturmadığı, tersine bu tip PVD'nin makülayı diyabete bağlı vitreus kontraksiyonuna sekonder oluşabilecek her tür reaksiyona karşı koruduğu iddia edilmiştir. İlk çalışma mevcut çalışmamıza yaş grubu olarak benzemekle beraber farklı olarak bu çalışma, retrospektif olarak yapılmış, hastaların renal ve kardiyak durumu, daha önce yapılan PRP, hastaların açlık kan şekeri ve HbA1c düzeyleri çalışmada ele alınmamıştır. Maküla ödemi değerlendirilirken hastaların eski FFA ve fundus fotoğrafları kullanılmıştır. Ayrıca çalışmada maküla ödemi olmayan sadece 20 göz değerlendirilmiştir. Mevcut çalışmada ise maküla ödemi olmayan 70 göz değerlendirildi. Ek olarak bu çalışmanın prospektif olması ve tanıda klinik muayenenin ön planda tutulması önemli bir özellik idi. Çalışmada hastaların yaş ortalamaları, kadın ve erkek oranları, diyabet süreleri, hipertansiyon varlığı, açlık kan şekeri, üre, kreatinin, proteinüri ve HbA1c düzeyleri açısından iki grup arasında istatistiksel olarak anlamlı fark olmaması maküla ödemi oluşumunda vitreusun rolünü değerlendirmede daha objektif bir çalışma yapılmasını sağladı.

Günümüzde yapılan çalışmalar vitreusun çeşitli mekanik ve fizyolojik mekanizmalar yoluyla diyabetik maküla ödemi oluşumunda ve şiddetlenmesinde rol oynadığını, tüm bu mekanizmaların temelinde VEGF tarafından retinal vasküler permeabilite artışının rol oynadığını göstermiştir. Birinci muhtemel mekanizma; kan-retina bariyerinin bozulması ile serum kaynaklı kemoatraktanların vitreusdaki konsantrasyonunun artmasıdır. Bu, yapışık premaküler arka hiyaloide hücre göçü için bir uyarı oluşturur. Hücresel kontraksiyon, tanjansiyel traksiyona neden olabilir. Bu da maküla ödemi oluşumuna veya şiddetlenmesine ve/veya sığ maküla dekolmanı oluşumuna yol açar. Bu teoriyi destekler şekilde Sebag ve ark., diyabetik vitreusda enzimatik olmayan glikasyon ve enzim kaynaklı vitreus çapraz bağları bulmuşlardır. Anormal çapraz bağların kollajen yapısını etkilediğini, yapışık vitreus jelinin stabilitesini bozarak maküler traksiyon oluşturduğunu ifade etmişlerdir (14-16). Diğer muhtemel mekanizma; kan-retina bariyerinin bozulmasının vitreus boşluğunda büyüme faktörlerinin varlığı ile sonuçlanmasıdır. Anormal yapışık premaküler arka hiyaloidin varlığında, büyüme faktörleri maküler bölgede birikerek maküla ödemi oluşturur veya ödemi şiddetlendirir (17).

Diyabetik maküla ödemli gözlerde biyomikroskobik muayene ile, OCT ile, elektron mikroskobu ve elektron immunositokimya analizi ile yapılan çalışmalarda kalınlaşmış, gergin arka hiyaloid gözlenmiştir (7,18,19). Diyabetik maküla ödemli hastalarda perifoveolar PVD prevalansının yüksek olduğu gösterilmiştir (20). Diyabetik maküla ödemi olan ve PVD'si olmayan gözlerde vitrektomi sonrası maküla ödeminde azalma ve vizyon artışı tesbit edilmiştir (7-9,21-26). Vitrektomi yapılan maküla ödemli bazı olgularda ödemin absorbsiyonu sırasında intraretinal sıvının subretinal alana hareket ettiği OCT

ile gözlenmiş (27). Başka bir çalışmada ise vitrektomi sonrası maküla ödemli gözlerde perifoveal mikrosirkülasyonun arttığı gözlenmiş (28).

Yamamato ve ark. (29) yaptıkları bir çalışmada farklı olarak vitrektominin diyabetik maküla ödeminin azaltılmasında etkili olduğu ancak sonuçların PVD veya epimaküler mambranın varlığı veya yokluğu ile ilişkili olmadığı savunulmuştur. Buna göre maküla ödemi oluşumunun komplike bir olay olduğu ve diyabetik maküla ödemi patogenezinin vitroretinal yüzeyin durumuna bağlı olarak farklı olabileceği savunulmuştur. Vitreus traksiyonu, vitreusdaki sitokinler, epimaküler membran ve muhtemelen diğer bilinmeyen faktörler diyabetik maküla ödemi oluşturuyor olabilir. Vitrektomize gözlerde vitrektomize olmayan gözlere göre oksijen basıncının daha yüksek olduğu ve bunun retinal vazokonstriksiyon yaparak vasküler sızıntıyı ve böylece maküla ödemini azaltabileceği savunulmuştur. Başka bir hipoteze göre de vitrektomi ile VEGF ve İL-6 gibi permeabiliteyi arttırıcı sitokinlerin uzaklaştırılması maküla ödemini azaltabilir. Bazı çalışmalarda vitreusun rolünü değerlendirmek için vitreus enzimatik yolla maküladan uzaklaştırılarak maküla ödeminin seyri değerlendirilmiştir (30-32). Enzimatik yolla vitreolizis standart mekanik vitrektomiye yardımcı, hatta onun yerini almak için planlanmıştır (33). Yeni yapılan bazı çalışmalarda, diyabetik maküla ödemli hastalarda intravitreal anti-VEGF tedavisinin etkinliğinin, başlangıç PVD durumuna bağlı olmadığı gözlendi (34-35).

Daha önceki çalışmalarda vitreusun maküla ödemi oluşumunda ve şiddetlenmesinde önemli rolü olduğu ve vitreusun maküler yüzeyden uzaklaşması ile maküla ödeminin azaldığı, spontan PVD'si olan gözlerin de maküla ödemine karşı önemli ölçüde korunduğu savunulmasına rağmen mevcut çalışmada PVD varlığının, diyabetik retinopatili gözlerde, maküla ödemine karşı koruyucu rolü olmadığı görüldü. Bu, son dönemlerde belirtildiği gibi, diyabetik maküla ödeminin komplike bir olay olduğu ve vitreoretinal yüzeyin durumuna göre diyabetik maküla ödemi patogenezinin farklı olabileceği görüşünü destekler.

Bu çalışmada I. gruptaki hastaların %27,6'sı insülin kullanırken, II. grupta %33,3'ü insülin kullanmaktaydı ve fark istatistiksel olarak anlamlı bulundu. Ancak hastaların bir kısmı insülin kullanmaya yeni başladığı için insülin kullanımının maküla ödemi üzerindeki etkisini net olarak belirlemek güçtür.

Görme keskinliği karşılaştırıldığında II. grupta vizyonu 0.5 ve üzerinde olan göz sayısı anlamlı oranda fazla bulundu. Maküla ödemi olan grupta beklendiği gibi görme düşüktü. Ayrıca I. grupta 14 gözde (%14,58), II. grupta ise 5 gözde (%7,14) katarakt başlangıcı olması görme keskinlikleri arasındaki bu farkı bir ölçüde açıklayabilir.

Hihichi ve ark. (36) yaptıkları bir çalışmada PVD'si olan ve PVD'si olmayan diyabetik maküla ödemli 82 gözde, 6 aylık takip sonunda maküla ödeminin spontan çekilme oranlarını karşılaştırdılar. Çalışma sonunda PVD'si olan gözlerin %55'inde, PVD'si olmayan gözlerin ise sadece %25'inde 6 ay sonunda maküla ödeminin çekildiğini bildirmişlerdir. Mevcut çalışmamızda sadece tanı anında PVD oranları karşılaştırılmış, maküla ödeminin seyri üzerine PVD'nin etkisi değerlendirilmemiştir. Çalışmada hastalarımızı uzun dönem takip etseydik veya vitrektomi sonrası maküla ödeminin seyrini değerlendirseydik belki de daha önceki çalışmalara benzer sonuçlar alabilirdik. Daha geniş çaplı ve maküla ödemini uzun süre takibe alan çalışmalarla vitreusun maküla ödemindeki rolü kesin olarak açıklığa kavuşturulabilir.

SONUÇ

Diyabetik maküla ödeminin patogenezi multifaktöriyeldir. Vitreusun maküla ödeminin patogenezindeki rolünü değerlendirebilmek için patogenezde rol oynayan diğer faktörlerin ödem üzerindeki etkileri göz önüne alınmalıdır. Ancak bu faktörler açısından homojen olan gruplarda vitreusun rolü objektif olarak değerlendirilebilir. Biz çalışmamızda, diyabetik hastalarda PVD'nin maküla ödemine karşı koruyucu bir faktör olmadığı kanısına vardık. PVD'si olan olgularda da PVD'si olmayanlara benzer oranlarda maküla ödemi oluştu. PVD'si olmayan gözlerde yapışık arka hiyaloidin oluşturduğu traksiyon, maküla ödemi patogenezinde rol oynayabilir. PVD'si olan gözlerde ise maküla ödemi oluşumunda muhtemelen başka faktörler ön plandadır (sitokinler, epimaküler membran, PVD sonrası arka korteks kalıntıları vs).

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An investigation of cardiac effects in patients presenting to the pandemic clinic with suspected COVID-19

COVID-19 şüphesi nedeniyle pandemi polikliniğine başvuran hastalarda kardiyak etkilenmenin araştırılması

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ABSTRACT

Aim: COVID-19 is a virus capable of causing cardiovascular complications. This study investigates whether any cardiac effect is present in patients presenting with suspected COVID-19 in the light of Electrocardiography (ECG) findings.

Material and Method: This prospective study involved patients with chest pain presenting to the pandemic clinic with suspected COVID-19. Patients were divided into two groups based on their PCR results, PCR-positive and -negative. All participants' demographic characteristics, presentation symptoms and the duration thereof, physical examination findings, laboratory results, and ECG findings were recorded. Patients with positive PCR results were invited for checks on the 15th day, when repeat ECG was performed.

Results: A-50 patients with positive PCR results and 50 with negative PCR results were included in the study. The mean age of the entire patient group was 52.30±16.02 years, and 56% were women. No difference was determined between the positive and negative PCR result patients in terms of age or sex (p=0.116; 0.687, respectively). Presentation high sensitive cardiac Troponin (hs-cTn) levels were significantly higher in the patients with positive PCR results than in the PCR-negative patients (p<0.001). Rates of detection of ST-T change at presentation ECG were 38% in the patients with positive PCR results and 16% in those with negative PCR results (p=0.023). ST-T alteration persisted at 15th day ECG in 36% of the patients with positive PCR results. P-wave amplitude and mean heart rate were significantly higher at presentation ECG in the patients with positive PCR results than at ECG on day fifteen (p=0.038; <0.001 respectively).

Conclusion: A cardiac effect does occur in patients with COVID-19, and this can be shown by means of ECG findings. The increase in P-wave amplitude at presentation ECG in patients with positive PCR results may represent a marker of COVID-19-related cardiac overload. ECG should be performed both at presentation and in the following days on COVID-19 patients presenting with chest pain, and care should be taken against potential ischemic ST-T alterations.

Keywords: COVID-19, electrocardiography, emergency department, troponin

ÖZ

Amaç: COVID-19 kardiyovasküler komplikasyonlara neden olabilen bir virüstür. Bu çalışmada, COVID-19 şüphesi ile başvuran göğüs ağrılı hastalarda kardiyak etkilenme olup olmadığı Elektrokardiyografi (EKG) bulguları eşliğinde araştırılmıştır.

Gereç ve Yöntem: Bu çalışma, Pandemi polikliniğine COVID-19 şüphesi ile başvuran göğüs ağrılı hastalar üzerinde prospektif olarak yapıldı. Hastalar PCR sonucuna göre: PCR sonucu pozitif ve negatif olmak üzere iki gruba ayrıldı. Tüm katılımcıların demografik özellikleri, başvuru şikayetleri ve şikayetlerinin mevcudiyet süresi, fizik muayene bulguları, laboratuvar sonuçları ve EKG bulguları kaydedildi. PCR sonucu pozitif olan hastalar, 15. günde kontrole çağırılarak yeniden EKG çekildi.

Bulgular: Çalışmaya 50 PCR sonucu pozitif ve 50 PCR sonucu negatif hasta dahil edildi. Tüm hastaların yaş ortalaması 52.30±16.02/yıl ve %56'sı kadındı. PCR sonucu pozitif olanlarla PCR sonucu negatif olanlar arasında yaş ve cinsiyet bakımından farklılık saptanmadı (Sırasıyla p=0.116; 0.687). Başvuru yüksek duyarlıklı kardiyak Troponin (hs-cTn) düzeyi, PCR sonucu pozitif olanlarda PCR sonucu negatif olanlara göre anlamlı olarak daha yüksekti (p<0.001). Başvuru EKG'sinde ST-T değişikliği saptanma oranı PCR sonucu pozitif olanlarda %38 iken, PCR sonucu negatif olanlarda ise %16 idi (p=0.023). PCR sonucu pozitif olan hastaların %36'sının 15. gün EKG'sinde ST-T değişikliği izlenmeye devam ediyordu. PCR sonucu pozitif olan hastaların başvuru EKG'sinde P-dalga amplitüdü ve ortalama kalp hızı değeri 15. gün EKG'sine göre anlamlı olarak daha yüksekti (Sırasıyla p=0.038; <0.001).

Sonuç: COVID-19 hastalarında kardiyak bir etkilenme olmakta ve bu durum EKG bulguları vasıtasıyla gösterilebilmektedir. PCR sonucu pozitif hastaların başvuru EKG'sinde saptanan P-dalga amplitüdündeki artış, COVID-19'a bağlı kardiyak yüklenmenin göstergesi olabilir. Göğüs ağrısı ile başvuran COVID-19 hastalarına hem başvuru anında hem de ilerleyen günlerde EKG çekimi yapılmalı ve oluşabilecek iskemik ST-T değişikliklerine karşı dikkatli olunmalıdır.

Anahtar Kelimeler: COVID-19, elektrokardiyografi, acil servis, troponin

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INTRODUCTION

Following its emergence in the Chinese city of Wuhan in 2019, COVID-19 spread rapidly across the world (1). Although the virus essentially causes dry cough, sore throat, fever, lethargy, malaise, muscle and joint pain, or gastrointestinal tract symptoms, it may also worsen to give rise to pneumonia and respiratory failure (1). In addition, due to the direct and indirect effects of the virus, several fatal complications associated with the cardiovascular system may also be observed. These complications include acute coronary syndrome, myocarditis, heart failure, cerebrovascular stroke, pulmonary embolism, and disseminated intravascular coagulopathy (2,3). Cardiac damage responsible for these complications can be shown both by Electrocardiography (ECG) findings and by measuring such biomarkers as cTn, creatine kinase (CK), brain natriuretic peptide (BNP), and D-dimer (4).

The aim of this study was to investigate the presence or absence of a cardiac effect in patients with chest pains presenting to the pandemic clinic on suspicion of COVID-19 in the light of ECG findings.

MATERIAL AND METHOD

The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 10.12.2020, Decision No: 20/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This prospective study was performed with patients with suspected COVID-19 presenting with chest pains to the Kırıkkale University Medical Faculty pandemic clinic. Written voluntary consent was obtained from all participants.

Establishment of the Study Groups

Patients with suspected COVID-19 presenting to the pandemic clinic were divided into two groups based on PCR results from nasopharyngeal swabs, PCR result-negative and PCR result-positive. All patients' presentation symptoms, the duration thereof, demographic characteristics (age, sex, chronic disease, and medication use status), and laboratory and PCR results were recorded. Additionally, patients with positive PCR results were invited to control visits on the 15th day, at which time repeat ECG was performed and the results were again recorded.

Patients with previously diagnosed cardiovascular system diseases (coronary artery disease, hypertension, heart failure, dysrhythmia, cor pulmonale, valve diseases, etc.), using any medications capable of affecting the cardiovascular system, with no chest pains at time of presentation, aged under 18, with missing data, or refusing to consent to participate were excluded from the study.

ECG Performance and Interpretation

ECG was performed using a 12-lead, six-trace Nihon Kohden-1350K device. The procedure was carried out by a specialist ECG technician at a room temperature of 25o C. The ECG results were evaluated by an emergency medicine specialist using an ECG goniometer. P-wave amplitude, width, and morphology, PR interval, QRS complex, QT interval (calculated using Bazett's formula), T-wave amplitude, width, and morphology, ST-T alteration, heart rate, rhythm, and flow axis were evaluated and recorded for all patients.

Statistical Analysis

Data analysis was performed on Statistical Package for Social Sciences) for Windows version 21.0 software (IBM Corporation, Armonk, New York, USA). Variables were expressed as number (n), percentage (%), mean, and standard deviation (±SD). Normality of distribution was assessed using the Kolmogorov-Smirnov test. The independent sample t-test was used for intergroup comparisons in case of normal distribution, and the Mann-Whitney U-test in case of non-normal distribution. Qualitative data were compared using the chi-square test. The presentation and day 15 ECG results of PCR-positive patients were compared using the paired sample t-test. The results were evaluated at a 95% confidence interval, and p values <0.05 were regarded as statistically significant.

RESULTS

The study was completed with 50 PCR-positive and 50 PCR-negative patients, after 4723 of the 4823 patients presenting to the pandemic clinic had been excluded for meeting the exclusion criteria (**Figure 1**).

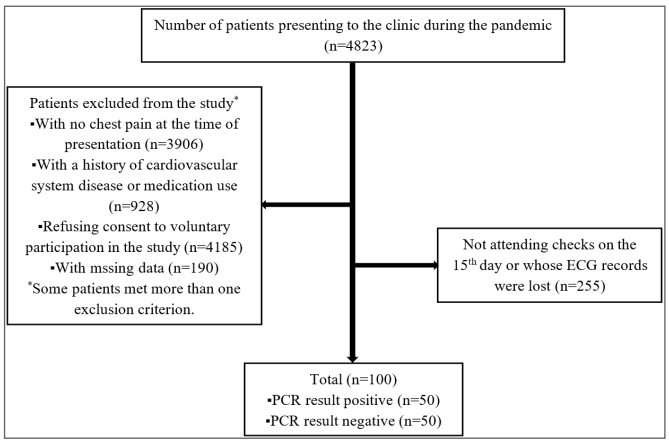

Figure 1. Patient selection and the constitution of the study groups

The mean age of the entire patient group was 52.30±16.02 years (range 21-94), and 56% were women. No difference was determined between the groups in terms of age or sex (p=0.116 and 0.687, respectively). Eighty-nine percent of the patients had no chronic disease and were not on medication. Disregarding chest pain, the most common presentations

symptoms were lethargy/malaise (50%), followed by myalgia/arthralgia (39%) and dyspnea (23%) (**Table 1**).

Table 1. A comparison of the study groups' demographic characteristics

	PCR (+) (n=50)	PCR (-) (n=50)	Total (n=100)
Age (years), (mean±SD)	54.98±17.02	57.66±17.72	52.30±16.02
Gender			
Male, n (%)	21 (42.0)	23 (46.0)	44 (44.0)
Female, n (%)	29 (58.0)	27 (54.0)	56 (56.0)
History of medication use			
Yes, n (%)	5 (10.0)	6 (12.0)	11 (11.0)
No, n (%)	45 (90.0)	44 (88.0)	89 (89.0)
Additional disease			
Diabetes mellitus, n (%)	2 (4.0)	1 (2.0)	3 (6.0)
COPD, n (%)	2 (4.0)	--	2 (2.0)
Psychiatric disease, n (%)	1 (2.0)	4 (8.0)	5 (5.0)
Thyroid disease, n (%)	--	1 (2.0)	1 (1.0)
More than one disease, n (%)	3 (6.0)	4 (12.0)	7 (14.0)
Unremarkable, n (%)	45 (90.0)	44 (88.0)	89 (89.0)
Presentation symptom (except for chest pain)			
Headache, n (%)	7 (14.0)	2 (4.0)	9 (9.0)
Sore throat, n (%)	6 (12.0)	3 (6.0)	9 (9.0)
Cough, n (%)	7 (14.0)	4 (8.0)	11 (10.0)
Myalgia/Arthralgia, n (%)	20 (40.0)	19 (38.0)	39 (39.0)
Lethargy/fatique, n (%)	25 (50.0)	25 (50.0)	50 (50.0)
Fever, n (%)	4 (8.0)	--	4 (4.0)
Dyspnea, n (%)	9 (18.0)	14 (28.0)	23 (23.0)
Anosmia, n (%)	4 (8.0)	2 (4.0)	6 (6.0)
Number of symptom days			
≤1 day	10 (20.0)	13 (26.0)	23 (23.0)
2-3 days	34 (68.0)	27 (54.0)	61 (61.0)
≥3 days	6 (12.0)	10 (20.0)	16 (16.0)

COPD, Chronic obstructive pulmonary disease

No difference was observed between the two groups in terms of physical examination findings (**Table 2**). However, hs-cTn levels were significantly higher in the PCR-positive group than in the PCR-negative group (p <0.001) (**Table 3**).

Table 2. A comparison of the study groups' physical examination findings

	PCR (+) (n=50)	PCR (-) (n=50)	p*
	mean±SD	mean±SD	
Body temperature (oC)	36.63±0.53	36.63±0.57	0.986
Heart rate (beats/min)	91.66±14.02	90.26±14.18	0.621
Respiration rate (/min)	22.30±10.04	21.10±2.15	0.410
Systolic blood pressure (mmHg)	138.18±21.76	132.44±17.55	0.150
Diastolic blood pressure (mmHg)	83.96±11.26	82.42±11.24	0.495
Oxygen saturation (%)	95.84±2.10	96.28±2.26	0.316

*Independent sample t-test

The incidence of ST-T alteration at presentation ECG was significantly higher in the PCR-positive group (38.0%) than in the group with negative PCR results (16.0%) (p=0.023) (**Table 4**). Comparison of ECG at time of presentation and after 15 days in the PCR-positive group revealed that P-wave amplitude and heart rate were significantly higher at presentation than on the 15th day (p=0.038; <0.001, respectively) (**Table 5**).

DISCUSSION

This study investigated, in the light of ECG findings, the cardiac effect in patients with chest pain presenting to the pandemic clinic with suspected COVID-19. The results show that COVID-19 leads to ischemic cardiac alterations at ECG and temporary cardiac overload.

Table 3. A comparison of the study groups' laboratory findings

Reference interval		PCR (+) (n=50)	PCR (-) (n=50)	p*
		mean±SD	mean±SD	
CK (u/L)	0-145	126.10±285.50	100.28±52.20	0.531
CK-MB (u/L)	0-24	30.1±25.25	38.52±25.77	0.105
Creatinine (mg/dL)	0.6-1.1	0.86±0.18	0.82±0.17	0.297
WBC (103uL)	4-10	6500.0±1976.53	8914.02±334.24	<0.001
Neutrophil (103uL)	2-7	4053.86±1407.10	6384.74±2710.23	0.546
Monocyte (103uL)	0.12-1.2	519.21±209.90	524.80±217.02	0.896
Lymphocyte (103uL)	0.8-4	1700.0±668.32	2082.14±803.92	0.011
CRP (mg/L)	0-5	18.30±21.44	20.95±36.75	0.662
Sodium (mmol/L)	136-145	139.26±3.52	139.64±2.70	0546
Potassium (mmol/L)	3.5-5.1	4.44±0.42	4.44±0.41	0.935
Calcium (g/dL)	8.8-10.6	9.53±0.68	9.80±0.52	0.030
D-dimer (ug/L)	0-500	352.91±408.62	333.10±324.08	0.630
		median (min-max)	median (min-max)	p†
Presentation hs-cTn (ng/ml)	0-14	75 (2-1680)	4.70 (2-11)	<0.001†
Day 15 hs-cTn (ng/ml)	0-14	7.6 (2-21)	--	

CK, Creatine kinase; WBC, White blood cell; CRP, C-reactive protein; hs-cTn, High sensitive cTn, Cardiac troponin, *Independent sample t-test, †Mann-Whitney U-test

Table 4. A comparison of the study groups' demographic characteristics

	PCR (+) (n=50)	PCR (-) (n=50)	p*
	mean±SD	mean±SD	
P-wave amplitude (mV)	1.69±0.44	1.63±0.45	0.501
P-wave width (msn)	85.20±17.52	88.0±19.38	0.450
PR interval (msn)	191.6±190.40	190.40±24.32	0.824
QRS interval (msn)	78.80±10.99	80.80±13.97	0.521
QT interval (msn)	412.22±36.05	412.28±25.62	0.992
Heart rate (beats/min)	89.36±14.39	86.18±16.84	0.313
	n (%)	n (%)	p†
ST-T alteration present	19 (38.0)	8 (16.0)	0.023
T-wave morphology			
Normal	32 (64.0)	42 (84.0)	
Negative	13 (26.0)	6 (12.0)	
Biphasic	4 (8.0)	2 (4.0)	
More than one morphology	2 (2.0)	--	
Rhythm			
Normal sinus rhythm	40 (80.0)	44 (88.0)	
Sinus arrhythmia	4 (8.0)	2 (4.0)	
Sinus tachycardia	6 (12.0)	4 (8.0)	
Axis			
Normal axis	45 (90.0)	46 (92.0)	
Sol axis	5 (10.0)	3 (6.0)	
Right axis	--	1 (2.0)	
Other findings			
Unremarkable	45 (90.0)	45 (90.0)	
Pathological Q-wave	2 (4.0)	2 (4.0)	
LAFB	2 (4.0)	2 (4.0)	
VES	1 (2.0)	1 (2.0)	

LAFB, left anterior fascicular block; VES, ventricular extrasystole, *Independent sample t-test, †Chi-square test

Table 5. A comparison of the PCR-positive patients' presentation and 15th day ECG findings

	Presentation ECG (n=50)	15th day ECG (n=50)	p*
	mean±SD	mean±SD	
P-wave amplitude (mV)	1.69±0.44	1.55±0.38	0.038
P-wave width (msn)	85.20±17.52	85.20±13.88	0.761
PR interval (msn)	191.6±190.40	184.40±21.10	0.124
QRS interval (msn)	78.80±10.99	82.40±7.70	0.322
QT interval (msn)	412.22±36.05	414.04±24.26	0.765
Heart rate (beats/min)	89.36±14.39	78.28±11.70	<0.001
	n (%)	n (%)	p†
ST-T alteration present	19 (38.0)	18 (36.0)	0.799
T-wave morphology			
Normal	32 (64.0)	32 (64.0)	
Negative	13 (26.0)	13 (26.0)	
Biphasic	4 (8.0)	4 (8.0)	
More than one morphology	2 (2.0)	1 (2.0)	
Rhythm			
Normal sinus rhythm	40 (80.0)	47 (94.0)	
Sinus arrhythmia	4 (8.0)	3 (6.0)	
Sinus tachycardia	6 (12.0)	2 (4.0)	
Axis			
Normal axis	45 (90.0)	45 (90.0)	
Sol left axis	5 (10.0)	5 (10.0)	
Right axis	--	--	
Other findings			
Unremarkable	45 (90.0)	42 (84.0)	
Pathological Q-eave	2 (4.0)	5 (10.0)	
LAFB	2 (4.0)	2 (4.0)	
VES	1 (2.0)	--	

LAFB, left anterior fascicular block; VES, ventricular extrasystole, *Paired sample t test, †Chi-square test

Cardiac ischemic damage in patients with COVID-19 may occur due to direct damage to myocardial tissue or increased adrenergic stimulation, systemic inflammatory response, cytokine storm, hypoxia, hypotension or microthrombus, caused by the disease process (5-8). The cardiac damage that develops causes ST-T alterations at ECG. These changes may persist for one year on the ECGs of some patients, and are a marker of increased mortality, particularly in patients with severe COVID-19 (9-11). In one of two previous studies examining the prognostic value of presentation ECG in COVID-19 patients, McCullough et al. (11) reported an ST elevation incidence of 0.7% and a T-wave innervation incidence of 10.5%; in the other study Chorin et al. (12) reported an incidence of ST-T alteration of 17.6%. Li et al. (13) reported that the incidence of ST-T alteration increased still further among patients hospitalized in the intensive care unit (65.2%). Another study examining presentation ECGs of patients with COVID-19 pneumonia reported an incidence of ST-T alteration of 30%, and that these alterations were observed on ECGs a mean 30 (12-51) days after the first onset of symptoms (14). Bergamaschi et al. (15) reported an incidence of ST-T alteration of 5.6% among COVID-19 patients at the time of presentation, rising to 8.2% on the seventh day. The authors therefore emphasized that ischemic ST-T alterations can be detected, and a decrease in major cardiac event and mortality achieved, through serial ECG monitoring. In the present study, the incidence of ST-T alteration was significantly higher in the PCR-positive group. This is consistent with previous studies showing that the direct or indirect effect of COVID-19 causes ischemic damage to myocardial tissue. ST-T alteration at ECG was also observed in the PCR-negative patients in our study. We attributed this either to the patients having COVID-19 even if their test results were negative, or to cardiac involvement due to the effect of infection by another virus (such as influenza or RSV). In addition, the ST-T alteration in the PCR result-positive group persisted on both presentation and 15-day ECGs, suggesting that cardiac ischemic alterations also persisted in these patients after 15 days. Therefore, in exact agreement with Bergamaschi et al. (15) , we also think that regular ECG will be useful for the purpose of monitoring cardiac effects in such patients infected with COVID-19.

In addition to the diagnosis of arrhythmias, alterations in the P-wave morphology and PR interval are also useful in detecting the presence of cardiac pathologies (16). An extended PR interval is associated with conduction disorders such as AV blocks, while an increased P-wave amplitude (>2.5 mm) is a messenger of right atrial dilatation, while an extended duration (>120 msn) indicates left atrial dilatation (17). Studies have shown that prolongation of the P-wave duration is associated with an increased risk of cardiovascular disease and mortality (18). Atrial tachyarrhythmias, particularly atrial fibrillation (AF), are frequently seen in COVID-19, and diagnosis of AF is linked to the presence (or absence) of the P-wave (19). Interatrial block is a form of rhythm disorder in which conduction is delayed in the Bachman region between the right and left atria. This lays the foundation for P-wave dispersion, and thus to the development of AF (20). Yenerçağ et al. (21) reported a greater likelihood of AF development in COVID-19 patients with P-wave dispersion at ECG (>36 msn) compared to healthy. In that study, P-wave amplitude was 0.12±0.009 mV at V1 and 0.141±0.016 mV at DII, values significantly higher than in the healthy controls. No difference was determined in the present study in terms of P-wave amplitude, P-wave width, or PR interval between the PCR result-positive and –negative patients. No AF, AV block, or other dysrhythmia were observed in any patient. This may be due, in contrast to other studies in the literature, to our study involving clinically milder cases (patients with a history of cardiovascular disease and drug use were excluded from the study). To put it another way, the ECGs of less and/or non-problematic patients in cardiovascular terms were examined in the present study. On the other hand, the P-wave amplitude on admission ECG among patients with positive PCR results was significantly higher than that on the 15th day. We thought that this might be related to right atrial tension caused by the increased disease burden resulting from COVID-19. In subsequent days, as the patients responded positively to COVID-19 treatment, the disease burden may have decrease and the previously elevated right atrial tension and associated P-wave amplitude may have recovered on the 15th day and returned to normal.

Acute phase reactant levels, liver and kidney function tests, complete blood count, coagulation tests, and cardiac biomarkers are frequently used in COVID-19 for diagnosis, follow-up, and predicting prognosis (22-24). One study reported that increasing leukocytosis and cTnI levels significantly raised ICU admission rates among COVID-19 patients (1.5- and 2.2-fold, respectively) (22). Another study emphasized changes in leukocytosis and albumin levels as important markers in the evaluation of admission to the ICU (a 2-fold increase and 0.8-fold decrease, respectively) (24). A study comparing PCR (+) and (-) patients reported significantly lower serum CRP, WBC, and neutrophil, lymphocyte, monocyte, and eosinophil counts and significantly higher ALT, AST, and LDH values in the patients with PCR (+) results (25). Chinese researchers reported significantly lower WBC and platelet values in PCR (+) patients compared to PCR (-) patients, while no difference was observed in terms of CRP, sedimentation, or lymphocyte and neutrophil counts (26). Albumin is a negative acute phase reactant, and the decrease in plasma Calcium (Ca^{++}) levels may due to decreased albumin in patients with COVID-19. Other factors that reduce Ca^{++} levels in patients with COVID-19 include diarrhea-related gastrointestinal losses and vitamin-D deficiency (27). WBC, lymphocyte counts, and Ca^{++} levels in this study were significantly lower in the PCR (+) patients than in the PCR (-) patients. This is consistent with the results of previous studies. However, it should also not be forgotten that although there was no statistically significant difference between the two groups in terms of Ca^{++} levels, serum Ca^{++} levels were within physiological limits.

Limitations

There are a number of limitations to this study. First, although large numbers of patients presented to the pandemic clinic due to COVID-19, many had to be excluded from the study due to the fear and psychological effects produced in the community by COVID-19 and lockdowns, and individuals being unwilling to attend hospital (for 15-day controls) unless absolutely necessary. This had an adverse impact on our patient numbers and the study findings. A second limitation concerns the accuracy of the tests used in the diagnosis of COVID-19 patients. The accuracy value of the RT-PCR test performed at the time of the study was different from the current accuracy, and this may have affected the grouping of patients with positive and negative PCR results. Finally, in our study, individuals with previously diagnosed cardiovascular system diseases were excluded from the study. We therefore accepted their ECGs as normal since they had no cardiovascular problems. Moreover, the protocol applied by the Turkish Ministry of Health in the treatment of PCR-positive patients consisted of favipiravir and hydroxychloroquine, and azithromycin or floroquinolone in suspected patients, and it is not known for certain whether the patients included in the present study were using these medications regularly or not, nor the effects of those medications on ECG findings (apart from the QT interval) (28). This may also have affected our results.

CONCLUSION

The incidence of ST-T alteration at ECG was significantly higher among the PCR-positive patients than in the PCR-negative patients. The significantly higher presentation hs-cTn levels observed among the PCR-positive patients also confirms that COVID-19-related ischemic changes occur in these patients. Moreover, P-wave amplitudes were also higher at presentation ECG among the PCR-positive patients compared to the 15th day ECG.

These findings all suggest that a cardiac effect does occur in patients with COVID-19 and that this can be detected with ECG alterations. An increased P-wave amplitude at presentation ECG in PCR-positive patients may be indicative of COVID-19-related cardiac overload. ECG should be performed both at presentation and in subsequent days on COVID-19 patients presenting with chest pain, and care must be taken regarding potential ischemic ST-T alterations.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kırıkkale University Clinical Researches Ethics Committee (Date: 10.12.2020, Decision No: 20/01).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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MEDICINE PALLIATIVE CARE

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The C-reactive protein-to-albumin ratio predicts one-year mortality in living donor kidney transplantation

C-reaktif protein albumin oranı canlıdan böbrek naklinde ilk yıl mortaliteyi öngörmektedir

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ABSTRACT

Aim: The aim of this study was is to evaluate the effectiveness of the preoperative C-reactive protein (CRP)/albumin ratio on first year mortality after living donor kidney transplantation.

Material and Method: This retrospective single-center study includes a total of living kidney transplant recipients' data who were transplanted between 2011-2020 years. Thirty-six patients who died within the first year after kidney transplantation among 2143 living kidney transplant recipients were included in the study group. Patients who have similar comobordities like mortality group patients who survives than one year after living donor kidney transplantation were enrolled as control group.

Results: First year mortality was 1.67% (36/2143) in ten years. Patients in the mortality group were older than the control group (53±13 vs 43±12, p=0.002). The median time spent on dialysis in the mortality group was longer than in the control group (13 months vs 1 month, p=0.029). The median CRP/albumin ratio was higher in the mortality group (2.77 vs 0.85, p=0.001). CRP and CRP/albumin ratio were determined as independent factors affecting mortality in the first year after living donor kidney transplantation as a result of multivariate Cox regression analysis (HR=1.040;95% CI, 1.011-1.069; p=0.004 vs HR=1.148 95% CI, 1.044-1.262; p=0.007, respectively). ROC analysis showed that the CRP/albumin ratio had the power to predict one-year mortality (AUC 0.650 95% CI 0.513-0.787, p=0.041). Kaplan-Meier survival analysis showed a statistically significant difference between the two groups in terms of the cut-off value for CRP/albumin ratio (1.52).

Conclusion: This study shows that the CRP/albumin ratio can be used to predict mortality in the first year after living donor kidney transplantation.

Keywords: Living donor kidney transplantation, mortality, C-reactive protein, albumin

Our research's data was presented in 13th Istanbul University Capa Medical School, Capa Nephrology Congress as 'Oral Presentation' on Jan 2021.

ÖZ

Amaç: Bu çalışmanın amacı, preoperatif C-reaktif protein (CRP)/albumin oranının canlıdan böbrek nakli sonrası ilk yıl mortalite üzerinde etkinliğini değerlendirmektir.

Gereç ve Yöntem: Çalışmaya 2011-2020 yılları arasında canlıdan böbrek nakli yapılmış 2143 hastadan ilk yılda ölen 36 hasta mortalite grubu olarak alındı. Kontrol grubu olarak benzer kronik hastalıklara sahip bir yıldan daha uzun süredir takipli olan canlıdan böbrek nakli yapılmış benzer sayıda hasta kontrol grubu olarak alındı.

Bulgular: On yıl için ilk yıl mortalitesi %1,67 (36/2143)'dir. Mortalite grubunda hastalar kontrol grubuna göre daha yaşlıdır (53±13 karşılık 43±12, p=0,002). Mortalite grubundaki hastaların diyalizde geçirdiği ortanca süre kontrol grubuna göre uzundur (13 aya karşılık 1 ay, p=0,029). Ortanca CRP/albumin oranı mortalite grubunda daha yüksekti (2,77 karşılık 0,85, p=0,001). CRP ve CRP/albumin oranı, çok değişkenli Cox regresyon analizi sonucunda, canlıdan böbrek nakli sonrası ilk yıl mortaliteye etki eden bağımsız faktörler olarak saptandı (HR=1,040 %95 CI 1,011-1,069; p=0,004 karşılık HR=1,148 %95 CI, 1,044-1,262; p=0,007 sırasıyla). ROC analizi CRP/albumin oranının bir yıllık mortaliteyi tahmin etme gücüne sahip olduğunu gösterirken (AUC 0,650 %95 GA 0,513-0,787, p=0,041). CRP/albumin oranı eşik değerine (1,52) göre yapılan Kaplan-Meier sağkalım analizi iki grup arasında fark olduğunu göstermiştir.

Sonuç: Bu çalışma, CRP/albumin oranının canlıdan böbrek nakli sonrasında ilk yıl içerisinde gelişen mortaliteyi öngörmede kullanılabileceğini göstermektedir.

Anahtar Kelimeler: Canlı donörden böbrek nakli, mortalite, C-reaktif protein, albumin

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INTRODUCTION

All acute-phase reactants respond to inflammatory events to varying degrees. Among these markers, C-reactive protein (CRP) is a positive acute phase protein, and the prognostic value of CRP levels in many diseases has been demonstrated in studies since there may be a relationship between the increase in CRP level and the severity of the infection (1-3). Albumin is a negative acute phase protein whose level decreases in response to infection and has been proposed as a clinical tool for estimating the severity of inflammation and malnutrition in patients with chronic diseases such as chronic kidney disease (4-6). The CRP/albumin ratio, a combined index of CRP and albumin levels, has been investigated in many clinical studies as an indicator of inflammatory status. These studies stated that the CRP/albumin ratio could be used as a prognostic indicator of morbidity and mortality to evaluate clinical outcomes (7-11). Chronic inflammation, common in patients with end-stage renal disease (ESRD), is a critical factor in the pathogenesis of atherosclerosis and affects the development of cardiovascular disease in renal transplant recipients (12-14). Thus, renal transplant recipients have a higher risk of cardiovascular system-related mortality compared to the general population (15-17). Despite major advances in organ transplantation, there are no reliable pre-transplant tests that can consistently identify patients who may be at high risk for mortality after kidney transplantation and that can be used to guide treatment decisions.

The present study aimed to determine the value of the preoperative CRP/albumin ratio as an independent prognostic indicator to predict the mortality of kidney transplant recipients (KTRs) in the first year following living donor kidney transplantation (LDKT).

MATERIAL AND METHOD

The study was retrospective, single-center, and approved by Istanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 17.11.2020, Decision No: 11-533). All procedures involving human participants were approved in accordance with the ethical standards of the Institutional and/or National Research Committee, including the Helsinki Declaration of 1964 and its subsequent amendments or comparable ethical standards.

In this study, KTRs who developed mortality within the first year (n=36, mortality group) among patients (total 2143 patients) who had a living donor kidney transplant at our center from 2011 to end of 2020 were included. As the control group, we selected patients with similar comorbidities, followed for more than one year. Control group patients were manually selected from patients who survived for more than one year, by matching them with the chronic diseases of mortality group patients. The two groups regarding donor and recipient characteristics and CRP/albumin ratio were compared.

Demographic characteristics, chronic diseases and laboratory information of the patients at their first hospitalization for kidney transplantation were reviewed and recorded in the hospital information management system. Serum CRP (mg/L) levels were studied in the Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) autoanalyzer using the immunoturbidimetric method, and albumin (g/dL) in the Roche Cobas 6000 c501 (Roche Diagnostics, Mannheim, Germany) autoanalyzer using the colorimetric BCG method. CRP/albumin ratio was calculated by dividing the patients' pre-transplant CRP levels by their albumin levels.

Statistical Analysis

Nominal and ordinal parameters were described by frequency analysis. Means and standard deviations were used for the description of scale parameters. Kolmogorov Smirnov Test was used for the normality distribution test of scale parameters. Mann-Whitney U test was used for non-normally distributed parameter differences, whereas the independent samples t-test was used for normally distributed parameters. Chi-square test and chi-square likelihood ratio were used for categorical parameter differences. ROC (receiver operating curve) analysis was used for diagnostic values of research parameters. Multivariate Cox regression analysis was used to determine the factors affecting first-year mortality after LDKT. All variables were subjected to univariable multivariate regression analysis to reveal the factors affecting first-year mortality. Multivariable Cox regression analysis was performed, in which the variables observed to be statistically significant as a result were included in the univariable multivariate regression analysis. Kaplan-Meier analysis was used for survival estimation. SPSS 22.0 for Windows version was used for analysis at 95% Confidence Interval with 0.05 alpha levels.

RESULTS

The causes of mortality in patients who died in the first year were infection (n=20, 55.6%, three of these patients died due to SARS-COV-2), cardiovascular events (n=11, 30.6%), cerebrovascular events (n=3, 8.3%), and unknown causes (n=2, 5.5%), respectively.

A comparison between the characteristics of the patients who developed mortality in the first year and the control group is presented in **Table 1**. The first-year mortality rate (36/2143) was 1.67% which means first

year survival was 98.33%. A statistically significant difference was determined between the groups in terms of gender, body mass index (BMI), and age (p=0.007, p=0.044, p=0.002, respectively). While most patients (83.3%) who died in the first year were receiving renal replacement therapy (RRT, mostly hemodialysis), this rate was 50% in the control group, and this difference was statistically significant (p=0.004). It showed KTRs who undergone preemptive kidney transplantation have less mortality. The spending time on dialysis in the mortality group was significantly longer than the control group (median, 13 months vs 1 month, p=0.029). There was no difference between the groups regarding primary disease causing ESRD and cardiovascular disease. In terms of immunological evaluation, the number of HLA mismatches was higher in the mortality group compared to the control group (median, 4 vs 3, p=0.022). While there was no difference between the groups in terms of albumin, CRP was statistically significantly higher in the mortality group (median, 10.1 vs 3.7, p=0.002). Also, the CRP/albumin ratio was also statistically significantly higher in the mortality group (median, 2.77 vs 0.85, p=0.001).

Multivariate Cox regression analysis revealed that (Forward: LR), female gender, BMI, recipient age, receiving RRT, number of HLA mismatches, CRP, and CRP/albumin ratio had an impact on mortality. Since the CRP/albumin ratio is affected by the CRP value, the CRP/albumin ratio and CRP were subjected to multivariable Cox regression analysis in 2 separate models. CRP/albumin ratio in model 1 and CRP in model 2 were effective variables on mortality in the first year after LDKT (p=0.004, p=0.007, respectively). In Model 1, CRP/albumin ratio was found to increase first year mortality by 1.148 times, while in model 2, CRP increased by 1.040 times. The Cox regression analysis of the factors affecting mortality in the first year after LDKT is presented in **Table 2**.

ROC analysis (**Figure 1**) indicated that the CRP/albumin ratio had the power to predict one-year mortality (AUC 0.650 95% CI 0.513-0.787, p=0.041 cut-off CRP/Albumin ratio 1.52), whereas CRP had no power to predict one-year mortality (AUC 0.635 95% CI 0.497- 0.773, p=0.065, cut-off CRP 5.5). ROC analysis determined that the cut off value for the CRP/albumin ratio >1.52 (61.3% sensitivity, 68.8% specificity) was statistically significant for one-year mortality. A statistically significant difference was observed between the two groups (log-rank p= 0.034) according to the one-year Kaplan-Meier survival analysis, according to the cut-off value of CRP/albumin ratio of 1.52 (**Figure 2**).

Table 1. Characteristics of the first year recipient mortality and control group

	Mortality at One Year		p
	Yes (n=36)	No (n=32)	
Donor age, years	45±14	49±14	0.272
Donor sex, f/m (m%)	23/13 (36.1%)	10/22 (68.8%)	**0.007**
Donor BMI, (kg/m²)	28 (20-42)	25 (20-34)	**0.044**
Recipient age, years	53±13	43±12	**0.002**
Recipient sex, f/m (m%)	21/15 (58.3%)	15/17 (46.9%)	0.345
Recipient BMI, (kg/m²)	26±6	27±4	0.730
Relative,(yes %)	16/20 (55.6%)	14/18 (56.3%)	0.954
RRT/Preemptive, (RRT%)	6/30 (83.3%)	16/16 (50%)	**0.004**
RRT duration, months	13 (0-228)	1 (0-156)	0.029
Primary disease			
DM	12 (34.3%)	7 (24.1%)	
HT	6 (17.1%)	3 (10.3%)	0.589
Chr.Gn	5 (14.3%)	6 (20.7%)	
Other	12 (34.3%)	13 (44.8%)	
CVD, (yes%)	18/18 (50%)	22/10 (31.3%)	0.117
HLA mismatch	4 (2-6)	3 (1-6)	**0.022**
Class I PRA	27/8 (22.9%)	24/7 (22.6%)	0.979
Class II PRA	23/12 (34.3%)	24/7 (22.6%)	0.295
Immunologic risk			
Low	18 (50%)	21 (65.6%)	
Moderate	12 (33.3%)	7 (21.9%)	0.424
High	6 (16.7%)	4 (12.5%)	
Induction			
Bsx	0 (0%)	1 (3.1%)	0.547
ATG	31 (86.1%)	26 (81.3%)	
ATG+PF	5 (13.9%)	5 (15.6%)	
ATG total dose	950 (0-2200)	600 (0-2000)	0.067
BPAR			
No	27 (75%)	21 (65.6%)	0.632
ATCMR	5 (13.9%)	5 (15.6%)	
AAMR	4 (11.1%)	6 (18.8%)	
CRP (mg/L)	10.1 (0.8-46.8)	3.7 (0.1-15.8)	**0.002**
Albumin (g/L)	4.1 (2.5-5)	4.2 (2.2-4.8)	0.060
CRP/Alb ratio	2.77 (0.20-15.20)	0.85 (0.02-3.81)	**0.001**

Numbers which are normally distributed are given as mean and standart deviation. Numbers which are not normally distributed are given as median and minimum, maximum, and percentages by row. BMI: Body mass index RRT: Renal replacement therapy DM: Diabetes mellitus HT: Hypertension Chr Gn: Chronic glomerulonephritis CVD: Cardiovascular disease HLA: Human lokocyte antigen PRA: panel reactive antibody Bsx: Basiliximab ATG: Anti-thymoycyte globulin PF: Plasmapheresis BPAR: Biopsy proven acute rejection ATCMR: Acute T-cell mediated rejection AAMR: Acute antibody mediated rejection CRP: C-reactive protein

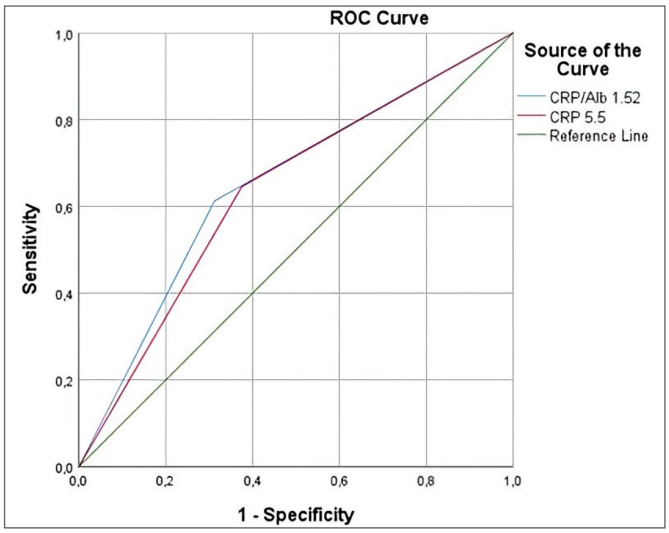

Figure 1. Receiver operating curve for CRP and CRP/Albumin ratio

Table 2. Factors affecting recipient mortality in the first year after living donor kidney transplantation

Mortality at 1st year (Cox regression)	Univariable		Multivariable (model 1)		Multivariable (model 2)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Donor age, years	0.989 (0.966-1.013)	0.354				
Donor sex, female	2.297 (1.161-4.546)	0.017	2.253 (0.972-5.222)	0.058	2.206 (0.956-5.089)	0.064
Donor BMI, (kg/m²)	1.068 (1.006-1.134)	0.031	1.059 (0.984-1.140)	0.125	1.061 (0.985-1.142)	0.117
Recipient age, years	1.044 (1.014-1.073)	0.003	1.016 (0.986-1.048)	0.302	1.015 (0.984-1.047)	0.337
Recipient sex, female	0.700 (0.360-1.358)	0.291				
Recipient BMI, (kg/m²)	0.996 (0.928-1.069)	0.909				
Relative,yes	1.012 (0.831-2.789)	0.972				
RRT/Preemptive	3.041 (1.261-7.333)	0.013	2.479 (0.973-6.317)	0.057	2.211 (0.872-5.607)	0.095
RRT duration, (months)	1.004 (0.998-1.009)	0.174				
DM	1.448 (0.733-2.860)	0.286				
HT	1.589 (0.663-3.820)	0.301				
CVD	1.543 (0.802-2.970)	0.194				
HLA mismatch	1.298 (1.035-1.629)	0.024	1.203 (0.899-1.609)	0.214	1.192 (0.890-1.598)	0.238
Class I PRA	0.909 (0.414-1.997)	0.812				
Class II PRA	1.274 (0.635-2.556)	0.495				
Immunologic risk						
Low	Reference category					
Moderate	1.332 (0.640-2.770)	0.443				
High	1.250 (0.495-3.156)	0.637				
Induction						
ATG	Reference category					
ATG+PF	0.845 (0.328-2.176)	0.727				
ATG total dose	1.270 (0.388-4.155)	0.692				
BPAR						
No	Reference category					
ATCMR	0.869 (0.334-2.257)	0.772				
AAMR	0.595 (0.208-1.701)	0.332				
CRP/Albumin ratio	1.127 (1.045-1.216)	0.002	1.148 (1.044-1.262)	**0.004**		
CRP	1.043 (1.018-1.069)	0.001			1.040 (1.011-1.069)	**0.007**

Numbers are given as median and minimum, maximum, and percentages by row; BMI: Body mass index RRT: Renal replacement therapy DM: Diabetes mellitus HT: Hypertension CVD: Cardiovascular disease HLA: Human lokocyte antigen PRA: panel reactive antibody ATG: Anti-thymocyte globulin PF: Plasmapheresis BPAR: Biopsy proven acute rejection ATCMR: Acute T-cell mediated rejection AAM: Acute antibody mediated rejection CRP: C-reactive protein

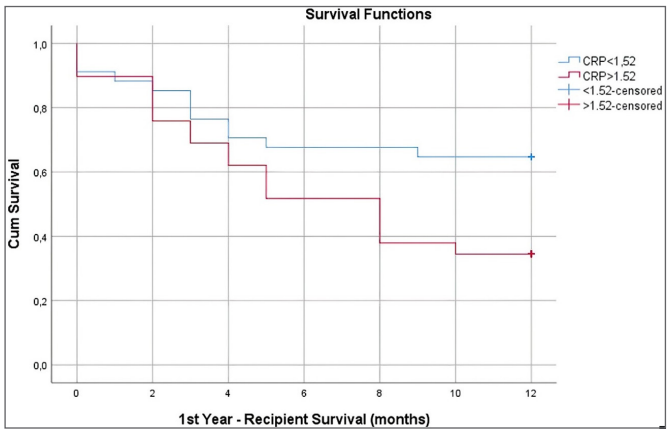

Figure 2. First year recipient survival according to CRP/Albumin cut-off value Kaplan-Meier survival analyses demonstrating the probability of first year survival based on CRP/Albumin ratio cut-off value (1.52) in the kidney recipient patients.

DISCUSSION

Early mortality after LDKT is one of the most undesirable outcomes of kidney transplantation. The first-year mortality in LDKT is mostly associated with infections and cardiovascular events (26,27). However, there is no current useful predictor tool for posttransplantation early mortality. Therefore, our study aimed to determine the value of the preoperative CRP/albumin ratio as an independent prognostic indicator to predict mortality in the first year following LDKT.

The present study revealed that the patients in the mortality group were older, had a longer median time on dialysis, had a higher HLA mismatch, and had lower preemptive transplant rates than the survivors. Since the establishment of the control group was based on the similarity of comorbid diseases that may affect mortality, differences of comorbidities did not found between the groups. The present study determined the CRP and CRP/albumin ratio as an effective independent risk factor for one-year mortality. We demonstrated that CRP levels and CRP/albumin ratios were significantly higher in the mortality group before LDKT. Van Ree et al. (18) reported that kidney transplant recipients who had a functioning graft one year after kidney transplantation

with higher CRP and lower albumin levels have high mortality risk. Although there was no difference between the groups in terms of albumin in our study, the fact that it was close to statistical significance gives the opinion that a significant difference may occur in larger case numbers.

Many studies have revealed that systemic inflammation is common in ESRD patients due to elevated serum proinflammatory cytokines and chemokines, and this inflammatory state can lead to severe complications and death (2,18-21). Acute phase reactants respond to inflammatory events in varying degrees and directions. Of these, CRP is a positive acute phase protein synthesized in the liver by inducing proinflammatory cytokines such as IL-1 and tumor necrosis factor (TNF), especially interleukin (IL)-6, whose level increases in response to infection, ischemia, and trauma (7,8,22,23). On the other hand, the albumin level decreases inversely with the degree of the inflammatory response due to the hypercatabolic state occurring in inflammatory processes and increased serum cytokines reducing albumin synthesis in the liver (6,24). In the present study, we think that high CRP levels and high CRP/albumin ratios in the mortality group may be associated with the high level of an inflammatory situation in ESRD patients.

Inflammation indicators are objective markers that show inflammation noninvasively and are used to evaluate disease activity. The CRP/albumin ratio, determined by the level of CRP and albumin parameters to each other, is a newly used prognostic biomarker based on inflammation (7-11). It was indicated in many studies that the CRP/albumin ratio could be used as a prognostic indicator of morbidity and mortality in patients with sepsis, cancer, and chronic inflammatory diseases (7-11). Park et al. (9) reported that the CRP/albumin ratio was significantly associated with early allograft dysfunction and poor patient survival in patients undergoing living donor liver transplantation. Kim et al. (10) stated that the CRP/albumin ratio of patients at admission can be used as an independent predictor of 180-day mortality in patients with severe sepsis or septic shock and that the optimal cut-off value for CRP/albumin ratio as a predictor of mortality, being 5.09. Our study revealed that the CRP/albumin ratio is a crucial independent predictor of mortality in living donor kidney transplant recipients as 1.52. Although our study showed that both CRP/albumin and CRP were the only independent risk factors affecting one-year mortality in living donor kidney transplant recipients, the ROC curve analysis showed that CRP did not have the power to predict mortality in the first year after LDKT in our study group. In the ROC curve analysis, we demonstrated that when the cut-off value of 1.52 was chosen for the CRP/Albumin ratio, it had the power to predict one-year mortality with a sensitivity of 61.3% and a specificity of 68.8%. Therefore, this suggests that the CRP/albumin ratio may be more effective in predicting one-year mortality in LDKT recipients than CRP alone. Also, in the present study, it was found patients with values higher than the optimal cut-off value of the CRP/albumin ratio had a significantly higher probability of developing mortality.

Krüger et al. (14) reported that high pretransplantation serum CRP levels were associated with all-cause and cardiovascular mortality after kidney transplantation. Varagunam et al. (21) revealed that high CRP level before renal transplant is independently associated with all-cause and cardiovascular mortality in renal transplant recipients and can be used as a useful predictive marker in the follow-up of patients after transplantation. In their study, Molnar et al. (25) associated low pre-transplant serum albumin concentration with increased all-cause and cardiovascular mortality, a higher risk of delayed graft function, and higher graft loss in renal transplant recipients. Hsiung et al. (5) showed that the presence of hypoalbuminemia in the pre-ESRD-predialysis phase was associated with increased cardiac mortality, hospitalization, infection-related mortality, and mortality in the first year after dialysis. However, our study indicated that although CRP and albumin parameters are good predictors of mortality in renal transplant patients, the CRP/albumin ratio, which is the combined index of CRP and albumin, is better at predicting mortality because it has a higher AUC value than CRP.

Our study has some limitations. First, not all factors that could be confusing could be excluded due to its retrospective design, and some factors may not have been included in the study. Secondly, there is no repeated measurement of CRP and albumin values and, thus CRP/albumin ratios. So it was not possible for the present study shows reflecting the inflammatory process after kidney transplantation. Third, although the control group was selected as patients with similar characteristics in comorbid diseases, a possible selection bias cannot be excluded. Fourth, the preference for first-year mortality limited the number of cases, which did not allow for subgroup analysis according to causes of mortality. As a result, although all variables that may affect first-year mortality were tried to be included in the multivariate analysis, selection bias cannot be excluded entirely, so the results should be interpreted with caution. For the CRP/albumin ratio to accurately predict mortality, prospective studies involving a larger number of cases involving multiple centers are required.

CONCLUSION

We demonstrated that the CRP/albumin ratio, which can be easily calculated from simple, inexpensive, and routinely used clinical tests, has predictive power in predicting mortality in the first year after LDKT. We think that the evaluation of the CRP/albumin ratio reflecting systemic inflammation would be more useful in predicting the clinical course of the patients, as opposed to separately analyzing CRP and albumin in renal transplant patients where inflammation plays an important role.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Yeni Yüzyıl University Clinical Researches Ethics Committee (Date: 17.11.2020, Decision No: 11-533).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Neuroprotective effect of methanol extract of *Capparis spinosa* L. fruits in an in-vitro experimental model of Parkinson's disease

Capparis spinosa L. meyvelerinin metanol ekstraktının Parkinson hastalığının in-vitro deneysel modelinde nöroprotektif etkisi

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ABSTRACT

Aim: Parkinson's disease (PD) is the second most widespread neurodegenerative disease. This study, it was aimed to investigate the effect of methanol extract obtained from *Capparis spinosa* L. fruits, which are known to have important bioactive components, on in-vitro experimental PD model.

Material and Method: After collecting *Capparis spinosa* L. fruits from Alanya/Antalya, methanol extract was prepared by drying and grinding. SH-SY5Y cells grown in flasks were transferred to 96 well plates and were incubated until 80% cell density was reached. Different doses of methanol extract were applied to the cells 30 minutes before the PD model was formed. For the PD model, SH-SY5Y cells were exposed to 200 µM 6-OHDA for 24 hours. MTT analysis was performed to assess the viability of SH-SY5Y cells at the end of the 24-hour period. TOS, TAC, and IL-17A levels in the cell medium were determined using the ELISA method. Expression of TNFα and α-synuclein was defined using the immunohistochemical method.

Results: Cell viability was found to be higher in all treatment groups than in the 6-OHDA group. Moderate levels of TNFα and α-synuclein positivity were observed in the 1500 µg/ml methanol extract group. It was determined that TOS and TAC levels change depending on the dose. It has been determined that the level of IL-17A decreases at low doses. Statistical significance was found between the groups.

Conclusion: When the findings were examined, it was determined that the methanol extract obtained from *Capparis spinosa* L. fruits reduced oxidative stress and IL-17A levels at low doses and provided a neuroprotective effect by increasing the antioxidant capacity.

Keywords: *Capparis spinosa* L., SH-SY5Y, Parkinson's disease, neuroprotective

ÖZ

Amaç: Parkinson hastalığı, en sık görülen ikinci nörodejeneratif hastalıktır. Bu çalışmada, önemli biyoaktif bileşenlere sahip olduğu bilinen *Capparis spinosa* L. meyvelerinden elde edilen metanol ekstraktının in vitro deneysel Parkinson hastalığı modeline etkisinin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Alanya/Antalya'dan *Capparis spinosa* L. meyveleri toplandıktan sonra kurutulup öğütülerek metanol özütü hazırlandı. Flasklarda geliştirilen SH-SY5Y hücreleri, 96 oyuklu plakalara aktarıldı ve %80 hücre yoğunluğuna ulaşılana kadar inkübe edilmiştir. Parkinson hastalığı modeli oluşturulmadan 30 dakika önce hücrelere farklı dozlarda metanol özütü uygulanmıştır. Parkinson hastalığı modeli için SH-SY5Y hücreleri, 24 saat boyunca 200 uM 6-OHDA'ya maruz bırakılmıştır. 24 saatlik sürenin sonunda SH-SY5Y hücrelerinin canlılığını değerlendirmek için MTT analizi yapılmıştır. Hücre ortamındaki TOS, TAC ve IL-17A seviyeleri ELISA yöntemi kullanılarak belirlenmiştir. TNFα ve α-sinüklein ekspresyonu, immünohistokimyasal yöntem kullanılarak tespit edilmiştir.

Bulgular: Hücre canlılığının tüm tedavi gruplarında 6-OHDA grubuna göre daha yüksek olduğu bulundu. 1500 µg/ml metanol özütü grubunda orta düzeyde TNFα ve a-sinüklein pozitifliği gözlendi. TOS ve TAC düzeylerinin doza bağlı olarak değiştiği belirlendi. Düşük dozlarda IL-17A seviyesinin düştüğü bulundu. Gruplar arasında istatistiksel anlamlılık saptandı.

Sonuç: Bulgular incelendiğinde *Capparis spinosa* L. meyvelerinden elde edilen metanol ekstraktının düşük dozlarda oksidatif stres ve IL-17A düzeylerini azalttığı ve antioksidan kapasiteyi artırarak nöroprotektif etki sağladığı belirlendi.

Anahtar Kelimeler: *Capparis spinosa* L., SH-SY5Y, Parkinson hastalığı, nöroprotektif

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INTRODUCTION

PD is a neurodegenerative, progressive disease. PD, whose incidence increases with the aging population, has been predicted to affect approximately thirteen million people by 2040 (1). The increasing prevalence of PD has caused some health professionals to define it as a non-communicable pandemic disease like diabetes. This increase has been related to decreased smoking rates, increased exposure to environmental waste, and diet, in addition to the aging population (2,3).

The substantia nigra pars compacta (SNc) are one of the nuclei forming the basal ganglia. Progressive neurological degeneration in this region is the most important pathological sign of PD. Neurons located in the SNc are involved in the transmission of dopamine to other basal ganglia nuclei and the striatum. Degeneration of neurons in the SNc leads to dysfunction of neuronal circuits, including the basal ganglia and motor cortical areas including. This causes movement abnormalities that affect the individual's standard of living and are the main symptoms of PD. Motor dysfunctions and non-motor symptoms occur clinically in idiopathic PD. Motor dysfunctions; stiffness, tremors, loss of spontaneous movement, and impaired balance. Non-motor symptoms appear as dementia, sleep, mood, and personality changes (4).

Intracellular accumulation of misfolded α-synuclein protein in the striatum of PD patients is a histopathological distinctive finding. Among the mechanisms causing this pathophysiology, attention was drawn mostly to oxidative stress, mitochondrial dysfunction, apoptosis, and neuroinflammation. It is also known that the expression levels of proinflammatory cytokines such as IL-1β, IL-6, IL-17A, and TNFα increase in relation to neuroinflammation in these patients (4,5). In recent clinical studies, it has been reported that vitamins, β-carotene, caffeine, omega-3, omega-6, and Mediterranean diet supplements slow the progression of Parkinson's Disease and provide cognitive and behavioral improvement (6-8).

Cappari spinosa L. is a thorny perennial shrub belonging to the Capparidaceae. Widespread in the Mediterranean, it shows a wide distribution including Europe, Africa, Madagascar, and Asia. It is known that different parts of the plant have been used in the treatment of skin diseases, cough, asthma, headache, diabetes, ulcer, and sciatica since ancient times (9). During the excavations in Syria (Tell es-Sweyhat, Syria), the seeds of *Capparis spinosa* L. dated to 2400-1400 were discovered in a sarcophagus. It was concluded that these seeds were used for medicinal purposes by the researchers due to the presence of *Cannabis sativa* plant residues (10). The flower buds of the plant are utilized as a spice, while the fruits are consumed after fermenting (11). Various have been determined components of *Capparis spinosa* L. including alkaloids, furan, flavonoids, and pyrrole derivatives, phenolic acids, tetraterpenes, sterols, capparisine A, capparisine B, capparisine C, glucocapparin, isoginkgetin, ginkgetin, protocatechuic acid (11,12). It has been reported that methanol extracts of ripe fruits collected from Turkey contain cappariloside A, cappariloside B, gentisic acid, sinapinic acid, and benzoic acid (13,14). In clinical and experimental studies, it has been proven that extracts obtained from *Capparis spinosa* L. fruits have anti-viral, anti-diabetic, hypolipidemic, hepatoprotective, anti-hypertensive, and anti-inflammatory effects (15-19).

In this study, methanol extract obtained from *Capparis spinosa* L. fruits was investigated for the first time in experimental Parkinson's disease in-vitro and the neuroprotective effect of the extract was presented. Expression of α-synuclein, which has a specifically important place in the diagnosis of PD, was evaluated immunohistochemically. While oxidative stress level was determined by TAC and TOS biochemical analysis, neuroinflammation level was investigated using TNFα and IL-17A immunohistochemical and biochemical analyzes.

MATERIAL AND METHOD

This study was carried out using immortal cell lines. Ethics committee approval was not obtained because human or animal subjects were not used in the study. However, all procedures were carried out in accordance with ethical rules and the principles.

Capparis spinosa L. Extraction

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. *Capparis spinosa* L. (CS) fruits were collected from their natural environment in Alanya/Antalya in August. Dried and ground fruits (20 g) of CS were extracted with 300 ml of methanol utilizing a Soxhlet extractor (ISOPAD, Heidelberg, Germany) for 6 hours at a temperature below boiling point (<64°C). Extract filtered out Whatman fiber paper no 1 and then concentrated under vacuum at 40°C using an evaporator (Buchi Labortechnic AG, Flawil, Switzerland) and the extract, determined to have a yield of 10.5%, was stored at +4°C in the dark until use (20).

Cell Culture and MTT Test

DMEM/F12 medium containing 10% FBS and 1% antibiotic/antimitotic solution was prepared for cell culture. An amount of the prepared medium was taken and transferred to flasks together with the SH-SY5Y

cell line. The flask was incubated at 5% CO2 and 37°C. SH-SY5Y cells grown in flasks were then transferred to 96 well plates and incubated until 80% cell density was reached. Different doses of CS extract (1000-3000 µg/ml) were applied to the cells 30 minutes before the PD model was created. For the PD model, SH-SY5Y cells were exposed to 200 µM 6-OHDA for 24 hours. 3-(4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide (MTT) (SigmaAldrich) analysis was performed to assess the viability of SH-SY5Y cells at the end of the 24-hour period. After applying 20 µL of MTT solution to all wells, it was incubated at 37 °C for 4 hours. For spectrophotometric examination of the formed formazan crystals, 150 µl of DMSO was added to the wells whose supernatants were removed. Completely dissolved formazan crystals were measured at 570 nm with the aid of a spectrophotometer. Statistical analyses were performed using one-way analysis of variance (ANOVA) with post hoc Tukey's test (IBM SPSS 22.0) ($p<0.05$, $p<0.001$) (21,22).

Immunohistochemical Analysis

Based on the results from the MTT assay, the in vitro model of PD and the administration of the extract at a dose range of 1500-2500 µg/ml were repeated in 24-well plates for immunohistochemistry staining. After 24 hours of exposure, SH-SY5Y cells were fixed with methanol for 5 minutes at -20°C and washed with PBS (Phosphate Buffered Saline). Then, PBS containing 0.1% Triton X-100 was added and incubated at 22°C for 15 minutes. After washing, it was incubated with PBS containing 2% Bovine Serum Albumin for 1 hour at room temperature. After rewashing, it was incubated overnight at +4°C with monoclonal anti-α-synuclein (Santa cruz, sc-69977), and monoclonal anti-TNFα (Santa cruz, sc-52746) primary antibodies at a dilution ratio of 1/300. Cells washed away with PBS were incubated with goat anti-mouse (FITC) secondary antibody (Jackson ImmunoResearch, no: 115-095-003) at a dilution of 1/50 for 1 hour at 22°C in the dark, consistent with the primary antibodies used. Lastly, DAPI (4',6-diamidino-2-phenylindole) was instilled into the washed cells and investigated under a fluorescent microscope (Zeiss Axio). In the examination, the density of fluorescence positivity in the cells was evaluated with the Fiji Image J program.

In the data analyzed with the SPSS 20.00 program, the difference between the groups was determined by the Kruskal Wallis test, and the group that created the difference was determined by the Mann Whitney U test ($p<0.05$) (23).

Biochemical Analysis

Oxidative stress parameters, total oxidant status (TOS), and total antioxidant capacity (TAC) in the medium of SH-SY5Y cells for which an in-vitro PD model was created were investigated (Rel Assay Diagnostics, Gaziantep, Turkey). The level of IL-17A (BT LAB, Zhejiang, China) in the medium related to neuro-inflammation was determined in accordance with the protocol recommended by the ELISA kit manufacturer. Biochemical analysis was performed with post hoc Tukey test (IBM SPSS 22.0) ($p <0.05$, $p<0.001$) and one-way analysis of variance (ANOVA) (23,24).

RESULTS

MTT Test

Compared with the 6-OHDA group, cell viability was found to be higher in all treatment groups. While the cell viability changed depending on the dose, the groups with the highest cell viability were determined as the groups treated with 1000-1500 µg/ml CS methanol extract. A statistically significant difference was defined in all treatment doses compared to the 6-OHDA group (**Figure 1**).

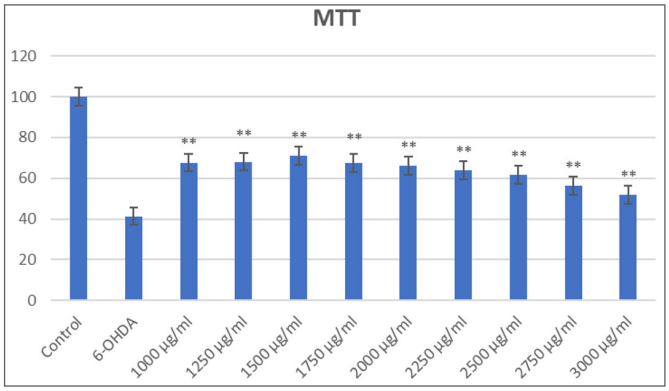

Figure 1. MTT analysis results. *p<0.05, **p<0.001

Immunohistochemical Results

A statistically significant difference was defined between the groups in immunofluorescent staining with α-synuclein and TNFα (**Table 1**, $p<0.001$). While mild fluorescence positivity was a sight in the control group, severe positivity was detected in the 6-OHDA group. In the application groups, moderate positivity was found at 1500 µg/ml, and severe positivity at 1750-2500 µg/ml (**Figure 2**).

Table 1. Statistical differences in α-synuclein and TNFα immunofluorescence staining

Groups	α-synuclein	TNFα
Control	28.42±1.92[a]	30.13±0.52[a]
6-OHDA	71.62±0.43[b]	73.41±1.38[b]
1500 µg/ml	54.07±0.25[c]	58.24±1.34[c]
1750 µg/ml	69.92±0.34[b]	74.04±1.82[b]
2000 µg/ml	70.71±0.22[b]	73.22±0.62[b]
2250 µg/ml	71.46±1.34[b]	72.49±0.50[b]
2500 µg/ml	68.16±1.69[b]	72.81±1.63[b]

a,b,c indicate the difference between groups, p<0.001.

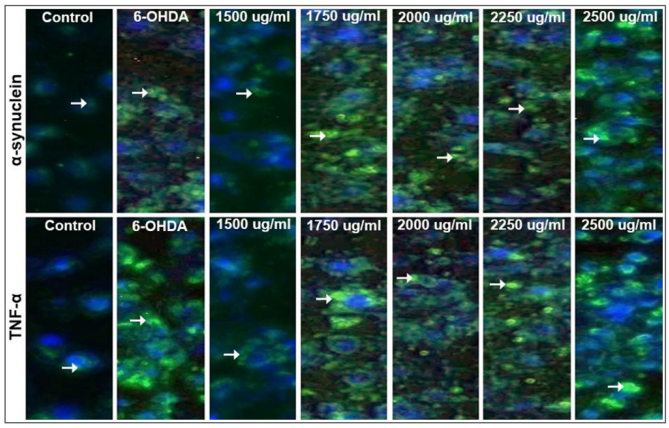

Figure 2. α-synuclein and TNFα expression levels

Control group-Mild, 6-OHDA group-Severe, 1500 µg/ml group-Moderate, 1750 µg/ml, 2000 µg/ml, 2250 µg/ml, and 2500 µg/ml groups-Severe positivity (arrows), IF.

Biochemical Analysis Results

It was determined that the oxidative level in the medium of the PD-modeled cells increased at high doses, while it decreased at low doses consistent with the MTT test. The antioxidant capacity was detected to be at the highest level at 1500 µg/ml and 1750 µg/ml doses. Besides, antioxidant levels were higher in all treatment groups than in the control and 6-OHDA groups, except for the 2750 µg/ml and 3000 µg/ml doses. Statistically, a significant difference was determined in all treatment groups (**Figure 3**, **Figure 4**). The group with the highest level of IL-17A, a proinflammatory cytokine, was found as 6-OHDA. It is remarkable that the IL-17A level increased with increasing doses in the treatment groups. A statistically significant difference was determined in all groups compared to the 6-OHDA group (**Figure 5**).

DISCUSSION

PD is an important neurodegenerative disease with an increasing incidence. In this study, the application of methanolic extract obtained from CS fruits in the dose range of 1000 µg/ml-2250 µg/ml increased cell viability in the PD model created using the SH-SY5Y cell line. It has also been determined that it has shown antioxidant and anti-inflammatory effects. In immunohistochemical analyzes, moderate α-synuclein and TNFα expression have been detected at a dose of 1500 µg/ml. When the results obtained were evaluated, it was determined that the methanol extract of CS fruits showed a dose-dependent neuroprotective effect in the in-vitro PD model.

Classified among medicinal plants, CS is used in the remedy of diverse illnesses due to the flavonoids, alkaloids, and phenolic acids it contains. Studies have shown that CS fruits contain p-Coumaric acid (5.53 ± 0.01 mg/100 g DW), Ferulic acid (0.73 ± 0.00 mg/100 g DW), Catechin (0.91 ± 0.02 mg/100 g DW), Epicatechin (1.14 ± 0.01 mg/100 g DW), Rutin (17.12 ± 0.00 mg/100 g DW), Kaempferol (3.44 ± 0.01 mg/100 g DW), and Quercetin

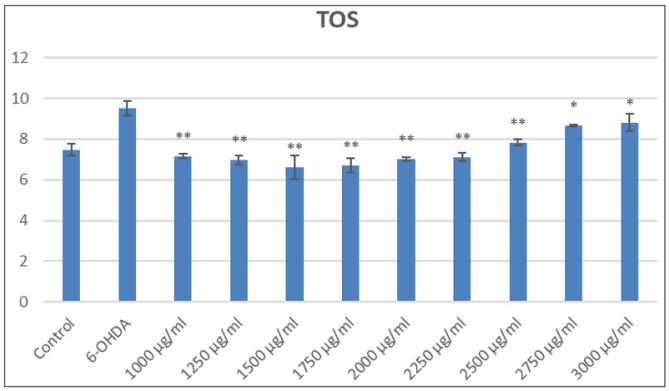

Figure 3. TOS analysis results

*p<0.05, **p<0.001

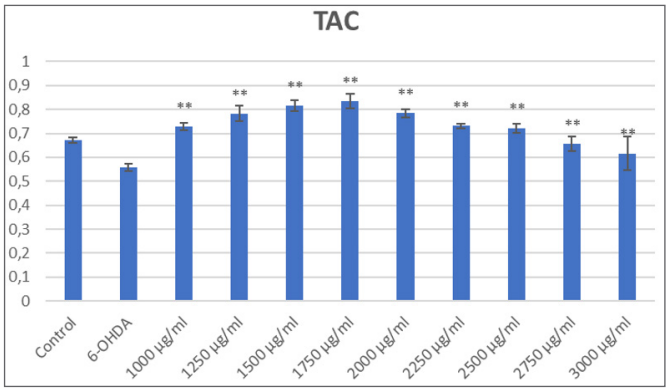

Figure 4. TAC analysis results

*p<0.05, **p<0.001

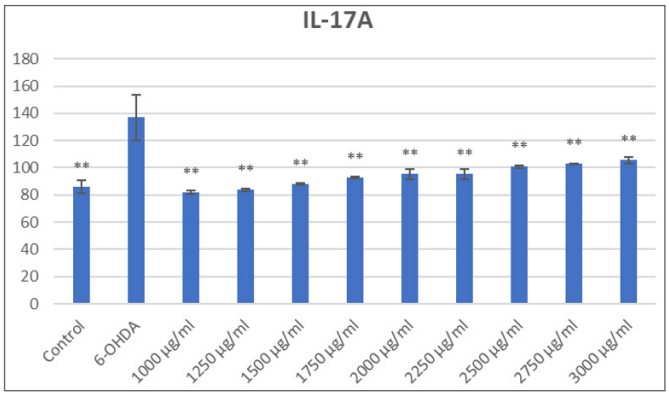

Figure 5. IL-17 analysis results

*p<0.05, **p<0.001

(0.29 ± 0.01 mg/100 g DW) (25). Zhu et al, who created an experimental ulcerative colitis model in mice, have been used water extracts of CS fruits in the treatment. They have reported that after seven days of treatment, the expression IL-6, IL-1β, and TNFα was suppressed, and improvement was achieved in mice by reducing oxidative stress (26). In another study, a streptozotocin-induced diabetes model was established in rats by Jalali et al. (27) and diabetic rats were treated with water extracts from CS fruits for 28 days. As a result of the analysis, they determined that it lowered blood sugar and lipid levels independently of insulin. In a randomized controlled trial, Vahid et al. (18) reported that CS oxymel treatment applied to patients diagnosed with type 2 diabetes did

not show any difference in HbA1c level compared to the placebo group, however, it prevented the progression of hyperglycemia. In terms of the components, it contains, CS has a strong antioxidant effect. It was determined that CS ethanol extract reduced Doxorubicin-induced apoptotic induction and cardiotoxicity in cardiomyoblast cells (28). It has been proven that hydro-ethanolic extract of CS aboveground parts significantly reduces IL-1β, NO, iNOS, PGE2, IL-6, TNF-α, and COX-2 levels in brain tissue and improves cognitive impairment associated with lipopolysaccharide-induced inflammation (29). They found that it increased learning and memory functions in mice treated with CS methanol extract in an Alzheimer's disease (AD) model induced by D-galactose injection in mice. It is known that the D-galactose model acts on oxidative stress. In this study, in which SOD, CAT and GPx activities increased, the improvement in AD model was associated with antioxidant mechanisms (30). 6-OHDA, which is frequently preferred in experimental PD models, is structurally similar to dopamine and norepinephrine. By inducing mitochondrial dysfunction, 6-OHDA increases oxidative stress, leading to neuronal degeneration (23). In our study, it was determined that in the in-vitro PD model created by 6-OHDA in SH-SY5Y cells, the total oxidant level decreased, and the antioxidant level increased in a dose-related manner in the treatment groups.

In a model of AD induced by injection of amyloid-beta peptide in rats, CS hydroalcoholic extracts have been shown to provide more effective up-regulation of the expression of genes encoding Gamma-secretase and Beta-secretase enzymes compared to the Rutin-treated group. In this study, the neuroprotective effect was associated with anti-inflammatory mechanisms as well as the antioxidant effect of the bioactive compounds contained in CS (31). The proinflammatory cytokines IL-17A and TNFα, which are known to increase in neurodegenerative disorders, were found to increase in our study in a dose-dependent manner. In addition, it was determined that α-synuclein expression, which is a distinctive biomarker in the diagnosis of PD, was moderate at 1500 μg/ml, and severe in 6-OHDA and high-dose treatment groups. This situation was thought to be related to the doses administered.

CONCLUSION

This study, the neuroprotective effect of methanol extract of *Capparis spinosa* L. fruits on in-vitro PD was investigated for the first time and it was proven that the extract provided a dose-dependent neuroprotective effect. These findings showed that the methanol extract of *Capparis spinosa* L. fruits with its antioxidant and anti-inflammatory properties may be a potential candidate for neuroprotection in PD. In-vivo experiments and detailed analysis are needed to understand the efficacy and mechanism.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was carried out using immortal cell lines. Ethics committee approval was not obtained because human or animal subjects were not used in the study.

Informed Consent: Since this study used an immortal cell line and was not a human study, written consent is not required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Exploring clinical and laboratory findings and treatment outcomes in pregnant inpatients with COVID-19: a single-center experience

COVID-19 tanısıyla yatarak izlenen gebe hastalarda klinik, laboratuvar bulguları ve tedavi sonuçlarının değerlendirilmesi

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ABSTRACT

Aim: The literature seems to miss the clinical course of COVID-19 infection among the pregnant and its effects on the fetus. The present study aimed to evaluate a total of 21 pregnant inpatients in Ankara Training and Research Hospital with the diagnosis of COVID-19 in terms of symptoms, physical examination findings, laboratory findings, treatment results, and complications.

Material and Method: A total of 21 pregnant patients diagnosed with COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) in Ankara Training and Research Hospital between 22.04.2020 and 27.09.2021 were included in the study. The clinical symptoms, physical examination findings, laboratory findings, and treatment outcomes of the patients, and the health status of the pregnant and newborn were retrospectively evaluated.

Results: Of the 21 pregnant patients, 10 were Turkish citizens, and 11 were foreign nationals. The patients were aged 20-41 years with a mean age of 28.76 years. All patients were unvaccinated. Considering underlying diseases among the patients, it was found that one patient had hypertension, and one patient had thyroid disease. In order of frequency, the symptoms in the patients were cough (n =10), fatigue (n=8), sore throat (n=6), dyspnea (n=5), fever (n=3), myalgia (n=3), joint pain (n=1), and diarrhea (n=1). Physical examinations of the patients yielded a fever of 37.4 °C above in 3 patients and rales in one patient. Although one patient with COVID-19 pneumonia was followed up in the intensive care unit, all were discharged upon recovery. Chloroquine tablets were started in 6 patients, a combination of ritonavir (50 mg) and lopinavir (200 mg) in 4 patients, and favipiravir in one patient. Cesarean section was performed in 9 patients, while 12 patients gave normal delivery.

Conclusion: Overall, the clinical course of COVID-19 infection in the pregnant followed up in this study was mild, and all newborns were healthy except for one. It is thought that close follow-ups for the pregnant are needed to minimize complications that may develop in them and their fetuses due to COVID-19 infection. Finally, the COVID-19 vaccine seems to be a must for the pregnant to prevent all possible COVID-related complications.

Keywords: COVID-19, pregnancy, newborn, clinical follow-up

This study was presented as an oral presentation at the 9th BUHASDER Congress (November 24–28, 2021 - Antalya).

ÖZ

Amaç: Gebelerde COVID-19 infeksiyonunun klinik seyri ve fetüse olan etkilerine ilişkin sınırlı sayıda çalışma mevcuttur. Bu çalışmada, Ankara Eğitim ve Araştırma Hastanesinde, COVID-19 tanısıyla yatarak izlenen toplam 21 gebe hastanın semptomlar, fizik muayene bulguları, laboratuvar bulguları, tedavi sonuçları ve komplikasyonlar açısından değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 22.04.2020 ile 27.09.2021 tarihleri arasında Ankara Eğitim ve Araştırma hastanesinde COVID-19 tanısı revers transkriptaz Polimeraz zincir reaksiyonu (RT-PZR) ile konan toplam 21 gebe hasta dahil edildi. Hastaların semptomları, fizik muayene bulguları,laboratuvar bulguları, uygulanan tedavi sonuçları, gebe ve yenidoğanın sağlık durumları retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 21 gebe hastanın 10'u Türk vatandaşı, 11'i ise yabancı uyruklu bireylerden oluşmaktaydı. Gebelerin yaş aralığı 20-41 yıl arasında, yaş ortalaması 28,76 idi. Gebelerin tamamı aşısızdı. Gebe hastalarda altta yatan hastalıklar değerlendirildiğinde; bir hastada hipertansiyon, 1 hastada tiroid hastalığı mevcuttu. Gebe hastalarda görülen semptomlar sıklık sırasıyla; öksürük (n=10), halsizlik (n=8), boğaz ağrısı (n=6), dispne (n=5) , ateş (n=3), miyalji (n=3), eklem ağrısı (n=1), ve ishaldi (n=1) . Fizik muayenede; 3 hastada 37.4°C üzerinde ateş, bir hastada ise raller mevcuttu. Gebe hastaların biri COVID-19'a bağlı pnömoni nedeniyle yoğun bakım ünitesinde izlendi, hepsi şifa ile taburcu edildi. Gebe hastaların 6'sına klorokin tablet, 4'üne ritonavir (50 mg) ve lopinavir (200 mg) kombinasyonu, birine ise favipiravir başlandı. Gebelerin 9'una sezeryan, 12'sine ise normal doğum uygulandı.

Sonuç: Bu çalışmada izlenen gebelerde COVID-19 infeksiyonunun klinik seyrinin hafif olduğunu, biri dışında tüm bebeklerin sağlıklı olarak doğduğunu gözlemledik. COVID-19 infeksiyonuna bağlı olarak gebelerde ve fetüste gelişebilecek komplikasyonların en aza indirilmesi için hastaların yakın takibinin gerekli olduğu düşüncesindeyiz. Ayrıca, gebelere COVID-19 aşısı uygulanması, hastalıktan korunmada önem taşımaktadır.

Anahtar kelimeler: COVID-19, gebelik, yenidoğan, klinik izlem

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INTRODUCTION

Novel coronavirus disease 2019 (COVID-19) caused by the SARS-Cov-2 virus is a viral infection that was first detected in Wuhan, China in December 2019. It is obvious to affect many organs and systems, such as the lungs, heart, and central nervous system, and its rapid spread has led it to be declared a pandemic in the world. A study involving 215 pregnant women in the United States reported SARS-CoV-2 positivity in 33 (15%) of the cases, the majority of whom were asymptomatic (1). In a further study, it was reported that 71% of the cases that were asymptomatic during pregnancy developed symptoms during labor or in the postpartum period (2). While pregnancy is not reported as a risk factor for COVID-19, the clinical symptoms may be more severe due to the physiological changes in the natural course of pregnancy (2).

There is a paucity of research in our country regarding the clinical course of COVID-19 among the pregnant and fetuses (3,4). Therefore, the present study evaluated the clinical and laboratory findings and treatment outcomes of the pregnant diagnosed with COVID-19 who were admitted different clinics in the Ankara Training and Research Hospital.

MATERIAL AND METHOD

The study included 21 pregnant women diagnosed with COVID-19 by RT-PCR (Bioksen, Turkey) in Ankara Training and Research Hospital between 22. 04. 2020 and 27.09.2021. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The clinical symptoms, laboratory findings, and treatment outcomes of the patients, as well as the health status of the pregnant and newborns, were retrospectively examined. Up until the postpartum period, the patients were examined by both obstetricians and infectious disease specialists, who further followed the symptoms and health status of both the patients and their babies.

The Ministry of Health and the Ethics Committee of Ankara Training and Research Hospital granted ethical approval to this study (Date: 09.29.2021 and Decision No: E-21-667), and all patients provided their written informed consent for voluntary participation in the study.

RESULTS

The sample consisted of 10 Turkish 11 foreign national pregnant patients aged 20–41 years with a mean age of 28.76 years. All patients were unvaccinated. Considering underlying diseases, one had hypertension, and one had thyroid disease. Moreover, the clinical course of COVID-19 was severe in one patient, mild in 14 patients, and moderate in six patients.

The symptoms detected at the time of presentation were as follows by frequency: cough (n=10), fatigue (n=8), sore throat (n=6), dyspnea (n=5), fever (n=3), myalgia (n=3), joint pain (n=1), and diarrhea (n=1). None of the patients had complaints of loss of taste and/or inability to smell.

In the physical examination of the patients, a fever of 37.4 °C and above was found in 3 patients, and rales were detected in one patient. In addition, tachycardia was present in eight patients, and one patient had hypotension.

One patient had tachypnea (respiratory rate: 32) with a SpO_2 of 78, while SpO_2 was ranged between 95–98 in the other patients. The patient with the low SpO_2 was followed in the intensive care unit (ICU) with a preliminary diagnosis of COVID-19 pneumonia and was not treated with chloroquine or antiviral treatment for COVID-19. The patient recovered fully following ICU supportive therapies (oxygen and low-molecular-weight heparin). It was also determined that the newborn had a low birth weight (1750 g) in this patient with a cesarean delivery.

Laboratory findings revealed lymphopenia in six patients (normal lymphocyte count: ≥1,000), leukocytosis in four patients (normal leukocyte count: 10,300/mm3), elevated C-reactive protein (CRP) in 13 (61.9%) patients (reference: 0-5 mg/dL), elevated ALT in one patient, and elevated AST in three patients. D-dimer was above the reference value (500 micg/l) in 13 (61.9%) patients.

Although one (4.7%) pregnant patient was followed up in ICU, all patients were eventually discharged upon full recovery.

Six of the patients were initiated on chloroquine tablets, four on a combination of ritonavir (50 mg) and lopinavir (200 mg), and one on favipiravir in the postpartum period. The others were followed up without medication. Neither those receiving medication nor their babies developed complications.

Nine patients (42.8%) had a cesarean section, and 12 (57.1%) had a normal delivery. During follow-ups, one (4.7%) patient developed intrauterine fetal death at the 27th week of gestation, but a definite conclusion could not be ascertained whether it was associated with COVID-19. Besides, two (14.2%) of the 14 newborns had low birthweight (<2500 g). The other fetuses were reported to be healthy during follow-ups, and none developed complications following birth. The mean weight of the 14 newborns was 2,815 g (max=3,460 g and min=2,200 g). The findings of the patients and newborns are presented in **Table 1**.

The symptoms and physical examination findings of the patients are presented in **Table 2**.

Table 1. Findings of the pregnant with COVID-19 and newborns

Patient no.	Age (years)	Gestational week	Length of hospitalization (days)	Treatment	ICU admission	Type of delivery	Birth weight (g)	Newborn status
1	37	28	6	Chloroquine	No	Cesarean section	3070	Healthy
2	24	18	6	None	No	Normal	-*	-
3	26	4	7	Lopinavir/Ritonavir	No	Normal	-	-
4	29	14	9	Lopinavir/Ritonavir/ Chloroquine	No	Cesarean section	3000	Healthy
5	20	29	1	None	No	Normal	-	-
6	21	32	6	Chloroquine	No	Normal	2580	-
7	36	6	2	Lopinavir/Ritonavir	No	Normal	-	-
8	30	38	9	None	Yes	Cesarean section	3020	Healthy
9	30	32	4	Chloroquine	No	Cesarean section	2200	Healthy
10	27	38	1	None	No	Normal	3460	Healthy
11	21	-	6	Chloroquine	No	Normal	2750	-
12	29	39	1	None	No	Normal	3150	-
13	27	32	11	Chloroquine	No	Cesarean section	2900	Healthy
14	25	33	5	Lopinavir/Ritonavir	No	Normal	2940	-
15	28	-	14	Chloroquine	No	Normal	2500	Healthy
16	31	38	2	None	No	Cesarean section	3215	Healthy
17	39	28	2	None	Yes	Cesarean section	1750	Healthy
18	23	-	2	None	No	Normal	2880	Healthy
19	27	27	2	None	No	Cesarean section	-	Intrauterine death
20	41	36	1	None	No	Cesarean section	-	-
21	33	22	3	None	No	Normal	-	-

(*) Patient data not available.

Table 2. Symptoms and physical examination findings of the patients

Symptoms	n	%
Fever	3	14.2
Cough	10	47.6
Dyspnea	5	23.8
Shore throat	6	28.4
Fatigue	8	38.1
Arthralgia	1	4.7
Myalgia	3	14.2
Headache	1	4.7
Diarrhea	1	4.7
Anosmia/Hypogeusia	0	0
Physical examination		
Fever	3	14.2
Tachypnea	0	0
Tachycardia	8	38.1
Hypotension	1	4.7
Low SPO_2 (<93%)	1	4.7
Rales in the lungs	1	4.7

The laboratory findings of the pregnant COVID-19 patients are presented in **Table 3**.

DISCUSSION

COVID-19 is a viral infection that quickly evolved into a pandemic and is associated with fever, cough, shortness of breath, nausea, vomiting, headache, sore throat, fatigue, and loss of smell and tastes. Even though the previous research reported similar COVID-19-related symptoms in both pregnant and non-pregnant adults, primary symptoms reported in pregnant patients are often new-onset fever, cough, shortness of breath, headache, sore throat, and loss of taste and/or smell (2) .

In their prospective study on 533 Turkish pregnant patients with COVID-19, Sahin et al. (3) reported comorbid diseases in 161 (30.2%) of the patients: 44.1% obesity, 17.4% hypothyroidism, 514.3 hypertension, 4.3% Type 2 diabetes mellitus (T2DM), and 4.9% asthma, respectively. Given the underlying diseases among the patients in the present study, one patient (4.7%) had hypertension, and one (4.7%) had thyroid disease. In this study, the pregnant with COVID-19 aged between 20-41 years with a mean age of 28.76 years. Not all patients were vaccinated against COVID-19. In the study by Sahin et al. (3), the mean age of the patients was reported to be 28.04±5.84 years. In the same study, the most common

Table 3. Laboratory findings of the patients

Patient no.	NLO*	White blood cell	Lymphocyte	Thrombocyte	Sedimentation rate	Prothrombin time	Fibrinogen	CRP	ALT	AST	LDH	GFR**	CRE	CK	CK-MB	Troponin	D-Dimer	Ferritin
1	2.76	6,660	1,510	217,000	21	14.7	435	43.17	95	236	242	147	0.3	16	-		650	-
2	2.42	3,750	970	202,000	34	-*	-	9.04	6	16	-	133	0.53	55	-		1,180	-
3	3.31	4,470	910	181,000	15	14.8	325	1.17	12	16	-	114	0.73	46	-	12.87	370	23.9
4	10.73	7,300	560	186,000	25	14.9	403	15.2	13	16	140	131	0.5	-	0.85	7.56	430	-
5	3.83	6,960	1,250	353,000	62	-	494	21.68	12	14	210	146	0.45	65	-	3.45	3,310	-
6	3.81	6,390	1,240	54,000	51	15.3	-	8.21	9	18	273.08		0.53	53.85	-	3	490	10.7
7	3.19	5,260	1,140	239,000	42	14.1	487	43.99	18	20	238	122	0.54	47	<0.3	6.93	400	81.3
8	4.8	8,350	1,340	119,000	11	12.4	503	2.39	20	40	364	119	0.66	212	18.06	316.8	1,040	18.2
9	6.42	10,900	1,360	202,000	36	10.9	147	4.23	9	15	172	136	0.44	85	3.68	9.45	460	22.7
10	4.74	7,830	1,290	153,000	53	-	508	53.84	14	24	284	122	0.67	312		<0.3	790	-
11	3.82	6,790	1,360	144,000	19	13.1	393	24.99	11	17	207.44	142	0.47	69.12	1.98	3.86	750	-
12	6.38	11,760	1,510	208,000	22	14.6	-	0.55	6	17	-	126	0.58	-	-	-	520	-
13	3.29	6,270	1,290	123,000	15	-		3.64	9	17	-	136	0.47	-	-	-	210	67.1
14	5.98	6,010	830	316,000	80	19.8	711	58.2	11	20	311	124	0.64	72	1.94	3.09	550	26.9
15	1.49	4,060	1,400	187,000	11	13.6	306	0.58	22	21	175.64	127	0.57	73.95	1.19	<0.3	440	-
16	3.8	8,000	1,550	285,000	16	13.2	-	1.02	11	25		134		-	-	2.08	1,610	-
17	5.5	7,610	1,090	216,000	6	-	-	57.2	24	6	427	130	0.42	69	-	-	1,690	-
18	8.6	9,770	920	168,000	63	12.1	-	15.1	22	12	-	141		-	-	-	1,630	-
19	8.3	13,470	1,350	111,000	2	16.7	105	4.5	11	27	365	130	0.54	246	-	-	8,580	-
20	3	12,360	2,820	236,000	31	13.3	-	6.5	8	13		127	0.43	-	-	-	410	-
21	5.7	5,880	830	122,000	33	11.9	-	59.4	32	57	283	128	0.5	-	1.48	<0.3	810	-

(-)*: Patient data not available, NLO*: Neutrophil lymphocyte ratio; GFR**: Glomerular filtration rate

symptoms in patients were reported to be cough (33.4%) and myalgia (31.5%), followed by dyspnea (18.8%), dry throat (15.6%), fever (13.3%), headache (12.2%), anosmia (12%), dysgeusia (8.6%), diarrhea (3.9%), and chest pain (2.2%).

Shmakov et al. (5) prospectively evaluated 66 pregnant patients and 46 newborns with PCR-confirmed COVID-19. In the study, the major clinical symptoms in the patients were detected to be cough (51.5%), anosmia (34.9%), and hyperthermia (33.3%).

In this study, the most common symptoms in the patients were found to be cough (47.6%), fatigue (38.1%), sore throat (28.4%), and dyspnea (23.8%), followed by headache, joint pain, and diarrhea (4.7%). Yet, there was no loss of taste and/or the inability to smell in any of the patients.

The physical examinations of the participants yielded a fever of 37.4 °C and above in 14.2% and rales in 4.76%. Moreover, tachycardia and hypotension were present in 38% and 4.76% of the patients, respectively. On the other hand, Sahin et al. (3) reported tachycardia (28.1%), fever (13.3%), tachypnea (3.4%), and low oxygen saturation (2.8%; ≤ 93%) in the physical examinations of their patients.

In this study, the laboratory findings yielded lymphopenia in 6 patients, higher CRP values in 13 patients, and excessive D-dimer values (above 1000) in 6 patients. Moreover, AST in one patient and ALT in three patients were above reference values. Shmakov et al. (5) reported the laboratory findings of their patients as increased lactate dehydrogenase (LDH), creatinine, D-dimer, and C-reactive protein (CRP) values, anemia, and leukopenia. In the same study, spontaneous abortion was reported in 6.1% of the patients. The mean weight of newborns was found to be 3283±477 g., and no COVID-19 infection was diagnosed in any of the newborns. In another study, nine pregnant women with PCR-confirmed COVID-19 pneumonia were retrospectively evaluated at Wuhan University in China. Accordingly, five patients had lymphopenia, and three had elevated aminotransferase enzyme levels. None of the patients developed severe pneumonia or death, and the newborns were all alive. Amniotic fluid, cord blood, newborn throat swab, and breast milk samples from six patients were tested for COVID-19, and no infection was detected in any of the samples. The study also reported that the clinical features of COVID-19 pneumonia in the pregnant were similar to non-pregnant adult patients with COVID-19 pneumonia (11).

In this study, all patients were followed up in the wards, and none of the patients required imaging tests (PA chest X-ray, computed tomography) due to

pregnancy. In their study, Sahin et al. (3) hospitalized 297 (55.7%) of 533 pregnant patients with COVID-19 and detected suspicious lesions in the radiological imaging of 39 (7.3%) patients. While 261 (49%) of the patients received treatment for COVID-19, 509 (95.5%) had a mild course, 7 (1.3%) were followed up in the intensive care unit, and two patients required mechanical ventilation. Maternal mortality developed in 2 (0.4%) cases, and 66 patients developed the following complications: preterm delivery (4.1%) and miscarriage (2.2%). In the same study, the rate of cesarean section was determined to be 66.4%, while the PCR test for COVID-19 was found to be negative in all newborns, and COVID-19 was reported in only one mother's breast milk sample. The authors recruited 261 (48.9%) patients for treatment for COVID-19 and 33 (6.2%) for pregnancy-specific treatment (tocolytic agents, antenatal corticosteroids, etc.). In this study, low molecular weight heparin was administered to 220 (41.3%) patients; 55% (10.3%) of the patients were treated with chloroquine, 33 (6.2%) received lopinavir-ritonavir, and 17 (3.2%) received azithromycin, and 6 (1.1%) had favipiravir.

In the present study, the clinical course was determined to be severe in one patient, moderate in 6 patients, and mild in 14 patients. The diagnosis was decided upon RT-PCR test positivity, and no mortality occurred in any of the patients.

Only one patient was followed up in the intensive care unit because of her tachypnea and SpO_2 value of 78. After supplement therapy (oxygen and low-molecular-weight heparin), the patient completely recovered. Intrauterine death occurred in the infant of a 27-year-old pregnant woman in her 27th week of pregnancy, and the pregnancy was terminated by cesarean section. Yet, a definitive conclusion could not be reached as to whether the infant loss was associated with COVID-19. No health-related problems were detected in other patients and newborns. In this study, we started chloroquine in six patients, ritonavir (50 mg) and lopinavir (200 mg) combination in four, and favipiravir in one patient in the postpartum period.

The previous findings of screening for pregnant patients yielded about 15% SARS-CoV-2 positivity (1,2). Although the pregnancy was not reported as a risk factor for COVID-19, it should be noted that symptoms and clinical findings may be severe due to physiological and immunological changes during pregnancy. In a study in which more than 90,000 patients with COVID-19 were screened in the United States, it was reported that the rates of hospitalization in the intensive care unit and intubation in pregnant patients were significantly higher than those in non-pregnant patients (2, 6).

In the COVID-19 treatment of the pregnant, the adult treatment guideline of the Ministry of Health released in July 2020 recommended that chloroquine and lopinavir/ritonavir combination and favipiravir could be used in severe cases (7). In this study, drug-related side effects did not develop in any of the patients and newborns who were started on drug therapy for COVID-19, according to the treatment guideline above. Recent randomized controlled studies have shown that chloroquine has no help in COVID-19 treatment (2, 8). Although the lopinavir/ritonavir combination used in the treatment of HIV in pregnant COVID-19 patients was reported to be safe, subsequent studies documented that it was ineffective in the treatment. In contrast, it might cross the placenta and, thus, increase the risk of premature birth. In addition, insufficient evidence was reported regarding the efficacy and safety of remdesivir, one of the antiviral drugs recommended for the treatment of the pregnant with COVID-19 (9). The literature also hosts studies indicating an increased risk of thromboembolism in pregnant COVID-19 patients. Therefore, routine thromboprophylaxis is often recommended for hospitalized pregnant patients with no contraindications (severe thrombocytopenia or bleeding) (1,2,5,10). In this study, low-molecular-weight heparin therapy was administered to all patients for thromboembolism prophylaxis according to findings of D-dimer values and glomerular filtration rates.

In the study, nine patients had a cesarean section, and 12 had a normal delivery. During the follow-ups, intrauterine death developed in one of the patients at the 27th week of pregnancy. Since any microbiological tests or autopsy could not be performed for the diagnosis of the dead newborn, it could not be concluded whether intrauterine death was associated with COVID-19. The mean birth weight of 14 newborns followed up after birth was 2,815 g (max=3,460 g and min=2,200 g), but two of them (14.2%) had low birth weight (< 2,500 g). No postnatal pathological findings and no complications were detected in the newborns. In a study with 125 pregnant women from Turkey, the rates of cesarean delivery, prematurity, and low birth weight were reported as 71.2%, 26.4%, and 12.8%, respectively. In this study, 8 (6.4%) of the COVID-19-positive patients were treated with mechanical ventilation, but six patients (4.8%) died. Most of the newborns were followed up in the neonatal intensive care unit, and RT-PCR positivity was detected in 4 (3.3%) of 120 newborns (4).

The previous research reported pregnancy-related adverse events such as pneumonia and preterm delivery among the pregnant with coronavirus, including COVID-19. Moreover, it was discovered that COVID-19 infection is associated with higher rates of preterm birth, fetal distress, preeclampsia, cesarean section, and perinatal death

among the pregnant (3, 10). However, there is no evidence of vertical transmission from the mother with COVID-19 to the infant (11, 12). In this study, only one patient was followed up in the ICU without being connected to a mechanical ventilator, and this patient recovered following oxygen and low-molecular-weight heparin treatment. Besides, the newborn had a low birth weight (1,750 g) in this patient undergoing cesarean delivery.

A meta-analysis study reported that COVID-19 infection in the pregnant to be often asymptomatic. Severe and critical illness rates were found to be similar to those in the general population (13).

Another meta-analysis reported that the incidence of symptoms (e.g., fever, shortness of breath, and muscle pain) becomes lower in the pregnant with COVID-19 applying to a healthcare institution for any reason. In contrast, the same study revealed that the pregnant might have higher rates of ICU admission or the need for invasive ventilation. Moreover, pre-existing comorbidities, non-Caucasian ethnicity, chronic hypertension, older maternal age, and increased body mass index were determined to be the risk factors for severe COVID-19 in pregnancy. In addition, pregnant women with COVID-19 infection are more likely to give birth prematurely than those without COVID-19. In turn, the newborns of pregnant COVID-19 patients are more likely to be admitted to the neonatal unit than those without COVID-19 (14).

The American Society of Obstetrics and Gynecology has published guidelines recommending that the pregnant be vaccinated against COVID-19 since the relevant research reported COVID-19 vaccines to be highly safe during pregnancy (15).

mRNA or inactivated vaccines administered during pregnancy are relatively safe. In addition, initial teratogenicity research on COVID-19 vaccines in animal models showed no adverse effects on embryonic and fetal development or reproduction (16).

In Turkey, the Ministry of Health recommends inactivated or mRNA vaccines against COVID-19 to the pregnant. Yet, none of the pregnant in this study were vaccinated at the time of the study.

The present study is not free of a few limitations. Since it employed a retrospective design, some data of the patients could not be reached. Moreover, sampling was not performed for RT-PCR tests for COVID-19 in newborns. Finally, long-term follow-up data on the patients were lacking.

Overall, it is thought that close follow-ups for the pregnant are needed to minimize complications that may develop in them and their fetuses due to COVID-19 infection.

CONCLUSION

The COVID-19 vaccine seems to be a must for the pregnant to prevent all possible COVID-related complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of The Ministry of Health and the Ethics Committee of Ankara Training and Research Hospital granted ethical approval to this study (Date: 09.29.2021, Decision No: E-21-667).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

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Evaluation of the measurement of tendon and ligament thicknesses and the presence of enthesitis in lower extremities in female patients with acne vulgaris: a randomized controlled trial

Akne vulgarisli kadın hastalarda tendon ve bağ kalınlıkları ölçümünün ve alt ekstremitelerde entezit varlığının değerlendirilmesi: randomize kontrollü bir çalışma

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ABSTRACT

Aim: Acne Vulgaris (AV) is a multifactorial disease which affects young population and is most common in adolescents. There are no studies in the literature invastigating the presence of enthesitis and lower extremity tendons and ligaments thicknesses in patients with AV. To investigate the presence of enthesitis and to evaluate the tendon and ligament thicknesses in lower extremities in patients with AV.

Material and Method: Thirty patients with a diagnosis of AV and 18 healthy participants, were included. Acne severity was determined with the Global Acne Grading System (GAGS). A single radiologist performed ultrasonographic evaluation with respect to Glasgow Ultrasonographic Enthesitis Scoring System (GUESS). Measurement were done on quadriceps tendons, patellar tendons, Achilles tendons and plantar fascias of the bilaterally lower extremity.

Results: Age, body mass index, alcohol usage and smoking were similar between groups. GUESS score was similar in both group. Proximal patellar ligaments, distal patellar ligaments, Achilles tendons and plantar fascias thicknesses were significantly increased in dominant and non-dominant legs in patients with AV ($p<0.05$).

Conclusion: This study suggest that AV may lead to increase leg tendons and ligaments' thicknesses.

Keywords: Acne vulgaris, enthesitis, GUESS score

ÖZ

Amaç: Akne Vulgaris (AV), genç popülasyonu etkileyen ve en sık ergenlerde görülen multifaktöriyel bir hastalıktır. Literatürde AV'li hastalarda entezit varlığını ve alt ekstremite tendon ve bağ kalınlıklarını araştıran çalışma yoktur. AV'li hastalarda entezit varlığını araştırmak ve alt ekstremite tendon ve bağ kalınlıklarını değerlendirmek.

Gereç ve Yöntem: Çalışmaya AV tanılı 30 hasta ve 18 sağlıklı katılımcı dahil edildi. Akne şiddeti Global Acne Grading System (GAGS) ile belirlendi. Glasgow Ultrasonografik Entezit Skorlama Sistemine (GUESS) göre tek bir radyolog ultrasonografik değerlendirme yaptı. Ölçümler bilateral alt ekstremite kuadriseps tendonları, patellar tendonlar, aşil tendonları ve plantar fasyalardan yapıldı.

Bulgular: Gruplar arasında yaş, vücut kitle indeksi, alkol kullanımı ve sigara kullanımı benzerdi. GUESS skoru her iki grupta benzerdi. AV'li hastalarda dominant ve nondominant bacaklarda proksimal patellar ligaman, distal patellar ligaman, aşil tendonu ve plantar fasya kalınlıkları anlamlı olarak artmıştı ($p<0.05$).

Sonuç: Bu çalışma AV'nin bacak tendon ve bağ kalınlıklarında artışa yol açabileceğini düşündürmektedir.

Anahtar Kelimeler: Akne vulgaris, entezit, GUESS skor

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INTRODUCTION

Acne vulgaris (AV) is a multifactorial disease which affects pilosebaceous unit and 85% of the young population and is most common in adolescents (1). Abnormal follicular keratinization, excessive sebum production, bacterial colonization of Propionibacterium acnes (P. acnes) are involved in the pathogenesis of AV. It is believed that p. acnes are involved in the information of the inflammatory response (1). P. acnes activates the CD4+ lymphocytes and Toll like receptor-2 (TLR-2) on the monocytes by damaging the follicular wall (1). Thus IL-8 and similar proinflammatory cytokines are released. Also, other cytokines such as IL-1α, IL-1β and IL-17 are also released (1). In some studies, it was shown that p. acnes is a powerful stimulant of CD4+ T cells for releasing IFN-γ and IL-17 (2). Additionally, in biopsies of inflammatory acne lesions, IL-17 + cells were found in the perifollicular infiltrate. Therefore, it was thought that acne vulgaris may be a Th-17- related disease (2). It is known that the cytokines IL-17, IL-22, IL-23 and TNF- α play an active role in the formation mechanism of enthesis (3). The presence of enthesitis has also been shown in some syndromes accompanied by acne vulgaris such as SAPHO, psoriasis and Behcet's disease (4). So patients with AV may be susceptible to the development of enthesis. We aimed to evaluate the presence of enthesitis and the measurement of tendon and ligament thicknesses in legs in patients with AV in this study.

MATERIAL AND METHOD

The study was planned as randomized controlled study. This study was carried out with the permission of Hitit University, Clinical Researches Ethic Committee (Date: 11.12.2019, Desicion No: 131). Among the participants with AV who applied to the dermatology outpatient clinic, those with a single line were included in the study. Thirty patients who admitted to Dermatology clinic with a diagnosis of AV and eighteen healthy controls, were included to the study (5). The number of participants was determined by power analysis with 80% power and 0.5% standard error (5). Participants with concominant rheumatic and neurological diseases, psoriasis, acne rosacea, history of trauma, orthopedic surgery, other systemic diseases such as diabetes mellitus, hypothyroidism and hyperthyroidism, obese participants were excluded. Demographic and clinical characteristics, patients' acne type, duration and medications were recorded.

Acne severity was evaluated with the Global Acne Grading System (GAGS) (6). It divides the face, chest, and upper back into 6 regions: the forehead, right/left cheek, nose, chin and torso. Comedos (1 point), papules (2 points), pustules (3 points), and nodules (4 points) record. Absence of a lesion has a score of 0 points. The local score for each anatomic area is determined by multiplying the score of the most severe lesion by an area factor (one-three).The local scores of the 6 regions are summed to obtain the total score. Acne severity is graded as non (0 points), mild (1-18 points), moderate (19-30 points) severe (31-38 points) and very severe (total score >38 points) (7).

Ultrasonographic Measurement

A single radiologist, who had considerable experience on musculoskeletal ultrasonography (US) and blinded to the participant's group assignment, performed ultrasonographic evaluation used a multi-frequency linear probe (5-12 MHz for knees and 12-18 for feet; Toshiba Applio 500). While obtaining images, a generous amount of water-soluble gel was applied between the transducer and the skin to aid acoustic coupling and to avoid compression or deformation of the muscle fibres. Ultrasonographic measurement was performed after a period of rest 30 minutes. US grey scale was used for tendon thickness, echogenity calcifications, enthesophytes, bursitis and erosions. Glasgow Ultrasonographic Enthesitis Scoring System (GUESS) was used for evaluating the enthesis areas (8). Examination of the superior pole of the patella (the insertion of quadriceps tendon), the inferior pole of the patella (the origin of patellar ligament), and the patellar ligament insertion at the tibial tuberosity was performed with the participants in the supine position with the knee flexed at 30 degrees (8). The Achilles tendon and the plantar aponeurosis were performed with the participants lying prone with the feet hanging over the edge of the examination table at 90 degrees of flexion (8). For each areas with an increase of tendon thickness, the presence of enthesophyte, bursitis or erosion was scored as 1 point. The minimum total score was 0 point and the maximum total score was 36.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) 16.0 program for Windows. Visual and analytical methods were used to determine whether or not variables were normally distributed. Continuous values were expressed as mean ± standard deviation (SD). Chi Square test and Fisher Exact test were used to compare nominal values. Independent sample t-test was used for comparison of normally distributed data, and the Mann-Whitney U test was used for comparison of non-normally distributed data. Pearson and Spearman correlation coefficients was used to investigate correlation between patient's characteristics and clinical parameters. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Age, body mass index, alcohol usage and smoking were similar between groups (**Table 1**). Disease characteristics of acne vulgaris were summerized in **Table 2**. Acne vulgaris duration was 4±2.30 years in patients with acne vulgaris. Previously, 29 patients used topical treatment, 8 patients used systemic antibiotherapy and 3 patients used isotretinoin (**Table 2**). There was non-inflammatory acne vulgaris in 16 patients with AV and inflammatory acne vulgaris in 30 patients with AV (**Table 2**). GAGS score was 19.5±5.78 in patients wİth AV (**Table 2**).

Table 1. Demographic and clinical characteristics of participants

	Patients with AV n= 30	Control group n= 18	p value
Age (years)	20 (19-22)	22.5 (20-25)	0.051
Weights (kg)	58.8±7.43	62.27±5.92	0.095
Heights (cm)	163.5±6.25	165.8±4.22	0.159
Body mass index	21.98±2.5	22.58±1.43	0.298
Alcohol use (n, %)	0	1 (5.6%)	0.375
Smoking (n,%)	3 (10%)	4 (22.2%)	0.400
Guess score	0 (0-0)	0 (0-0)	0.366

AV: Acne Vulgaris, GUESS: Glasgow Ultrasound Enthesitis Scoring System)
Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 2. Disease characteristics of acne vulgaris patients

	Patients with acne vulgaris n= 30
Acne duration (year)	4±2.30
Patients received treatment (n, %)	28 (93.3%)
Types of treatment (n, %)	
Topical	29 (96.7%)
Systemic antibiotherapy	8 (26.7%)
isotretinoin	3 (10%)
Types of acne vulgaris (n,%)	
Non-inflammatory	16 (53.3%)
İnflammatory	30 (100%)
Nodulocyctic	0
Truncal	0
Presence of scar (n,%)	30 (100%)
Types of scar (n, %)	
Macule	16 (53.3%)
Atrophic	14 (46.7%)
Hypertrophic	0
GAGS Score	19.5±5.78
Acne severity (n, %)	
Non	0
Mild	10 (33.3%)
Moderate	20 (66.7%)
Severe	0
Very severe	0

GAGS: Global Acne Grading System, Data are presented as the mean ± standart deviation for data normally distributed or n (%) for categoric values.

All participants were right dominancy. GUESS score was similar in both group (**Table 1**). Proximal patellar ligaments, distal patellar ligaments, Achilles tendons and plantar fascias thicknesses were significantly increased bilaterally in AV patients (**Table 3**, **4**). There was no significant difffence in quadriceps tendons thicknesses between groups in bilateral legs (**Table 3**, **4**). A significant correlation was found between quadriceps tendon thickness and weight in dominant and non dominant leg in AV patients(r=0.497 p<0.001 and r=0.398 p<0.05 respectively). There was no correlation between age, weight, height, body mass index and other tendon thicknesses in AV patients (**Table 5**). A significant correlation was found between weight, height, body mass index and quadriceps tendon thickness in dominant and non-dominant legs in healthy controls (**Table 6**). Also, in dominant leg there was a correlation between height and proximal patellar ligament thickness in healthy controls (r=0.531 p<0.05).

Table 3. Tendon thicknesses and GUESS scores of the participants in dominant leg.

	Patients with AV n= 30	Control group n= 18	p value
Quadriceps tendon thickness (mm)	5.22±0.67	4.86±0.60	0.068
Proximal patellar ligament thickness (mm)	3.36±0.38	2.95±0.53	0.003
Distal patellar ligament thickness (mm)	3.50 (3.35-3.72)	3 (2.67-3.35)	0.001
Achilles tendon thickness (mm)	3.98±0.41	3.60±0.53	0.008
Plantar fascia thickness (mm)	2.96±0.42	2.49±0.46	0.001

AV: Acne Vulgaris, Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 4. Tendon thicknesses and GUESS scores of the participants in non-dominant leg.

	Patients with AV n= 30	Control group n= 18	p value
Quadriceps tendon thickness (mm)	5.19±0.67	4.82±0.60	0.063
Proximal patellar ligament thickness (mm)	3.31±0.39	2.91±0.52	0.005
Distal patellar ligament thickness (mm)	3.4 (3.17-3.62)	3 (2.67-3.35)	0.003
Achilles tendon thickness (mm)	3.98±0.41	3.57±0.50	0.004
Plantar fascia thickness (mm)	2.96±0.41	2.5±0.44	0.001

AV: Acne Vulgaris, Data are presented as the mean ± standart deviation for data normally distributed or median (25-75%) for data not normally distributed. p< 0,05

Table 5. Correlation between age, height, weight, body mass index and tendon thicknesses in patients with AV.

	Age	Height	Weight	Body mass index
Dominant leg				
Quadriceps tendon thickness	-0.180[1]	0.178[2]	0.497**[2]	0.358[2]
Proximal patellar ligament thickness	-0.185[1]	0.255[2]	0.270[2]	0.148[2]
Distal patellar ligament thickness	-0.096[1]	0.104[1]	0.266[1]	0.147[1]
Achilles tendon thickness	-0.011[1]	0.271[2]	0.214[2]	0.129[2]
Plantar fascia thickness	0.012[1]	0.085[2]	0.139[2]	0.111[2]
Non-dominant leg				
Quadriceps tendon thickness	-0.180[1]	0.151[2]	0.398*[2]	0.339[2]
Proximal patellar ligament thickness	-0.244[1]	0.215[2]	0.199[2]	0.065[2]
Distal patellar ligament thickness	-0.317[1]	0.104[1]	0.266[1]	0.147[1]
Achilles tendon thickness	-0.017[1]	0.219[2]	0.253[2]	0.108[2]
Plantar fascia thickness	0.028[1]	0.089[2]	0.169[2]	0.120[2]

1: Spearman, 2: Pearson, *: p<0.05, **:p <0.001

Table 6. Correlation between age, height, weight, body mass index and tendon thicknesses in healthy controls.

	Age	Height	Weight	Body mass index
Dominant leg				
Quadriceps tendon thickness	-0.086[1]	0655**[2]	0.640**[2]	0.507*[2]
Proximal patellar ligament thickness	-0.340[1]	0.531*[2]	0.340[2]	0.143[2]
Distal patellar ligament thickness	-0.369[1]	0.366[1]	0.209[1]	-0.59[1]
Achilles tendon thickness	-0.351[1]	0.302[2]	0.071[2]	-0.118[2]
Plantar fascia thickness	-0.168[1]	0.379[2]	0.307[2]	-0.201[2]
Non-dominant leg				
Quadriceps tendon thickness	-0.114[1]	0.649**[2]	0.630**[2]	0.494*[2]
Proximal patellar ligament thickness	-0.345[1]	0.507*[2]	0.321[2]	0.134[2]
Distal patellar ligament thickness	-0.367[1]	0.398[1]	0.251[1]	-0.019[1]
Achilles tendon thickness	-0.287[1]	0.282[2]	0.066[2]	-0.108[2]
Plantar fascia thickness	-0.157[1]	0.353[2]	0.257[2]	0.146[2]

1: Spearman, 2: Pearson, *: p<0.05, **:p <0.001

DISCUSSION

In this study, some lower extremity tendon and ligament thicknesses were found increased in bilateral legs in AV patients compared to healthy controls. We did not found increased GUESS score in AV patients. Additionally, we did not found any enthesitis in patients with acne vulgaris. This is the first study which invastigated the relationship between acne vulgaris and the presence of enthesitis and tendons and ligaments thicknesses in lower extremities in the literature.

The causes of enthesopathy is the inflammation of tendons, ligaments or capsules' insertion into the bone. It is one of the most common findings in patients with spondyloarthritis. In murine models, TNFα or IL-23/17 pathway dysregulation was showed which leads to inflammation and plays important role for enthesitis in spondyloarthropathy pathogenesis (9-12). Recent studies showed that anti-IL-17A therapy is effective in ankylosing spondylitis (13,14).

In the literature, there are some studies demonstrating that the presence of IL-17A+ cells, in acne lesions that appear clinically early. Activations of cytokines, chemokines and antimicrobial peptides are typical for the Th17/IL-17 pathway (15). Th1, Th17 and CD8+ activation and neutrophil attraction with IL-17-related chemokine production may be important factors in the pathogenesis of AV (15) . Ebrahim et al. (16) showed higher serum IL-17 level in AV patients and it was associated with disease severity. They thought that IL-17 could be a potential prognostic predictor for severity and scarring in AV.

Since we know that IL-17 plays a role in both AV and enthesopathy pathogenesis, we found that it is valuable to evaluate the enthesis site by ultrasonography in patients with AV. In our study, proximal patellar tendons, distal patellar tendons, Achilles tendons and plantar fascias' thicknesses were significantly increased in both extremity in AV patients compared to healthy controls. But we found similar GUESS scores between AV patients and healthy controls. So we could comment that AV may be a predisposing factor for enthesitis development. In our study, all participant were young adults. Also, all patients had mild or moderate acne severity. If patients had a long duration of AV or had severe AV, perhaps enthesitis could be detected. For invastigating the relationship between AV and enthesopathy, prospective controlled studies are needed.

Hatemi et al. (17) found that Behçet's disease with acne and arthritis had increased presence of enthesopathy compared to Behçet's disease without arthritis. So acne vulgaris may contribute to the development of enthesopathy. Also there are some studies showing that the using isotretinoin can cause the development of sacroileitis (18). Altan et al. (19) invastigated the isotiretinoin-related spondyloarthropathy symptoms and they found unilateral Achilles enthesopathy in 3 patients and unilateral sacroileitis in 1 patient. They found the spondyloarthropathy findings in 23.1% of the patients who used isotretinoin. If AV is predisposing

to the development of enthesopathy, it will be valuable to evaluate the presence of enthesopathy when starting isotretinoin in patients with AV. In our study, there were only 3 patients with acne vulgaris who used isotretinoin before. In these patients, we did not found any enthesopathy.

This study has some limitations. Because of the cross-sectional design of the study, the changes of tendons and ligaments thicknesses in course of time remains unclear. Also we did not evaluate the physical activity levels of the participants. Tendon and ligament thickness can be affected by exercise and physical activity. In case-control studies, including more than one participant in the control group for each participant in the case group will increase the power of the study. Therefore, the small number of participants in the control group can be accepted as one of the limitation of the study.

CONCLUSION

This study suggest that AV may lead to increase in thickness of leg tendons and ligaments. To our knowledge, this is the first study to examine ultrasonographic findings of lower extremities' tendons and ligaments among the AV patients. Further prospective studies are needed that examine the relationship between Acne vulgaris and enthesopathies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University, Clinical Researches Ethics Committee (Date: 11.12.2019, Desicion No: 131). This study was registered to ClinicalTrials.gov with the number of NCT04224597.

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Twenty-year analysis of the rarely diagnosed nutcracker syndrome

Nadir görülen nutcracker sendromunun yirmi yıllık analizi

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ABSTRACT

Aim: Nutcracker syndrome is a very rare cause in patients presenting to the emergency department with abdominal pain. Early consideration in differential diagnosis will reduce the time spent for diagnosis and morbidity, as well as provide the correct treatment. We aimed to contribute to the literature by determining the clinical relations of these cases with laboratory, imaging and treatment data.

Material and Method: Twenty-seven patients over the age of 16 who presented to the emergency department with abdominal pain between January 2000 and December 2020 were included in this study. The ages of the patients were between 16-39 and the mean was 25.19±7.00 years. Demographic characteristics, clinical findings, laboratory parameters, radiological evaluations, and treatment modalities of patients were evaluated retrospectively.

Results: Abdominal pain and flank pain were the most common reasons for admission to the emergency department of 27 patients included in the study. In the anterior group, 17 (77%) patients had flank pain, 10 (45%) patients had dysmenorrhea, 11 (50%) hematuria, 10 (45%) proteinuria, and 9 (40%) patients hematuria and proteinuria. In the posterior group, there was no hematuria, proteinuria, anorexia, nausea and vomiting, and oral intolerance. In cases with anteior nutcracker syndrome, 12 (54%) doppler ultrasonography, 13 (59%) computed tomography, 5 (22%) magnetic resonance imaging were performed. Conservative treatment was applied to 11 (40%) patients in the anterior group and 3 (11%) patients in the posterior group. Endovascular surgery was performed on 5 (22%) female patients.

Conclusion: Nutcracker syndrome should be investigated in adult patients who present to the emergency department with abdominal pain and whose diagnosis is unclear. Early diagnosis is critical in terms of treatment and morbidity.

Keywords: Emergency department, abdominal pain, nutcracker syndrome, hematuria, proteinuria

ÖZ

Amaç: Acil servise karın ağrısı ile başvuran hastalarda nutcracker sendromu çok nadir ortaya çıkan bir nedendir. Ayırıcı tanıda erken dönemde akla getirilmesi, hastanın tanı için geçirdiği süreyi ve morbiditeyi azaltacağı gibi, doğru tedaviyi uygulamayı da sağlayacaktır. Literatür eşliğinde bu olguların değerlendirilmesi amaçlandı.

Gereç ve Yöntem: Bu çalışmaya, Ocak 2000-Aralık 2020 tarihleri arasında acil servise karın ağrısı nedeniyle başvuran 16 yaşından büyük 27 hasta dahil edildi. Hastaların yaşları 16 ile 39 arasındaydı ve ortalaması 25.19±7.00 yıldı. Bu hastaların demografik özellikleri, klinik bulguları, laboratuar parametreleri, radyolojik değerlendirmeleri ve tedavi şekilleri retrospektif olarak değerlendirildi.

Bulgular: Çalışmaya dahil edilen 27 olgunun acil servise en sık başvuru nedeni karın ağrısı ve yan ağrısıydı. Anterior grupta 17 (%77) hastada yan ağrısı, 10 (%45) hastada dismenore mevcutken, 11 (%50) hematüri, 10 (%45) proteinüri ve 9 (%40) hematüri ve proteinüri olgusu vardı. Posterior grupta hematüri, proteinüri, iştahsızlık, bulantı ve kusma ve oral intolerans yoktu. Anterior nutcracker sendromu grubunda 12 (%54) Doppler ultrasonografi, 13 (%59) bilgisayarlı tomografi, 5 (%22) manyetik rezonans görüntüleme yapıldı. Anterior grupta 11 (%40) hastaya, posterior grupta 3 (%11) hastaya konservatif tedavi uygulandı. 5 (%22) kadın hastaya endovasküler cerrahi uygulandı.

Sonuç: Erişkin dönemde acil servise karın ağrısıyla başvurun ve tanısı geciken olgularda nutcracker sendromu düşünülmelidir. Erken tanı değerlendirmesi; tedavi ve morbidite açısından önem taşımaktadır.

Anahtar Kelimeler: Acil servis, karın ağrısı, nutcracker sendromu, hematüri, proteinüri

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INTRODUCTION

In 1950, El Sadr and Mina demonstrated that the left renal vein was compressed between the abdominal aorta and superior mesenteric artery (1). De Schepper provided Nutcracker syndrome (NCS) its name in 1972 (2). It is characterized by compression of the left renal vein, however there are anatomical variants. At this level, it is defined as the narrowing of the left renal vein due to external compression and dilatation due to pressure increase before this segment. It is rarely diagnosed because there are no clear diagnostic criteria, the symptoms can show up in different ways, and it is not in the list of possible diagnoses. The Nutcracker Phenomenon defines the morphological findings due to compression of the left renal vein. It differs from NCS by the absence of clinical findings of the patient (3).

In the classification, NCS is defined in two main groups as anterior and posterior. The more prevalent anterior variant is caused by compression of the left renal vein between the aorta and the superior mesenteric artery (SMA). The posterior variant is rarer and results from compression of the retro aortic left renal vein between the aorta and vertebrae (4).

The most important point in diagnosis is to suspect this syndrome. In the laboratory, hematuria and proteinuria are directive findings. The imaging method to be preferred first is doppler ultrasonography (DUS), and retrograde venography is the gold standard in diagnosis. However, its invasiveness restricts its practical application. Other examinations include computed tomography (CT) angiography and magnetic resonance imaging (MRI) angiography (5). Treatment options are determined by the severity of the symptoms and include conservative and various surgical approaches. Conservative option comes to the fore, especially in children. Surgical methods include open surgery, laparoscopic surgery, and endovascular interventions (6).

In this study, we evaluated at 27 patients who were diagnosed with nutcracker syndrome and analyzed their clinical symptoms, laboratory results, imaging, and treatment options. We aimed to emphasize the clinical importance of the disease and to contribute to the clinical, diagnostic, and treatment management process.

MATERIAL AND METHOD

The study was carried out with the permission of Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.01.2021, Decision No: 2021.01.1.01.001). All procedures complied with the ethical norms of the institutional and national committees responsible for human experiments and the Helsinki Declaration.

Due to the retrospective design of the investigation, no written informed permission forms were acquired from patients. The corresponding author certifies, on behalf of all authors, that there are no conflicts of interest.

Study Design and Population

Patients diagnosed with NCS admitted to the emergency department between January 2000 and December 2020 were retrospectively analyzed using the electronic medical archive system. Patients older than 16 years old who presented to the emergency department due to abdominal pain and were diagnosed with NCS were included in the study. Patients' age, gender, clinical symptoms and physical examination findings, laboratory and radiological imaging findings, affected sides, surgical findings, methods, procedures, and examination results were recorded.

The cases were grouped as anterior nutcracker syndrome (ANCS) and posterior nutcracker syndrome (PNCS). The patients' white blood cell (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV), neutrophil (NEU), lymphocyte (LYM), neutrophil/lymphocyte ratio (N/L), glucose (GLC), alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase (CK), gamma glutamyl transferase (GGT) C-Reactive Protein (CRP) values were determined. Clinical symptoms and findings were grouped as side pain, abdominal pain, hematuria, proteinuria, hematuria+proteinuria (HP), side pain+hematuria (SPH), side pain + hematuria + proteinuria (SPHP), varicocele, pelvic congestion, dyspareunia, dysmenorrhea, intolerance, dyspepsia, anorexia, nausea, vomitting, weight loss. The cases were classified as renal doppler ultrasonography (RDUS), computed tomography, magnetic resonance imaging, retrograde venography (RV) according to imaging methods. Treatment conditions were grouped as conservative, surgical, and endovascular.

Statistical Analysis

The data obtained from the study were collected from the hospital's electronic archive system. This study's data were analyzed using the SPSS 20 (SPSS Inc., Chicago, IL, USA) software platform. Descriptive statistics were presented as mean±standard deviation or median (minimum-maximum) for continuous variables and as the number of cases and percentage (%) for nominal variables. Other data were analyzed using Microsoft Excel and simple descriptive statistics.

RESULTS

The study included 27 patients diagnosed with NCS. Sixteen of the patients were female and 11 were male. The ages of the patients were between 16 and 39 and the mean age was 25.19±7.00 years. Of the 22 ANCS patients, 14 were female, the mean age was 25.50±7.44 years, while two of the five PNCS patients were female and the mean age was 23.80±5.02 years. ANCS was common in women, while PNCS was common in men. Mean hemogram parameter values of all cases, WBC 9.49±2.95 (10^3/uL), MCV 85.11±10.77 (fl), RDW 14.30±1.22 (%), NEU 7.85±2.48 (10^3/uL), LYM 2.05±0.84 (10^3/uL) µL), and the NLR was 4.95±3.86. The mean biochemistry values are GLC 103.67±13.28 mg/dL, amylase 85.33±19.41 (U/L), ALP 55.89±15.24 (U/L), ALT 23.00±13.99 (U/L), LDH 198.74±35.10 (U/L)), CK 146.41±75.32 (U/L), GGT 34.52±12.01 (U/L), CRP 4.62±2.78 mg/L. The average of all biochemistry values evaluated was within normal limits. In the ANCS group, the neutrophil count was 7.57±2.56 (10^3/UL), NLR was 4.32±2.96, and the creatine kinase was 141.09±71.99 (U/L). In the PNCS group, these values vere 9.07±1.81 (10^3/UL), 7.71±6.27, and 169.80±93.91 (U/L) respectively. In addition, ALP values differed as 57.45±15.55 U/L in ANCS and 49.00±12.92 U/L in PNCS. (**Table 1**).

Side pain was present in 17 (63%) of 22 (81.5%) cases, and in 2 (7.4%) of 5 (18.5%) PNCS cases. Abdominal pain was observed in 15 (55.6%) cases in the ANCS group and in 4 (14.8%) cases in the PNCS. There were 11 (40.7%) hematuria, 10 (37%) proteinuria, 9 (33.3%) HP, 8 (29.6%) SPH, 7 (25.9%) SPHP cases in the ANCS group. Hematuria and proteinuria were not found in any of the PNCS cases. Common complaints were dyspareunia 7 (25.9%), dysmenorrhea 10 (37%), and dyspepsia 11 (40.7%) in the ANCS group. Varicocele, pelvic congestion, dyspareunia, dysmenorrhea, and dyspepsia were observed in 1 (3.7%) case in the PNCS group. Side pain was common in women and abdominal pain in men. Hematuria and proteinuria were observed more frequently in female cases. On the other hand, weight loss was also higher in female cases (**Table 2**).

Table 1. The relationship of nutcracker syndrome subtype and gender groups with baseline characteristics and laboratory values

NCS	All Patients n: 27	NCS Classification		Gender	
		ANCS n:22	PNCS n:5	Female n:16	Male n:11
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Baseline Characteristics					
Age (year)	25.19±7.00	25.50±7.44	23.80±5.02	24.81±7.66	25.73±6.23
Female (n) / Male (n)	16/11	14/8	2/3	-	-
Hemogram Parameters					
WBC (10^3/uL)	9.49±2.95	9.46±3.00	9.62±2.91	10.33±3.15	8.26±2.22
MCV (fL)	85.11±10.77	85.31±11.72	84.20±5.67	87.43±4.15	81.73±15.96
MCH (pg)	30.07±2.44	30.25±1.36	29.26±5.68	30.05±1.50	30.10±1.43
MCHC (g/dL)	33.66±1.29	33.65±1.29	33.72±1.41	33.58±1.35	33.79±1.24
RDW (%)	14.30±1.22	14.12±1.04	15.10±1.72	14.41±1.39	14.14±0.96
MPV (fl)	8.46±0.95	8.31±0.94	9.08±0.78	8.38±1.05	8.57±0.81
NEU (10^3/uL)	7.85±2.48	7.57±2.56	9.07±1.81	8.31±2.71	7.18±2.03
LYM (10^3/uL)	2.05±0.84	2.09±0.79	1.84±1.14	1.83±0.81	2.36±0.83
N/L	4.95±3.86	4.32±2.96	7.71±6.27	5.48±3.36	4.18±4.55
Biochemistry Parameters					
GLC (mg/dL)	103.67±13.28	103.54±13.88	104.20±11.61	104.88±13.42	101.91±13.52
Amylase (U/L)	85.33±19.41	85.82±18.09	83.20±26.94	85.56±24.06	85.00±10.57
ALP (U/L)	55.89±15.24	57.45±15.55	49.00±12.92	57.25±14.36	53.91±16.96
ALT (U/L)	23.00±13.99	23.68±14.96	20.00±9.11	22.75±16.45	23.36±10.11
AST (U/L)	24.15±9.25	24.37±9.83	23.20±6.91	22.94±10.74	25.93±6.62
LDH (U/L)	198.74±35.10	199.23±38.38	196.60±16.38	199.31±43.94	197.91±17.47
CK (U/L)	146.41±75.32	141.09±71.99	169.80±93.91	147.50±67.54	144.82±88.89
GGT (U/L)	34.52±12.01	34.04±11.17	36.60±16.62	36.19±10.11	32.09±14.53
CRP (mg/L)	4.62±2.78	4.51±2.68	5.10±3.49	5.05±2.77	4.00±2.81

NCS: Nutcracker Syndrome ANCS: Anterior Nutcracker Syndrome PNCS: Posterior Nutcracker Syndrome SD: Standart Deviation WBC: White Blood Cell MCV: Mean Corpuscular Volume MCH: Mean Corpuscular Hemoglobin MCHC: Mean Corpuscular Hemoglobin Concentration RDW: Red Cell Distribution Width MPV: Mean Platelet Volume NEU: Neutrophil LYM: Lymphocyte N/L: Neutrophil/Lymphocyte Ratio GLC: Glucose ALP: Alkaline Phosphatase ALT: Alanine Aminotransferase AST: Aspartate AminotransferaseLDH: Lactate dehydrogenase CK: Creatine kinase GGT: Gamma Glutamyl Transferase CRP: C-Reactive Protein

Table 2. Relation of symptoms snd signs with nutcracker syndrome type and gender

NCS	NCS Classification				Gender			
	ANCS		PNCS		Female		Male	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Symptoms And Signs								
Side Pain	17 (63.0)	5 (18.5)	2 (7.4)	3 (11.1)	13 (48.1)	3 (11.1)	6 (22.2)	5 (18.5)
Abdominal Pain	15 (55.6)	7 (25.9)	4 (14.8)	1 (3.7)	14 (51.9)	2 (7.4)	5 (18.5)	6 (22.2)
Hematuria	11 (40.7)	11 (40.7)	0 (0)	5 (18.5)	8 (29.6)	8 (29.6)	3 (11.1)	8 (29.6)
Protoeniuria	10 (37.0)	12 (44.4)	0 (0)	5 (18.5)	7 (25.9)	9 (33.3)	3 (11.1)	8 (29.6)
HP	9 (33.3)	13 (48.1)	0 (0)	5 (18.5)	6 (22.2)	10 (37.0)	3 (11.1)	8 (29.6)
SPH	8 (29.6)	14 (51.9)	0 (0)	5 (18.5)	7 (25.9)	9 (33.3)	1 (3.7)	10 (37.0)
SPHP	7 (25.9)	15 (55.6)	0 (0)	5 (18.5)	6 (22.2)	10 (37.0)	1 (3.7)	10 (37.0)
Varicocele	3 (11.1)	19 (70.4)	1 (3.7)	4 (14.8)	0 (0)	16 (59.3)	3 (11.1)	8 (29.6)
Pelvic Congestion	4 (14.8)	18 (66.7)	1 (3.7)	4 (14.8)	5 (18.5)	11 (40.7)	0 (0)	11 (40.7)
Dyspareunia	7 (25.9)	15 (55.6)	1 (3.7)	4 (14.8)	6 (22.2)	10 (37.0)	2 (7.4)	9 (33.3)
Dysmenorrhea	10 (37.0)	12 (44.4)	1 (3.7)	4 (14.8)	11 (40.7)	5 (18.5)	0 (0)	11 (40.7)
Intolerance	4 (14.8)	18 (66.7)	0 (0)	5 (18.5)	4 (14.8)	12 (44.4)	0 (0)	11 (40.7)
Dyspepsia	11 (40.7)	11 (40.7)	1 (3.7)	4 (14.8)	8 (29.6)	8 (29.6)	4 (14.8)	7 (25.9)
Anorexia	6 (22.2)	16 (59.3)	0 (0)	5 (18.5)	5 (18.5)	11 (40.7)	1 (3.7)	10 (37.0)
Nausea	6 (22.2)	16 (59.3)	0 (0)	5 (18.5)	5 (18.5)	11 (40.7)	1 (3.7)	10 (37.0)
Vomitting	5 (18.5)	17 (63.0)	0 (0)	5 (18.5)	4 (14.8)	12 (44.4)	1 (3.7)	10 (37.0)
Weight Loss	6 (22.2)	16 (59.3)	0 (0)	5 (18.5)	5 (18.5)	11 (40.7)	1 (3.7)	10 (37.0)

NCS: Nutcracker Syndrome ANCS: Anterior Nutcracker Syndrome PNCS: Posterior Nutcracker Syndrome HP: Hematuria + Proteinuria SPH: Side Pain + Hematuria SPHP: Side Pain + Hematuria + Proteinuria

On imaging evaluation, 12 (44.4%) of the ANCS patients had RDUS, 13 (48.1%) had CT, 5 (18.5%) had MRI, 17 (63%) had RDUS and/or CT, and eight had both RDUS and CT, and none of the patients had retrograde venography (RV). While RDUS was performed in all five patients in the PNCS group, none of them had CT. As expected, imaging preference by gender was unrelated and rates were similar. Eleven (40.7%) patients in the ANCS group received conservative treatment, 6 (22.2%) received surgery, and 5 (18.5%) received endovascular therapy. Three (11.1%) patients received conservative treatment in the PNCS group, 1 (3.7%) received surgery, and 1 (3.7%) received endovascular treatment. Six (22.2%) females and 8 (29.6%) males were treated conservatively. Six (22.2%) female patients received endovascular therapy. Three (11.1%) male patients received surgical treatment, but no male patients received endovascular treatment (**Table 3**).

DISCUSSION

Only after alternative causes of hematuria have been ruled out is the diagnosis of NCS considered. The left renal vein is compressed between the aorta and superior mesenteric artery in the anterior NCS, whereas the retroaortic or circumferential renal vein is compressed between the aorta and vertebra in the posterior NCS. It is characterized by the clinical presentation of increased distal pressure. A rupture of thin-walled veins in the renal calyces is the most typical cause of hematuria (3). Other subtypes besides anterior and posterior have been defined. Nakazawa et al. (7) shown that the left-sided larger inferior vena cava compresses the left renal vein. Shah et al. (8) reported a case of left renal vein duplication in which the retro aortic branch was entrapped between the vertebral column and the aorta at the aortic bifurcation. Although the majority of cases

Table 3. Relationship of imaging-therapy status with nutcracker syndrome type and gender

NCS	NCS Classification				Gender			
	ANCS		PNCS		Female		Male	
	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)	Yes n (%)	No n (%)
Imaging								
RDUS	12 (44.4)	10 (37.0)	5 (18.5)	0 (0)	11 (40.7)	5 (18.5)	6 (22.2)	5 (18.5)
CT	13 (48.1)	9 (33.3)	0 (0)	5 (18.5)	8 (29.6)	8 (29.6)	5 (18.5)	6 (22.2)
MRI	5 (18.5)	17 (63.0)	2 (7.4)	3 (11.1)	4 (14.8)	12 (44.4)	3 (11.1)	8 (29.6)
RV	0 (0)	22 (81.5)	3 (11.1)	2 (7.4)	1 (3.7)	15 (55.6)	2 (7.4)	9 (33.3)
RDUS CT	17 (63.0)	5 (18.5)	0 (0)	5 (18.5)	11 (40.7)	5 (18.5)	6 (22.2)	5 (18.5)
Treatment								
Conservative	11 (40.7)		3 (11.1)		6 (22.2)		8 (29.6)	
Surgical	6 (22.2)		1 (3.7)		4 (14.8)		3 (11.1)	
Endovascular	5 (18.5)		1 (3.7)		6 (22.2)		0 (0)	

NCS: Nutcracker Syndrome ANCS: Anterior Nutcracker Syndrome PNCS: Posterior Nutcracker Syndrome RDUS: Renal Doppler Ultrasonography CT: Computed Tomography MRI: Magnetic Resonans Imaging RV: Retrograd Venography

are anterior, it is also crucial to focus on the posterior group. 0.1% to 3.2% of left renal veins are circumaortic or retroaortic (9). Twenty-two of the twenty-seven participants in our study were anterior. Male patients exhibited higher posterior NCS than female individuals. This syndrome may exhibit symptoms in children, adolescents, and adults. In their second and third decades, men are diagnosed earlier than women (10). In a study involving pediatric patients, Çakıcı et al. (11) assessed 41 pediatric patients, of which 68.3% were female. In a separate study conducted by Orczyk et al. (10), 112 cases were analyzed, the distribution of males and females was determined to be equal, and the mean age at diagnosis for the entire group was 26.47±13.77 years. In our study, 16 (59%) of 27 patients were female, and their average age was determined to be 25.19±7.00 years.

The most common symptoms of the disease are hematuria and left flank pain. Hematuria can be observed macroscopically or microscopically. Macroscopic hematuria is associated with hypertension of the left renal vein. NCS should be investigated in patients with hematuria, proteinuria, left flank discomfort, and symptoms of pelvic congestion (12). In a study of 112 cases conducted by Orczyk et al. (10)., hematuria (78.57%), left flank pain (38.39%), proteinuria (30.36%), and anemia (13.39%) were the most common findings in patients. Besides, 35.71% of men had varicocele. Apart from anemia, hematuria, and proteinuria, no specific laboratory findings were observed in the cases in our study. Shin et al. (13) in a study conducted by the pediatric group, since the etiology was not found in 69% of the patients with hematuria, renal doppler ultrasonography was performed and NCS was detected in 40% of these patients. Microscopic hematuria is four times more common than macroscopic hematuria (13). The most common symptom was flank pain in 19 (70%) patients, followed by hematuria in 11 (41%) patients. While the prevalence of hematuria in our study was lower than that of comparable studies, the prevalence of flank pain was higher. Additionally, hematuria and proteinuria were common in patients with flank pain.

Similarly, orthostatic proteinuria occurs as a result of protein leakage from the calyceal system due to pressure increase. Hwang et al. (14) performed left renal venography and pressure evaluation of 23 children with orthostatic proteinuria, and showed that 12 (52%) cases had nutcracker syndrome. Although it is less common than hematuria, it can be seen in 0.6-10.7% (15). Proteinuria was observed in 10 (37%) patients in our case series, above the rates in similar studies. Shi et al. (16) identified 128 posterior NCS patients and showed that 22 of them had clinical findings, 11 had hematuria, and it was more prevalent in women than men, especially in the 18-40 age group. Even though posterior NCS was identified more frequently in male patients in our investigation, no hematuria nor proteinuria were detected in the posterior group. This indicates that the findings are less frequent in posterior NCS and that the diagnosis may be overlooked. In our study, patients in the anterior group had a higher prevalence of symptoms and findings, including dysmenorrhea, pelvic congestion, dyspareunia, dyspepsia, anorexia, nausea, vomiting, and weight loss.

Imaging is necessary in cases that require exclusion of other reasons for which the patient's clinic is compatible. Retrograde venography (phlebography) is the gold standard method for diagnostic accuracy because it evaluates both anatomy and pressure change. However, since it is invasive, it requires not routine practice in patients with poor clinical practice (17). Doppler US is preferred because it is a non-invasive diagnostic method. It provides information on both renal vein blood flow velocity and diameter measurement (18). In the studies conducted, important findings such as maximum diameter, flow velocity, and aortomesenteric angle were evaluated in terms of the diagnosis of NCS. Doppler US has disadvantages in terms of operator and patient cooperation. Another disadvantage in ultrasonography is to reveal a standard spectral doppler signal from the aortomesenteric segment of the left renal vein (19). In the studies conducted, it has been stated that the sensitivity of RDUS is between 69-90% and the specificity is between 89-100%. Kim et al (20) showed that it has 80% sensitivity and 94% specificity when the diameter and peak flow ratio measured by doppler US is greater than 5 in adult cases with NCS confirmed by venography. In our study, the most frequently used RDUS imaging technique was used on 17 patients. While no CT scan was available for five patients with posterior NCS, RDUS examination performed. We believe that with a good practitioner, RDUS can detect posterior NCS cases that are difficult to diagnose.

Since CT angiography does not cause invasive side effects (renal trauma, pseudoaneurysm) caused by retrograde venography, it is an important examination on the way to become the gold standard because of its rapid visualization of the renal vein and retroperitoneum with three-dimensional reconstruction (12). The narrowing of the diameter of the left renal vein in the aortomesenteric segment and the angle between the superior mesenteric artery and aorta below 41 degrees are the parameters that guide the diagnosis in axial tomography images. Also, MRI angiography can be preferred because it does not contain radiation, provides multi-planar

imaging, and shows the soft tissue anatomy in the compression area better. However, its transportation and use in practice are a little more difficult. However, CT angiography offers considerable diagnostic potential due to its greater accessibility. Shi et al. (16) scanned 6225 individuals, identified 128 patients with posterior NCS, and evaluated multi-slice spiral CT angiography as a viable non-invasive alternative to renal angiography for the study of renal vascular anatomy and variations. In our study, 13 individuals underwent CT and 7 experienced MRI. None of the patients in the posterior NCS group had a CT technique. But they all had RDUS. While there were no patients in the anterior NCS group who underwent retrograde venography, three of the five posterior NCS patients had RV. We think that this indicates the necessity of RV as an advanced invasive test for the diagnosis of posterior NCS. The absence of RV in any anterior NCS patients also suggests that advanced invasive examination may not be required in the diagnosis of anterior NCS.

Conservative, endovascular, laparoscopic, and surgical treatments are all possible treatment options. The treatment option may differ according on the clinic and renal vein pressure of the patient. Patients with moderate clinical conditions may utilize conservative therapy approaches. After 24 months of follow-up, patients with recurrent hematuria, significant flank discomfort, renal failure, and chronic orthostatic proteinuria must be referred to interventional treatment alternatives (21). Nephropexy, intravascular and extravascular stents, transposition of the left renal vein or superior mesenteric artery, gonadocaval bypass, renal autotransplantation, and nephrectomy are surgical procedures. In the pediatric age range, remission has been recorded to a considerable extent with growth and weight increase. Therefore, conservative treatment is the primary option (22). While surgery is the standard treatment, the recent success of endovascular interventions puts this option forward (23). Endovascular procedures have the disadvantages of necessitating long-term anticoagulant medication and the absence of information regarding long-term consequences (24). In 14 (61.8%) of the cases in our study, there was a correlation between conservative treatment and similar studies, suggesting that this approach is valid for the majority of patients. Eleven individuals with anterior NCS and two patients with posterior NCS received surgical and endovascular therapy. In addition, it is remarkable that only female patients had endovascular treatment in our study.

The most important limitation of the study was that it was retrospective, single-center. Another limitation was that the diagnosis studied was rare and could have been neglected.

CONCLUSION

NCS cases are frequently misdiagnosed or underdiagnosed because they are difficult to identify and need a complex diagnostic approach. In addition to patients who present with hematuria or flank pain in emergency or outpatient services, hematuric and proteinuric patients should also be investigated for the diagnosis of NCS. Considering this diagnosis, including in the differential diagnosis and planning the appropriate imaging method will contribute to the correct treatment process of the patients. Renal DUS can be used as an important non-invasive examination at both screening and diagnosis stages with a good practitioner. Tomography takes its place as a more risk-free diagnostic tool than venography. After early diagnosis, the success of conservative treatments is increasing. It can be said that non-invasive methods are gradually becoming more superior to invasive methods in both diagnosis and treatment processes.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bağcılar Training and Research Hospital Clinical Researches Ethics Committee (Date: 15.01.2021, Decision No: 2021.01.1.01.001).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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Virtual learning in ophthalmology training during the time of COVID-19: a perspective of clinicians' at a tertiary referral eye hospital, a cross-sectional study

COVID-19 sürecinde oftalmoloji eğitiminde sanal öğrenme: üçüncü basamak bir göz hastanesindeki klisyenlerin bakış açısı, kesitsel çalışma

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ABSTRACT

Aim: To evaluate the implementation of virtual learning in ophthalmology training during the time of COVID-19 through the perspective of clinicians.

Material and Method: A survey among physicians, who are actively involved in Ophthalmology-related training, was conducted. The expert survey comprised 29 questions and two parts addressing the application of virtual learning and the efficacy of webinars in increasing the clinical and surgical skills in Ophthalmology during the COVID-19 pandemic.

Results: A total of 42 Turkish ophthalmologists participated in the study. In the pre-pandemic period, lectures (92.9%), grand rounds with case studies (71.4%), and videos (61.9%) were among the first choices of the participants. A statistically significant increase in the use of e-learning modalities ($p < 0.001$ for all estimates) except for e-class with uploaded educational material was detected during the pandemic. Zoom® was recognized as the most used platform for virtual teaching. A statistically significant ($p=0.034$) decrease in time spent on surgical training was detected during the pandemic. 81% thought that webinars are good or very good in strengthening clinical skills within diagnosis and treatment. Also, 78.6% stated that webinars are good or very good in increasing surgical skills and management of complications. 64.3% supported webinars to be maintained even after the termination of the pandemic.

Conclusion: A considerable experience provided by virtual learning methods, especially webinars, may change conventional education practices and will also serve to build the foundation for teaching during future disasters and beyond.

Keywords: COVID-19, virtual learning, ophthalmologists, pandemic

ÖZ

Amaç: COVID-19 döneminde oftalmoloji eğitiminde sanal öğrenmenin uygulanmasını klinisyenlerin bakış açısıyla değerlendirmek.

Gereç ve Yöntem: Oftalmoloji ile ilgili eğitimlere aktif olarak katılan hekimler arasında anket yapılmıştır. Uzman görüşü anketi, COVID -19 pandemisi sırasında oftalmolojide klinik ve cerrahi becerileri artırmada sanal öğrenme uygulaması ile web seminerlerinin etkinliğini ele alan toplam yirmi dokuz soru ve iki bölümden oluşmaktaydı.

Bulgular: Çalışmaya toplam 42 göz hekimi katıldı. Pandemi öncesi dönemde, dersler (%92,9), olgu sunumlu toplantılar (%71,4) ve videolar (%61,9) katılımcıların ilk tercihleri arasındaydı. Pandemi sırasında yüklenen eğitim materyalleri ile e-sınıf dışında, e-öğrenme yöntemlerinin kullanımında (tüm tahminler için $p < 0,001$) istatistiksel olarak anlamlı bir artış tespit edildi. Zoom® sanal öğretim için en çok kullanılan platformdu. Pandemi sırasında cerrahi eğitim için harcanan sürede, istatistiksel olarak anlamlı ($p=0.034$) bir azalma tespit edildi. Katılımcıların %81'i, web seminerlerinin tanı ve tedavide klinik becerileri güçlendirmede, iyi veya çok iyi olduğunu düşünmekteydi. Katılımcıların %78,6'sı, web seminerlerinin cerrahi becerileri artırma ve komplikasyonların yönetimi konusunda, iyi veya çok iyi olduğunu belirtti. %64,3 katılımcı, web seminerlerinin pandeminin sona ermesinden sonra bile sürdürülmesini destekledi.

Sonuç: Sanal öğrenme yöntemleri, özellikle de web seminerleri ile edinilen önemli tecrübe, geleneksel eğitim uygulamalarını değiştirebilir. Sanal öğrenme, ayrıca gelecekteki olası felaketler sırasında ve hatta ötesinde, öğretim metodolojisinde yeni bir yapılanma oluşmasına hizmet edebilir.

Anahtar Kelimeler: COVID-19, sanal öğrenme, göz doktorları, pandemi

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has given rise to a global crisis in many sectors and severe changes in all aspects of our lives. A few months later the COVID-19 pandemic erupted; the vast majority of countries took drastic containment measures to control the rapid spread (1). As a consequence of that social distancing is an essential measure to limit the disease and decrease transmission, in many countries including Turkey, governments implemented lockdowns, curfews, and closures. In the following process, many areas such as the economy, lifestyle, industry, and healthcare dramatically changed in our deeply interdependent world. One of them was education as well (2, 3).

All outpatient activities were reduced, and elective surgical activities were suspended except urgent and emergency services indefinitely concerning the ophthalmology departments. As part of the combat against COVID-19, healthcare personnel including ophthalmologists were called to the front lines to cover COVID-19 wards such as inpatient floors and even intensive care units (ICUs). Scientific events, related to both theoretical and clinical practice, have either been canceled or deferred. Surgical and clinical training were impacted negatively (4, 5). Since providing high-quality training for residents and fellows remains vital and maintaining conventional in-person education in the course of restrictions is impossible; there has been a paradigm shift towards virtual learning strategies as the path to sustain academic continuity (4, 6).

Educators have utilized different virtual learning methods, especially webinars through various digital platforms such as Zoom, Microsoft Teams, Google Meet, Cisco WebEx, etc. to deliver lectures remotely. Trainees had the opportunity to attend by using laptops, smartphones, or tablets (7). It was important for participants to assess the efficacy and make a comparison between the previous traditional training system and newly implemented virtual learning strategies. To address these concerns, we aimed to assess the utilization of virtual learning and the efficacy of webinars in ophthalmology training from the perspective of clinicians at a tertiary referral eye hospital during the time of COVID-19.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 2021, Decision No: E1/1991/2021). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent details were obtained prior to the study commencement.

A cross-sectional survey-based study was conducted in April 2021 in the process of partially easing mandatory COVID-19 confinements including a curfew on weeknights and a full weekend. Moreover, a permit was also received for the study from the Directorate of Healthcare Services of the Ministry of Health. The survey of the study comprised a consent section declaring the aim of the study, the nature of the survey, study objectives, voluntary participation, declaration of confidentiality, and anonymity.

A total of 42 Turkish ophthalmologists including faculty, specialists, and residents participated in the study. Ophthalmologists who work at the aforementioned tertiary eye care referral center and who have participated in the virtual learning (webinar, etc.) program at least once or more during the pandemic period were included in the survey study. Those who have never participated in the pandemic process were excluded.

The survey was organized into two parts (see Supplementary Material X for the original survey). The first part (8) of the survey comprised 22 questions including the sections on demographics, educational status, teaching practice before the pandemic, teaching practice during the pandemic, and potential recommendations concerning the future implementation of virtual learning in ophthalmology. The types of questions involved single-choice (ten), multiple-choice "please select all that apply" (eight), five-point ordinal Likert Scales (three), and full-text answers (one). The second part (9) contained 7 single-choice questions that interrogate the efficacy of webinars in increasing the clinical and surgical skills of ophthalmologists during the time of obligatory social distancing of COVID-19.

The online survey (Google Forms) was conducted in the Turkish language and the link of the survey was shared via WhatsApp groups or individually to participants in the lists of contact persons belonging to the researchers. Respondents had the option of adding personal info such as names and email addresses, however, this was not obligatory. The survey could be answered only once, and it was available to participate in for 5 days.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences (SPSS) 22.0 program. Qualitative data were represented as numbers and percentages. Quantitative data were represented as means±standard deviation and median. McNemar test was used to compare "before" and "during" the pandemic periods for categorical data. The statistical significance level was considered as a $p<0.05$.

RESULTS

Of about 70 ophthalmologists who communicated, 43 responded to the survey. One of the participants was excluded from the study because of being on leave in the period before the pandemic, eventually yielding a response rate of 60%.

Demographics of the Participants

Overall, 14 out of 42 participants were males (33.3%) and 28 were females (66.7%). The mean (SD) age of participants was 34.3 (±9.04) years (range: 24–56 years). About 52.4% (n=22) were aged more than 30 years. Among the participants, 54.8% (n=23) were resident physicians, 33.3% (n=14) were ophthalmology specialists, and 11.9% (n=5) were faculty staff of ophthalmology. The rate of participants with more than 5 years of professional experience in the field was 47.6% (n=20). In **Table 1**, the participants' demographic profile is shown. 61.9% (n=26) of the participants had no primary area of expertise and were deemed as serving in comprehensive ophthalmology. The majority of participants with sub-specialties had expertise in the medical (21.4%, n=9) and surgical retina (19%, n=8) respectively, while other sub-specialties were also adequately expressed, as **Table 1** indicates.

Table 1. Demographic and special characteristics of survey participants (n=42).

Categories	Participants	n	%
Gender			
	Male	14	33.3%
	Female	28	66.7%
Age			
	<30	20	47.6%
	31–40	12	28.6%
	41–50	6	14.3%
	51–60	4	9.5%
Current academic status			
	Faculty	5	11.9%
	Specialist	14	33.3%
	Resident Physician	23	54.8%
Ophthalmology experience (years)			
	<5 years	22	52.4%
	5–10 years	5	11.9%
	11–15 years	8	19.0%
	>15 years	7	16.7%
Expertise			
	Medical retina	9	21.4%
	Surgical retina	8	19.0%
	Glaucoma	1	2.4%
	Cornea and refractive surgery	3	7.1%
	Cataract	7	16.7%
	Uveitis	1	2.4%
	Pediatric ophthalmology/Strabismus	3	7.1%
	Comprehensive ophthalmology	26	61.9%
	Neuro-ophthalmology	1	2.4%
	Low vision rehabilitation	1	2.4%

Virtual Learning Before and During the Pandemic

Our study revealed that the alternative methods employed for training in Ophthalmology varied during pre-pandemic and pandemic periods (**Figure 1**). In the pre-pandemic period, lectures (n= 39, 92.9%), grand rounds with case studies (n=30, 71.4%), and videos (n=26, 61.9%) were among the first choices of the participants for teaching residents and fellows, when web-based lessons with (n=4, 9.5%) or without (n=9, 21.4%) interactive participation, live streaming video conferences (n=9, 21.4%) access to virtual meetings from conferences (n=7, 16.7%), and e-class platforms (n=2, 4.8%) were uncommon. Whereas a statistically significant decrease in the preference for conventional teaching methods such as lectures and grand rounds with case studies ($p < 0.001$) in addition to an accompanying statistically significant increase in the use of e-learning modalities ($p < 0.001$ for all estimates) except for e-class with uploaded educational material were detected during the pandemic.

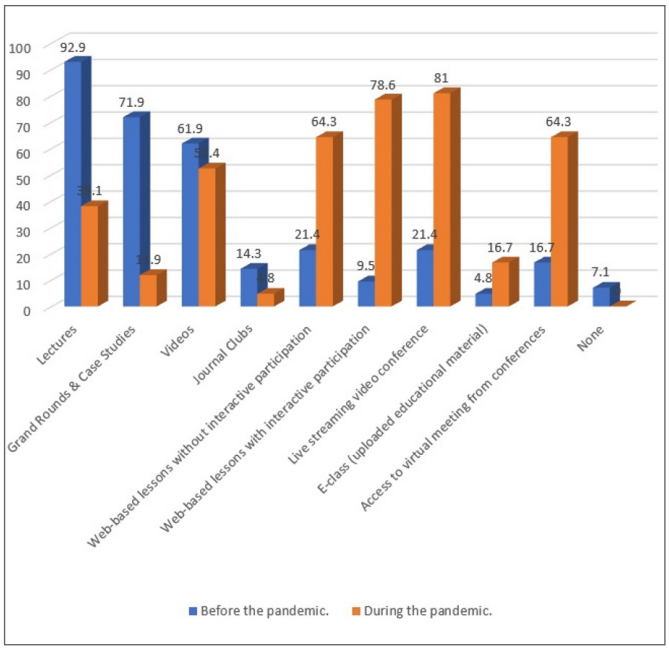

Figure 1. Teaching methods before and during the pandemic.

Specific platforms used for virtual learning are shown in **Figure 2**. Before the pandemic, Zoom® (Zoom Video Communications, San Jose, CA, USA, n=10, 23.8%) and Skype for Business® (Microsoft, Palo Alto, CA, USA, n=4, 9.5%) were among the main preferred platforms. During the pandemic, an increase in the use of Zoom® (n=42, 100%, $p < 0.001$) and Microsoft Teams® (n=16, 38.1%, $p < 0.001$) platforms was statistically significant, along with no difference in the use of other platforms before and during the pandemic. Participants indicated that neither facilities nor appropriate software and phone applications were provided by the institution for e-learning before the pandemic.

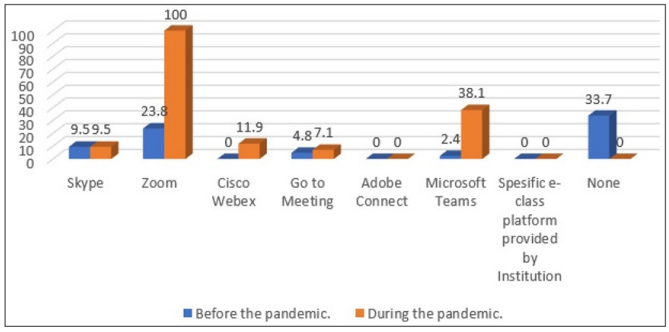

Figure 2. Specific platforms for e-learning before and during the pandemic.

There was no statistically significant difference in hours allocated for theory training between the pre-pandemic and pandemic periods. However, in terms of surgical training, a statistically significant (p=0.034) decrease in time spent was detected during the pandemic (**Figure 3**). The quality of teaching practice in the institution described as "good" on a five-point Likert scale was found to be statistically significant (p=0.014) decreased during the pandemic compared to before the pandemic (**Figure 4**).

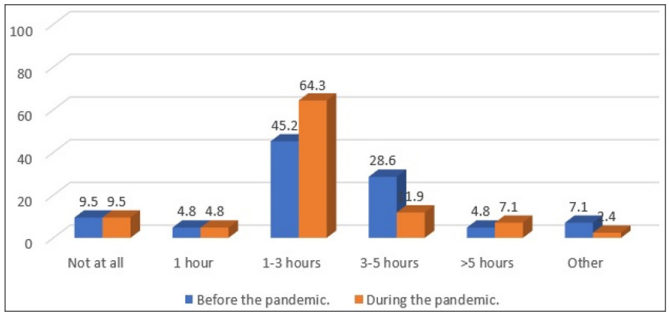

Figure 3A. Theory training weekly hours before and during the pandemic.

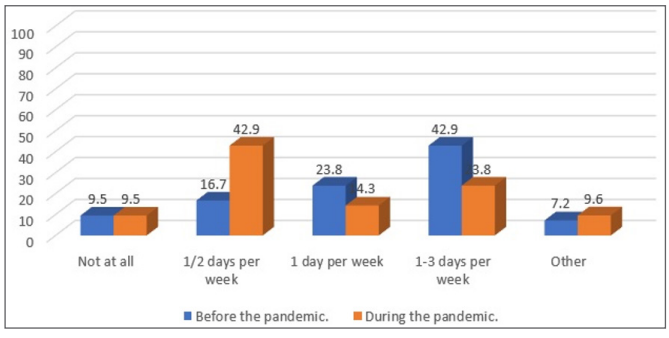

Figure 3B. Surgical training weekly hours before and during the pandemic.

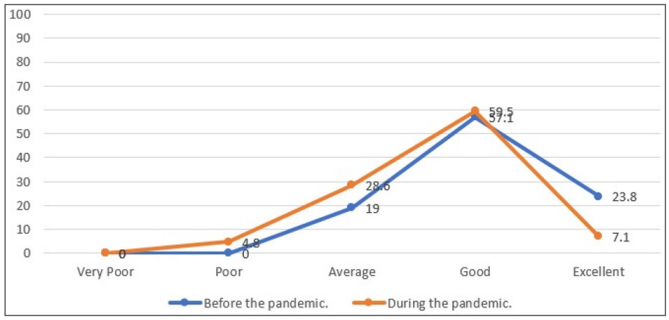

Figure 4. Current teaching practice description before and during the pandemic.

Efficacy of Webinars in Increasing the Clinical and Surgical Skills

81% of participants (n=34) were interested in the topic rather than the speaker or the company organizing the webinar. According to 40.5% of participants (n=17), the real regular conferences were better than the webinars. Still, 40.5% of participants (n=17) reported that they could keep their attention and concentration sometimes to the end. 81% of participants (n=34) thought that webinars are good or very good in strengthening clinical skills within diagnosis and treatment. Also, 78.6% (n=33) stated that webinars are good or very good in increasing surgical skills and management of complications. 47.6% (n=20) declared that an increased number of webinars affect their benefits and values negatively to some extent. Along with this, 64.3% (n=27) supported webinars to be maintained even after the termination of the pandemic (**Table 2**).

Table 2. Responses of the ophthalmologists related to efficacy of webinars in increasing the clinical and surgical skills during the time of COVID-19.

Questions	Options	n	%
Your interest in webinar is due to			
	The topic	34	81%
	The speaker	8	19%
	Institute/Company	-	-
In comparison, webinars to regular conferences, which is better?			
	Webinars are markedly better	2	4.8%
	Webinars are better	9	21.4%
	Webinars is the same as regular conferences	14	33.3%
	Webinars are worse than regular conferences	12	28.6%
	Webinars are markedly worse than regular conferences	5	11.9%
Your concentration and attention to webinar till its end:			
	Always to the end	2	4.8%
	Usually to the end	14	33.3%
	Sometimes to the end	17	40.5%
	Rarely to the end	5	11.9%
	Never to the end	4	9.5%
To which extent webinars increased your clinical skills indiagnosis and treatment?			
	Excellent	-	-
	Very good	3	7.1%
	Good	31	73.8%
	Bad	7	16.7%
	Very bad	1	2.4%
To which extent webinars increased your surgical skills and management of complications?			
	Excellent	-	-
	Very good	3	7.1%
	Good	30	71.4%
	Bad	7	16.7%
	Very bad	2	4.8%
Do you think increased number of webinars affect their benefits and values negatively?			
	Yes	5	11.9%
	No	17	40.5%
	To some extent	20	47.6%
Do you like to continue Webinars regularly after COVID-19 pandemic?			
	Yes	27	64.3%
	No	15	35.7%

Future Fulfillment of Virtual Learning in Ophthalmology

Our results revealed that 27 participants (64.3%) were "very" or "extremely" satisfied with practicing virtual learning in Ophthalmology as a teaching method. 23.8% of participants (n=10) think that virtual learning can replace "face-to-face" education. Noticeably, 88.1% (n=37) think that the experience of virtual learning modalities acquired during the time of pandemic will be utilized in future Ophthalmology training. Considerably, 26 participants (61.9%) felt that there were no barriers to the adoption of virtual learning for future training. 21.4% of participants (n=9) had no idea about potential barriers while the absence or restricted availability of e-learning facilities seemed the most significant barrier according to participants. Besides, ophthalmology is a surgical specialty that requires hands-on training. From this point of view, one of the biggest handicaps of virtual learning is that it does not offer an option for surgery at present.

DISCUSSION

The current study demonstrated a statistically significant increment in the adoption of virtual learning in ophthalmology training during the COVID-19 time. A considerable shift to distance learning from conventional methods was observed during the pandemic. Zoom was one of the most selected simultaneous distance learning platforms among the participants. Even though the time allocated for theoretical training seems to meet the requirements; a notable decline in the hours assigned for surgical training due to the cancellation of elective surgeries was found during the pandemic. This interruption of practical training in ophthalmology, a surgical specialty, prevents one from obtaining more exposure to the specialty and developing robust practical skills. Hence, causes concerns about surgical competency. Therefore, we hypothesized that when we leave the practical training perspective aside; virtual learning as an educational tool during the pandemic will go widespread gradually in the near future and become an indispensable auxiliary component of conventional education.

Virtual learning, defined as a method of learning designed for self-paced (asynchronous) or live web-conferencing (synchronous) in which the educator and trainees are physically separated and electronic technology along with the internet utilized in an online environment (10), has become more and more common among the learners in medicine (11). While virtual learning and e-learning (distance learning) are similar, there is one big difference virtual learning is an umbrella term for other terms and is more interactive (12). Flexibility in terms of place, time, or both; the convenience of access to big data; elimination of communication barriers such as the fear of talking to other participants that hinders participation; and cost-effectiveness are just a few of its advantages (13).

As the COVID-19 pandemic disrupted medical education and caused a suspension in traditional face-to-face learning activities, in-person academic activities have transformed into virtual learning globally. Similarly, in other eye clinics of the world (14, 15), rapid conversion to web-based education has taken place using specific platforms in our department of ophthalmology. In addition, elective operations were canceled and nonessential personnel in the operating room were minimized. Although innovative solutions through e-learning were offered for theory training; the dramatic drop in trainees' in-person exposure to patients negatively impacted surgical training. Even though surgical simulations are efficacious instruments for maintaining instructional requirements, they cannot replace real-life surgical situations. Moreover, the lack of wet labs or surgical simulators in our clinic has further deepened the crack in the quality of surgical training. That resulted in a statistically significant decrease in both times spent on surgical training and in the quality of teaching practice in the institution during the pandemic compared to before the pandemic in the current study. Our experiment confirms previous findings in the literature (15-17).

When the participants were asked about to which extent the online scientific webinars enhanced their clinical and surgical skills during the time of COVID-19; the majority commented that they were satisfied with the webinar's effectiveness in improving their knowledge and skills. This is in good agreement with previous findings (9, 18). 40.5% of participants found real regular conferences better than the webinars. This fits well with the results of Ebner et al. (19). Higher opportunities in face-to-face conferences for social networking and the reach of the audience could be counted among the reasons (20). Still, 40.5% of participants stated that they could focus their attention and keep concentration sometimes to the end. The characteristics of a webinar including the duration, frequency, and timing of the events or participants including gender, age, etc. could have a part in the effectiveness (21,22). Most of the participants supported webinars being maintained even after the termination of the pandemic. Some of the obvious advantages such as cost-effectiveness, convenience to attend, wider reachability, ubiquity, and geographical flexibility could play a major role in obtaining this result (9,18,19).

Several potential limitations relevant to the inherent nature of survey methodology need to be considered in the current study. First, the recall bias of the participants is incapable of being avoided as we asked them to state their

previous practices, and experiences, and remember their attitudes. However, responders consisted of participants with high education levels and socioeconomic status. Second, as it was purely online research, thus it can include uncertainty over the validity of the data and implementation issues. Another limitation was the relatively small sample size in the study.

CONCLUSION

The COVID-19 pandemic has rapidly evolved crisis globally and posed an unprecedented challenge to education. In this hard period, transformation in ophthalmology training, adaptation to virtual learning, and producing flexible approaches to maintain continuing professional development is inevitable. Virtual learning methods, especially webinars, have the potential to substitute face-to-face gatherings and open a new way to improve the knowledge of residents and fellows during these times of uncertainty. It is indefinite how long the COVID-19 pandemic lasts or whether there is another catastrophe awaiting humanity in the close future but beyond a doubt, virtual learning enables the dissemination of new advancements, provides educational convenience, and enhances academic experiences will become the future of ophthalmology training.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital Clinical Researches Ethics Committee (Date: 2021, Decision No: E1/1991/2021).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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Review / Derleme

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Pediatrik palyatif bakımda verilen hizmet kalitesini belirleyen faktörler

Factors determining the quality of service in pediatric palliative care

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ÖZ

Pediatrik palyatif bakım ülkemizde ve dünyanın pek çok ülkesinde yeni gelişen bir alt uzmanlık alanıdır. Hayatı tehdit eden hastalığı olan çocukların sayısı tüm dünyada olduğu gibi ülkemizde de gün geçtikçe artmaktadır. Bu hastalara verilecek olan palyatif bakımın kalitesinin belirlenmesi, verilecek hizmetin kalitesini arttıracaktır. Bu derlemenin amacı pediatrik palyatif bakımın hizmet kalite standartlarını tanımlamaktır.

Anahtar Kelimeler: Çocuk palyatif bakım, hizmet kalite standartları, hayatı tehdit eden hastalık

ABSTRACT

Pediatric palliative care is a recently developing sub-specialty in our country and many countries around the world. The number of children with life-threatening conditions is increasing gradually in our country. Determining the quality of palliative care provided to these patients will increase the quality of this care. The aim of this review is to define the quality standards of pediatric palliative care.

Keywords: Pediatric palliative care, service quality standards, life-threatening condition

GİRİŞ

20 yaşından küçükler olarak tanımlanan dünyanın pediatrik nüfusu, küresel nüfusun % 35'ini oluşturmaktadır (1). Dünya çapında 21 milyon kadar yeni doğan, bebek, çocuk ve ergenin Dünya Sağlık Örgütü (DSÖ) tarafından tanımlanan çeşitli koşullar için palyatif bakımdan fayda göreceği tahmin edilmektedir (2). Bu sayının sekiz milyonu ise uzmanlaşmış pediatrik palyatif bakım (PPB) hizmetine ihtiyaç duymaktadır (2,3). Bu derlemenin amacı pediatrik palyatif bakımın hizmet kalite standartlarını tanımlamaktır. Çocuklar için palyatif bakım, yetişkin palyatif bakımıyla yakından ilişkili olsa da özel bir alanı temsil eder. DSÖ'nün çocuklar ve aileleri için uygun palyatif bakım tanımı şöyledir:

- Çocuklar için palyatif bakım, çocuğun bedeninin, zihninin ve ruhunun aktif bütüncül bakımıdır ve aileye destek verilmesini de içerir.
- Hastalık teşhis edildiğinde başlar ve bir çocuğun hastalığa yönelik özgün tedavi alıp almadığından bağımsız olarak devam eder.
- Sağlık hizmeti sağlayıcıları çocuğun fiziksel, psikolojik ve sosyal sıkıntılarını değerlendirmeli ve hafifletmelidir.
- Etkili palyatif bakım, aileyi içeren ve mevcut toplum kaynaklarını kullanan geniş bir multidisipliner yaklaşım gerektirir; ve kaynaklar sınırlı olsa bile başarıyla uygulanabilir.
- Üçüncü basamak sağlık tesislerinde, toplum sağlığı merkezlerinde ve hatta çocukların evlerinde bile sağlanabilir (4).

Çocukluk çağındaki pek çok durum palyatif bakım yaklaşımından fayda görebilir (5). Dünya üzerinde her yıl ölen 2,5 milyon çocuğun %98'inin düşük ve orta gelirli ülkelerde yaşadığı bilinmektedir (5). PPB merkezlerinin dağılımında ise çok büyük eşitsizlikler söz konusudur. Knapp ve

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ark. dünyadaki ülkelerin% 65,5'inin uygun çocuk palyatif bakım hizmetine sahip olmadığını belirlemiştir (6). Arias-Casais ve ark. Avrupa Bölgesi'nde düşük ve orta gelirli ülkelerde yaşayan çocukların PPB hizmetine ulaşma şanslarının daha düşük olduğunu tespit etmiştir (7).

Ülkemizdeki Durum

Ülkemizde ilk PPB merkezi 2015 yılında Bursa'da açılmıştır. Şubat 2020 verilerine göre toplam 5438 palyatif bakım yatağının 129'unu pediatrik yataklar oluşturmaktadır. Dünya palyatif bakım atlasına göre dünya üzerinde palyatif bakım ihtiyacı olan hastaların %7'sini çocuklar oluşturmaktadır (8). Bu orana göre ülkemizde pediatrik yatakların sayısının 350'nin üzerinde olması gerekmektedir. Fakat PPB merkezlerinin tek sorunu yatak sayısı değildir. Bu alanın halihazırda; hizmetin tanımlanması, hangi hastaların bu hizmetten yararlanacağı, çocuğun yüksek yararı için kaliteli hizmet verilmesi gibi pek çok önemli sorunu vardır.

PPB'de Hizmet Kalitesini Neler Belirler?

2006 yılında İtalya'nın Trento şehrinde dünyanın farklı bölgelerinden bir grup sağlık profesyoneli bir araya gelmiş, ve bu grup 'The International Meeting for Palliative Care in Children, Trento (IMPaCCT)' olarak adlandırılmıştır. 2007'de IMPaCCT grubu Avrupa Palyatif Bakım Derneği'nin özel görev grubu olarak çalışmıştır. Üç gün boyunca, farklı ülkelerdeki pediatrik palyatif bakım hizmetleri karşılaştırılarak pediatrik palyatif bakım tanımlanmış, en iyi uygulamalar belirlenmiş, minimum standartlar kabul edilmiş ve bu çalışma 2007 yılında yayınlanmıştır (9). Bu çalışma grubunun belirlediği çekirdek standartlar ise şu şekildedir:

1. **Palyatif bakımın sağlanması:** Verilen bakımın amacı çocuk ve ailenin yaşam kalitesini artırmak olmalıdır. PPB programına ulaşmak kolay olmalıdır, aileler bu birime kendileri başvurabilmelidir. PPB, çocuğa hayatı sınırlayan veya tehdit eden bir durum teşhisi konduğunda başlamalı ve hastalığın seyri boyunca sürdürülmelidir. PPB küratif tedavilerle birlikte verilmelidir. Çocuk ve ailenin olmayı seçtiği her yerde palyatif bakım sağlanmalıdır (örneğin, ev, hastane veya hospis).

   Ülkemizde PPB merkezi sayısı ülkemiz nüfusuna oranla düşük olduğu için PPB programlarına ulaşım kolay olmamaktadır. Ayrıca çocuk hekimleri arasında palyatif bakımla ilgili farkındalığın az olması nedeni ile PPB tanı anında başlayamamaktadır (10).
2. **PPB'de bakım birimi:** PPB'de bakım birimi çocuk ve ailedir. PPB'nin gelişimi ile birlikte bu alanda çalışan klinisyenler, sadece aileyi hastanın bakımına dâhil etmeleri gerektiğini değil, aynı zamanda ölmekte olan bir çocuğun aile üyelerine de bakmaları gerektiğini öğrenmişlerdir. Bu durum artık yüksek kaliteli PPB hizmetinin temel bir bileşenidir (11). Çocuğun ve aile bireylerinin yaşına, bilişsel ve eğitimsel becerilerine ve kültürüne uygun, tam kapsamlı klinik destek ve eğitimsel kaynaklar mevcut olmalıdır. Çocuk ve aile, hastalık ve tedavi seçenekleriyle ilgili olarak bilgilendirildikten sonra, PPB ihtiyaçlarının ve önceliklerinin belirlenmesi sürecine mutlaka dâhil edilmelidir. Palyatif bakımda hastaya özel bakım planlanması esastır (11); burada hastanın ihtiyaçları ve öncelikleri tüm PB sağlık profesyonellerinin önceliği olmalıdır.
3. **Palyatif bakım ekibi:** Bakım ekibi, her çocuğun ve ailenin bireyselliğini tanımalı ve değerlerini, isteklerini ve inançlarını korumalıdır. Palyatif bakım ekibi, çocuğun ve ailenin fiziksel, psikolojik, duygusal, ruhsal ve sosyal ihtiyaçlarını ele almak için yeterli uzmanlığa sahip olmalıdır. Asgari palyatif bakım ekibi bir doktor, hemşire, sosyal hizmet uzmanı, çocuk terapisti veya psikolog ve manevi hizmet danışmanını içermelidir. Uzman PPB ekibi destek ve tavsiyeleriyle çocuğa ve ailesine 7/24 ulaşılabilir olmalıdır. Bakım ekibinin, planlama, strateji ve hedefleri paylaşarak evde, hastanede ve bakımevinde bakımın sürekliliğini sağlaması esastır. Çocuğa primer bakımı veren kişiye de psikososyal destek ve gözetim sağlanmalıdır.
4. **Bakım koordinatörü/Kilit çalışan:** Palyatif bakım ekibinden bir profesyonel, ailenin bakım koordinatörü veya kilit çalışan olarak belirlenmelidir. Bakım koordinatörü, ailenin sosyal hizmetlere, pratik desteğe (uygun yardımlar ve ev uyarlamaları dahil), manevi bakım hizmetlerine ve dinlenme bakım hizmetlerine erişiminin sağlanması için uygun bir profesyonel destek sistemi oluşturup sürdürmesine yardımcı olmalıdır. Bakım koordinatörü sistemi ülkemizde tam olarak oturmuş bir sistem değildir.
5. **Semptom yönetimi:** Her çocuk, ağrı ve diğer semptomlarının farmakolojik, psikolojik ve fiziksel yönetimine 7/24 sürekli erişebilmelidir. Uygun hayat kalitesine ulaşmak için her çocuğun semptomlarının ayrıntılı bir şekilde değerlendirilmesi gereklidir. Fiziksel semptomların yanı sıra psikolojik, sosyal ve ruhsal semptomlar da ele alınmalıdır. Semptom yönetimi hasta, aile ve sağlık profesyonelleri için kabul edilebilir yöntemlerle gerçekleştirilmelidir.

   Hastalık kaynaklı fiziksel, psikolojik, sosyal ve ruhsal semptomları yönetmek özel uzmanlık gerektirmektedir. Bunlar içinde en önemlisi ağrının yönetilmesidir. Pediatristlerin ağrı farkındalıkları tüm dünyada istenilen seviyeden düşüktür (12). Ülkemizde yapılan çalışmalarda da sağlık profesyonelleri arasında çocuklarda ağrı konusunda farkındalığın yeteri kadar gelişmediği belirlenmiştir (13).
6. **Dinlenme bakım hizmeti:** Birkaç saat veya birkaç gün dahi olsa, bakım verenler ve çocuk için mola vermek çok önemlidir. Aileye ve çocuğa kendi evinde veya evden uzakta bir kurumda dinlenme bakım hizmeti sağlanmalıdır.

Ülkemizde çocuklar için dinlenme bakım hizmeti uygulaması çok kısıtlıdır. Hayatı tehdit eden hastalığı olan çocuklara asıl bakım verenler aileleri, genellikle de anneleridir. Bu çocukların ebeveynlerinin, sağlıklı çocukların ebeveynlerinden çok daha farklı, yoğun ve karmaşık ebeveynlik rolleri vardır. Fakat bu rollerinde onlara yardımcı olacak yeterli hizmet ve desteği alamamaktadırlar (14,15). Bu durum çocuklarına evde bakım veren ailelerin ne kadar ağır fiziksel ve psikolojik yük aldıklarını gözler önüne sermektedir. Erişkin, özellikle geriatrik palyatif bakımda bir hastanın birden fazla bakım vereni olma şansı yüksektir ama PPB'de genellikle ebeveynler bu yükü tek başlarına yüklenmektedir.

7. **Yas desteği:** Yas desteği tanı anında başlamalı ve ihtiyaç duyulduğu sürece hastalık süreci boyunca, ölüm anında ve sonrasında devam etmelidir. Bir çocuğun hastalığından ve ölümünden etkilenen herkes için (aile, bakım verenler, akrabalar, arkadaşlar) bu destek sunulmalıdır. Kardeş desteğinin PPB'nin ayrılmaz bir parçası olması esastır.

   PPB'de özel olarak çalışılması gereken alanlardan biri de kardeş desteğidir. PPB alan çocukların çoğunun bir veya daha fazla kardeşi bulunmaktadır. Kardeşler bu süreçten en fazla etkilenen ve en kırılgan grubu oluşturmaktadır. Hayatı tehdit eden hastalığı olan çocukların kardeşlerinin ilgi ve desteğe ihtiyacı vardır. PPB üyeleri, yaşlarına uygun ve dürüst cevaplarla kardeşlere destek sağlamak ve hastanın kardeşlerini hastanın günlük yaşamının rutin faaliyetlerine dâhil etmek için ebeveynlerle ortak çalışmalıdır (16).

8. **Yaşa uygun bakım:** Ebeveynler, çocuğun yaşına ve isteklerine göre çocuklarının bakımının tüm yönlerinde hazır bulunmalı ve dâhil olmalıdırlar. PPB ekibi farklı yaşlardaki, gelişim aşamalarındaki ve farklı iletişimsel ve bilişsel yeteneklere sahip çocukların ihtiyaçlarını karşılamalıdır. Çocuklar ve genç yetişkinler, hem yaşlarına hem de bilişsel yeteneklerine uygun eğlence ve dinlenme fırsatlarına erişebilmelidir.

   Bu imkânının çocuk hastalara sunulması için bu hizmeti veren sağlık profesyonellerinin çocuğun gelişim aşamaları hakkında eğitim alması gerekmektedir. Bunu sağlayabilmek için PPB klinisyenlerinin yanı sıra çocuk yaşamı uzmanları, pediatrik psikologlar ve psikiyatristler, müzik terapistleri ve sosyal hizmet uzmanlarının da PPB ekibine katılması önem taşımaktadır (17).

9. **Eğitim ve Öğretim:** PPB'de çalışan tüm profesyoneller kapsamlı eğitim ve destek almalıdır. Palyatif bakım eğitimi, tüm pediatrik sağlık uzmanlıkları ve ilgili alt uzmanlık alanları için müfredatın temel bir parçası olmalıdır. Her ülke, PPB'de çalışan tüm profesyoneller için ulusal bir müfredat geliştirmelidir. PPB'nin tüm yönlerinde resmi öğretim ve mezuniyet sonrası eğitim sağlayabilecek, bu alanda özelleşmiş merkezler olmalıdır.

   Ülkemizde PPB için uzmanlaşmış bir eğitim bulunmamaktadır. Pediatri uzmanlık eğitiminin içinde PPB, sadece bu merkezlerin olduğu eğitim araştırma hastanelerinde yer bulabilmektedir.

10. **Palyatif bakım hizmetlerinin finansmanı:** Palyatif bakım hizmetleri, finansal veya sağlık sigortası durumlarına bakılmaksızın, ihtiyaç duyan tüm çocuklara ve ailelerine sağlanmalıdır. Hükümetlerin, ev, okul, hastane ve çocuk hastaneleri dahil olmak üzere çeşitli ortamlarda bütüncül palyatif bakım sağlamak için yeterli finansmanı sağlamaları gerekmektedir. PPB hizmeti veren profesyonellerin eğitimi için yeterli fon ayrılmalıdır.

    Ülkemizde gelişmiş sağlık sistemi nedeniyle, PPB kamu hastanelerinde ücretsiz olarak sunulmaktadır. Fakat bu hizmetten ülkemizin tüm çocuklarının yararlanabilmesi için PPB merkez sayısının arttırılması gerekmektedir. Mayıs 2020 tarihi itibari ile toplam 129 yatak olarak PPB hizmeti sunulmaktadır. T.C. Sağlık Bakanlığı, Kamu Hastaneleri Genel Müdürlüğüne bağlı Pediatrik Palyatif Bakım merkezleri bünyesinde; Bursa Dörtçelik Çocuk Hastanesi 7 yataklı, Aydın Kadın Doğum ve Çocuk Hastanesi 6 yataklı, Bolu İzzet Baysal Eğitim ve Araştırma Hastanesi 6 yataklı, Mersin Şehir Hastanesi 24 yataklı, Erzurum Bölge Eğitim ve Araştırma Hastanesi 10 yataklı, İzmir Dr. Behçet Uz Çocuk Hastalıkları ve Cerrahisi Eğitim ve Araştırma Hastanesi 17 yataklı, Gaziantep Cengiz Gökçek Kadın Doğum ve Çocuk Hastanesi 10 yataklı, Diyarbakır Çocuk Hastalıkları Hastanesi 10 yataklı, Ankara Şehir Hastanesi 24 yataklı ve Dr. Sami Ulus Kadın Doğum Çocuk Sağlığı ve Hastalıkları Eğitim ve Araştırma Hastanesi 15 yataklı pediatrik palyatif bakım hizmeti vermektedir.

2020 yılında Arias-Casais ve ark. PPB hizmetlerinin ulusal düzeyde gelişmişliğinin değerlendirilmesi için önemli indikatörleri belirlemiştir 7. Bunlar:

1. PPB derneklerinin canlılığı
2. PPB konularının doktorlar ve hemşireler için pediatri uzmanlık eğitim müfredatına dâhil edilmesi
3. Ulusal palyatif bakım derneklerinde bir PPB temsilcisinin varlığı ve PPB derneklerinde bir palyatif bakım temsilcisinin olması
4. PPB hizmetlerinin sayısı ve türü
5. Neonatologlar için PPB eğitim imkânının bulunması
6. En az bir ulusal PPB derneğinin varlığı
7. PPB uzmanlarının sayısı
8. PPB hizmetinin sağlanabilmesi için ulusal standartların ve normların varlığı
9. Perinatal PB referans merkezlerinin varlığı
10. PPB hizmet sunumunu düzenleyen politika, kanun ve yönetmeliklerin varlığı

Aynı çalışmada PPB'nin Avrupa Bölgesindeki durumu tespit edilmiştir. Buna göre 54 Avrupa ülkesinin 51'inin verilerine ulaşılabilmiştir. 51 ülkenin 48'inde (% 94) toplam 680 PPB merkezi tespit edilmiştir. Bunlardan 133'ü hospis, 385'i evde bakım hizmetleri ve 162'si ise hastanede verilen PPB hizmeti olarak rapor edilmiştir. Bu hizmetlerin % 92'si yüksek gelirli ülkelerde bulunmaktadır. Bu rapora göre Türkiye'de 4 tane hastane merkezli PPB ve bir tane çocuklara özel hospis mevcuttur. On dokuz Avrupa ülkesinde (19/51, %38) PPB için özel standartlar ve normlar olduğu bildirilmiştir. Yirmi ülkede PPB uzmanı mevcuttu. On dört ülke pediatri uzmanlık eğitiminde palyatif bakım bileşenlerine sahip olduklarını, 8 ülke ise neonataloglar için PPB eğitimi verdiğini bildirmiştir. Ne yazık ki ülkemiz bu özelliklerin hiçbirine sahip değildir. Beş yaş altı ölüm oranları OECD (Organisation for Economic Co-operation and Development) ortalamasına çok yakın olan ülkemizde kronik hastalıklarla yaşayan çocuk sayısı giderek artmaktadır. Yenidoğan ve pediatrik yoğun bakım alanlarında Türkiye çok önemli atılımlar gerçekleştirmiştir. PPB alanında da ülkemizin gerekli gelişmeleri bir an önce gerçekleştireceğine tüm kalbimizle inanmaktayız.

SONUÇ

Pediatrik palyatif bakım ülkemizde ve dünyanın pek çok ülkesinde yeni gelişen bir alt uzmanlık alanıdır. Hayatı tehdit eden hastalığı olan çocukların sayısı ülkemizde gün geçtikçe artmaktadır. Bu hastalara verilecek olan palyatif bakımın kalitesini belirlenmesi, verilecek hizmetin kalitesini arttıracaktır. PPB ülkemizde yeni kurulan bir alan olduğu için PPB merkezlerinin sayısının ve kalitesinin arttırılması için atılması gereken birçok adım vardır. Ülkemizde sağlık politikalarını belirleyen kurumlarla bu konuda ortak çalışılması gerekmektedir.

ETİK BEYANLAR

Hakem Değerlendirme Süreci: Harici çift kör hakem değerlendirmesi.

Çıkar Çatışması Durumu: Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir.

Finansal Destek: Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir.

Yazar Katkıları: Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir.

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Diş hekimliğinde esansiyel yağların kullanımı

Usage of essential oils in dentistry

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ÖZ

Periodontal hastalık, mevcut oral floranın disbiyozu nedeniyle periodonsiyumun yıkımına yol açan ilerleyici, enfeksiyöz bir inflamatuvar hastalıktır. Patojenik mikroorganizmalar, periodontal hastalığın etiyolojik faktörüdür, patojene karşı gelişen immüno-inflamatuvar yanıt hastalığın ilerlemesinde rol oynar. Periodontal hastalık sırasında, reaktif oksijen türlerinin aşırı üretimi ile onları detoksifiye eden antioksidanların yetersizliği sonucu oksidatif stres meydana gelir. Oksidatif stres, periodonsiyumun yıkımına neden olmaktadır. Bu nedenle, reaktif oksijen türlerinin antagonisti olarak, antioksidanlar periodontal hastalıkların tedavisinde yardımcı olabilmektedir. Bitkiler, periodontal sağlığın korunmasında eşsiz rol oynayan bazı dikkat çekici özelliklere sahiptir. Bu özellikler geleneksel periodontal tedavinin sonuçlarını iyileştirebilecek potansiyele sahiptir. Bu derlemenin amacı, periodontal hastalıkların tedavisine potansiyel katkıları olan çeşitli esansiyel yağlar hakkında bilgi vermektir.

Anahtar Kelimeler: Antioksidan, antimikrobiyal, esansiyel yağlar, periodontal hastalık

ABSTRACT

Periodontal disease is a progressive, infectious inflammatory disease that leads to the destruction of the periodontium due to dysbiosis of the existing oral flora. Pathogenic microorganisms are the etiological factor of periodontal disease, the immuno-inflammatory response against the pathogen plays a role in the progression of the disease. During periodontal disease, oxidative stress occurs as a result of overproduction of reactive oxygen species and insufficiency of antioxidants that detoxify them. Oxidative stress causes destruction of the periodontium. Therefore, as antagonists of reactive oxygen species, antioxidants can help in the treatment of periodontal diseases. Plants have some remarkable properties that play a unique role in maintaining periodontal health. These properties have the potential to improve the results of traditional periodontal treatment. The purpose of this review is to provide information about various essential oils that have potential contributions to the treatment of periodontal diseases.

Keywords: Antioxidant, antibacterial, essential oil, periodontal disease

GİRİŞ

Bitkiler, yüzyıllardır birçok hastalığın tedavisinde çok çeşitli amaçlarla kullanılmıştır. Antimikrobiyal özellikleri nedeniyle bitkilerin terapötik kullanımları tarih öncesi çağlardan beri iyi bilinmektedir ve uzun zamandır yaygın olarak kullanılmaktadır (1). Esansiyel yağlar, bileşenlerinin biyolojik ve yapısal çeşitliliği nedeniyle, yeni antimikrobiyal, antifungal ve antiparaziter bileşiklerin keşfi için benzersiz bir kaynak oluşturmaktadır (2,3). Periodontal tedavinin ilk hedefi mekanik enstrümantasyon yoluyla mikroorganizmaları ve mikroorganizmaların neden olduğu yan ürünleri ortadan kaldırmaktır (4). Periodontal hastalık etiyolojisinde belirli spesifik bakterilerin rolü vardır ve mekanik enstrümantasyon ile bakterilerilerin tamamı sulkustan ve çevre dokudan elimine edilememektedir. Bu nedenle çeşitli lokal ve sistemik antimikrobiyal ajanlar mekanik tedaviye yardımcı olarak kullanılmıştır (5). Ancak bu ajanların, başarı oranları istenilen seviyede değildir. Bitkisel ajanlar, antioksidan ve antienflamatuvar özellikleri sebebiyle periodontal hastalıkların önlenmesi ve tedavisi için merak uyandıran bir araştırma alanı olmuştur. Fenoller ve bunların türevleri olan aromatik maddeleri sentezleme yeteneğine sahip bitkilerden elde edilen esansiyel yağların birçoğunun antimikrobiyal aktivite gösterdiği tespit edilmiştir. Bu derlemenin amacı, çeşitli esansiyel yağların antimikrobiyal aktivitelerini ve periodontal hastalıkların tedavisinde kullanımını gözden geçirmektir (6,7).

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Son yıllarda, çeşitli araştırmacılar tarafından esansiyel yağ bazlı formülasyonlar ve bunların ağız bakımındaki uygulamaları ile ilgili birçok ürün patentlenmiştir (8). Birkaç aktif bileşenden birini içeren ağız gargaralarının antiplak ve antiinflamatuvar etkinlikleri, kısa ve uzun dönem klinik çalışmalarla iyi bir şekilde desteklenmiştir (9). Yakın tarihli bir meta-analizde bu tür klinik deneylerin sonuçları, esansiyel yağ kombinasyonlarını içeren ağız gargaralarının günlük ağız bakım rutininde kullanımını desteklemektedir (10). Bir başka kontrollü klinik çalışmada ise esansiyel yağ içeren antiseptik gargaranın 2 hafta kullanımının, erken ile orta dereceli periodontitisin göstergesi olarak 4 ile 7 mm'lik cep derinliklerine sahip bölgelerde subgingival periodontopatojenlerde önemli azalmalar sağlayabildiğini göstermiştir (11). Esansiyel yağ gargarası kullanan bireylerde esansiyel yağ bazlı gargaranın antiplak etkisini araştırmak için yapılan bir başka kontrollü klinik çalışmada vital boyama yöntemi kullanılmıştır (12). Çalışma sonucunda esansiyel yağ içeren gargara kullanan bireylerde plak bakterilerinin %78,7 oranında azaldığı gözlenmiştir. Kontrol grubunda ise bu oran %27,9 olarak bulunmuştur. Sonuçlar, formülasyonun in vivo bakterisidal aktivitesini doğrulamıştır (12). Periodontitisli kişilerde subgingival alanda bulunan spesifik periodontopatojenler üzerindeki etkisini inceleyen bir araştırma, esansiyel yağ gargarasının, plakta streptokokları ve *Streptococcus mutans*'ı sırasıyla %69,9 ve %75,4 oranlarında önemli ölçüde azalttığını göstermiştir (13). Hosamane ve ark. (14)'nın fesleğen özü kökenli çeşitli konsantrasyonlarda gargara formunu değerlendirdikleri çalışmalarında, fesleğen özü kökenli gargaranın, *Prevotella intermedia* ve *Fusobacterium nucleatum* mikroorganizmalarının inhibisyonunu sağlamıştır ve test ile plasebo grupları arasında istatistiksel olarak anlamlı bir fark bulunmuştur (14). Bir başka çalışmada, limon otu esansiyel yağı ≤%2 konsantrasyonda uygulandığında özellikle tetrasiklin hidroklorüre dirençli olan *Actinomyces naeslundii* ve *Porphyromonas gingivalis* gibi periodontal patojenleri inhibe ettiği tespit edilmiştir (11).

Esansiyel yağ ile formüle edilmiş diş macunlarının, periodontal inflamasyonu azaltarak yara iyileşmesi üzerinde de olumlu etkiler gösterebileceği düşünülmüştür. Bu durumu araştıran bir meta analizde yirmi çalışma dahil edilmiştir (15). Sayıları 20 ila 316 arasında değişen katılımcılar 1 ila 48 hafta boyunca günde en az iki kez esansiyel yağ ile formüle edilmiş diş macunları ile dişlerini fırçalamıştır. Araştırma sonuçlarına göre on dört klinik çalışma, test grubunda plasebo grubuna kıyasla azalmış periodontal inflamatuvar koşullar göstermiştir. Üç çalışmada, plasebo grubuna kıyasla test grubunda periodontal patojenlerde bir azalma olduğu gözlenmiştir. Bir çalışmada ise iki grup arasında anlamlı farklılık tespit edilememiştir (15). Araştırma sonuçlarına göre esansiyel yağ ile formüle edilmiş diş macunlarının periodontal inflamasyonun klinik ve mikrobiyolojik parametreleri üzerinde yararlı etkileri olduğu bulunmuştur (15). Hass ve ark. (16)'nın sabit ortodontik aparey kullanan hastalarda biyofilm ve dişeti inflamasyonu kontrolünde esansiyel yağların etkinliğini inceledikleri çalışmalarında, 6 ay sonra, mekanik tedaviye ek olarak kullanıldığında bu hastalarda plak ve dişeti inflamasyon düzeylerinin %50'ye kadar düştüğü sonucuna varmışlardır (16). Bir başka çalışmada ise, implant tedavisi sonrası 3 aylık takip döneminde günde iki kez esansiyel yağların sistematik kullanımı, plaseboya (hidroalkolik solüsyon) kıyasla plak ve gingival indeks yüzdelerinde önemli bir azalmaya yol açmıştır (17).

Tarçın, biberiye, hindistan cevizi portakal, nane, zencefil, kekik, karanfil, okaliptüs, mandalina ve misket limonu esansiyel yağları içeren diş macunlarını inceleyen bir çalışmanın sonuçları çürük oluşumuyla ilişkili mikroorganizmalara (*Streptococcus mutans* ve *Lactobacillus lactis*) karşı önemli antimikrobiyal ve antiplak aktiviteleri gösterdiğini ortaya koymuştur (18).

Esansiyel yağlar, kandida türlerine karşı da çok yönlü antifungal aktivite gösterebilmektedir. Özellikle protez kullanan hastalarda antifungal aktivite son derece önemlidir (19). Ağız boşluğu, mikroflora ve kandida türlerinin doğal yaşam alanıdır. Floranın bileşimi, yaş, ağız boşluğu topografyası, dişlerin durumu, beslenme, nefes alma alışkanlıkları, tütün kullanımı, ağız hijyeni, diş kaybı ve protetik restorasyonların kullanımından etkilenmektedir. Parsiyel protezlerin akrilik tabanı, mukoza yüzeyinin önemli bir bölümünü kaplayarak bakteri ve mantarların protez plağı şeklinde birikmesi için uygun koşullar yaratırken, yüksek nem, yüksek sıcaklık, anaerobik ortam ve tükürüğün temizleme etkisinden uzak bir alandır. Ayrıca heterojen ve gözenekli bir yapıya sahip olan akrilik materyal, suyu emerek ağız boşluğunda şişer ve mikroorganizmaların agregasyonunu daha da kolaylaştırır (20,21). Bu durum, özellikle biyofilmlerde artan ilaç direnciyle birleştiğinde, yeni antimikrobiyal ajanların, özellikle fungisitlerin keşfedilmesine daha büyük bir ilgiye yol açmıştır (22,23).

AĞIZ VE DİŞ SAĞLIĞINDA SIK KULLANILAN ESANSİYEL YAĞLAR

Kekik Yağı

Kekik, *Lamiaceae* familyasına aittir ve başlıca temsili türü *Origanum vulgare*'dir. Kekik 400-1.800 m rakımlarda ve güneşli yerlerde yetişmektedir ve dağ anlamına gelen oros ve parlaklık anlamına gelen ganos kelimelerinden türemiştir. Diş hekimliğinde halitozis tedavisi ve diş ağrılarında kullanılmaktadır. Antiinflamatuvar, antikaryojenik ve antioksidan özellikleri nedeniyle diş hekimliğinde kullanılmak üzere gargara ve diş macunu

şeklinde formülasyonlar üretilmesi adına birçok çalışma yapılmıştır (2,24).

Karanfil Yağı

Karanfil yağı, *Syzygium aromaticum* ağacından elde edilmektedir ve diş hekimliğinde önemli bir yeri olan öjenolün ana kaynağıdır (25). Karanfil yağı, siklo-oksijenaz-2 ve lipo-oksijenaz enzimlerini inhibe ettiği için spesifik bir antiinflamatuvar özelliğe de sahiptir. Günümüze kadar yapılan tüm çalışmalar karanfil esansiyel yağının periodontal hastalığın tedavisi için spesifik anti-plak ve antiinflamatuvar ajanlar olarak kullanılmak üzere büyük bir potansiyele sahip olduğunu göstermiştir (26). Ayrıca diş eti yaraları ve yoğun ağrı varlığında dişin, karanfil yağı emdirilmiş pamuk ile ovulması ağrıyı önemli miktarda azaltıcı etki göstermektedir. Bütün karanfil çiğnenmesi ise ağız kokusunu engellemektedir (27).

Lavanta Yağı

Lavanta esansiyel yağı, *Lavandula angustifolia* Mill (*Lamiaceae*) bitkisinin taze çiçekli kısımlarından su buharı distilasyonu ile elde edilmektedir. Antimikrobiyal, antiviral, antifungal, antiinflamatuvar etkiler göstermektedir ve bu özellikleri nedeniyle diş hekimliğinde kullanılmaktadır (28).

Okaliptüs Yağı

Anavatanı Avustralya olan okaliptus mersingiller familyasından bir ağaç türüdür (29). Okaliptus esansiyel yağı kuvvetli antiviral, antimikrobiyal ve antifungal aktiviteye sahiptir (30). Özellikle endodonti alanında tekrarlayan kanal tedavilerinde guta ve pat çözücü ajan olarak kendine önemli yer bulmuştur. Ayrıca okaliptus yağları, *Lactobacillus acidophilus* ve *Streptococcus mutans* gibi oral patojenler üzerinde inhibitör bir etki göstermektedir, bu durum da okaliptusun antikaryojenik bir ajan olarak kullanılmasını uygun hale getirmiştir (31).

Nane Yağı

Nane, mor çiçeklere ve yeşil yapraklara sahip, nemli bölgelerde yetişen, yoğun kokulu, mentol, metil asetat, tanen ve C vitamini içeren bir bitkidir (32). Yapraklarının sahip olduğu uçucu yağlarda bulunan mentol antiseptik, antispazmotik, karminatif özelliklere sahip olmasında oldukça etkilidir. Nane yağı gargarası gingival inflamasyona karşı oldukça etkin bir şekilde kullanılmaktadır. Gargara aynı zamanda ağız kokusuna karşı da oldukça etkilidir (27,33). Ayrıca nane yağı emdirilmiş pamuk uygulamasının diş ağrılarını gidermede önemli bir etkiye sahip olduğu belirtilmektedir (34).

Çay Ağacı Yağı

Çay ağacı yağı, diş hekimliğinde kullanılmasını sağlayabilecek birçok özelliğe sahip beyaz kabuğu, koyu yeşil iğne benzeri yaprakları ve renkli çiçekleri olan yerli bir Avustralya bitkisidir. Antimikrobiyal, antifungal ve antiseptik özelliklere sahiptir (35). Çay ağacı yağı, özellikle gargara ve diş macunu gibi birçok ağız diş sağlığı ürününün içeriğinde yer almaktadır. Son dönemlerde çay ağacı yağı içerikli birçok preparat diş eti sağlığı için kullanılmaktadır ve etkileri hala araştırılmaktadır. Ayrıca Patri ve Sahu tarafından yapılan klinik bir çalışmada aloe vera ile çay ağacı yağı kombine olarak kavite dezenfektanı olarak kullanılmış ve smear tabakasını anlamlı derecede uzaklaştırmıştır (36). Diş hekimliğinde oral kandidiyazis, anguler chelitis ve protetik stomatopati gibi kandida türlerinin neden olduğu bir grup enfeksiyon tedavisinde kullanılmaktadır (37). Wiatrak ve ark. (38) yaptıkları çalışmalarında, çay ağacı yağı içerikli diş macunu kullanan hareketli bölümlü protezli hastalarda kontrol grubuna göre izole edilen bakteri suşları ve mantarların sayısında azalma olduğu gösterilmiş ve bu ürünün antimikrobiyal ve antifungal aktivite gösterdiği sonucuna varılmıştır. Ayrıca, çalışmanın başlangıcında, çalışma grubu hastalarının %52'sinde sondalamada kanama görülürken, diş macununu 28 gün kullandıktan sonra, bu hastaların hiçbirinde sondalamada kanama görülmediği rapor edilmiştir. Çalışmanın sonuçları, modifiye dişeti kanama indeksi değerlerinde istatistiksel olarak anlamlı azalma göstermiştir. Bu durum çay ağacı yağı içeren diş macununun sadece periodonsiyum üzerindeki yararlı etkisini değil, aynı zamanda antiflojistik aktivitesini de doğrulamaktadır (38).

Tarçın Yağı

Defnegiller familyasından olan tarçın Güney ve Güneydoğu Asya'da yetişmektedir. Tarçın kabuğundan elde edilen tarçın esansiyel yağı, sinnamaldehitin varlığı nedeniyle antimikrobiyal özelliğe sahiptir (39). 1996 yılında Cai ve Wu tarafından yapılan çalışmada tarçının antifungal etkili olduğu ve karyojenik oral patojenlerin adezyonunu engelleyici özelliğinin bulunduğu saptanmıştır. Antikaryojenik etki gösterdiklerinden dolayı tarçından hazırlanan gargaralar oral patojenler için antimikrobiyal olarak kullanılabilmektedir (40).

Hint Yağı

Hint yağı *Euphorbiacea* familyasına aittir ve birçok mikroorganizma ve bakteri üzerinde antimikrobiyal etki göstermektedir. Yapılan çalışmalarda *Fusobacterium nucleatum*, *Prevotella nigrescens*, *Clostridium perfringens* ve *Bacteroides fragilis* gibi bakterilere karşı antimikrobiyal etkinliği belirtilmiştir. 2002 yılında yapılan çalışmada pulpa nekrozu olan dişlere uygulanan kanal tedavilerinde hint yağı kullanılmış ve sonuçlar antimikrobiyal etkinliği nedeniyle kanal tedavilerinde kullanılabileceğini göstermiştir (34).

Portakal Yağı

Latince adı *Citrus sinensis* olan portakal, buhar distilasyon yöntemi ile kabuğundan esansiyel yağ elde edilebilen bir meyvedir. Portakal esansiyel yağının içeriğindeki ana bileşen olan limonenin ve diğer bileşenlerinden beta

pirsen ve alfa pinenin güçlü antimikrobiyal ve antifungal özellikleri olduğu bilinmektedir (41,42). Antiseptik etkisi olan portakal esansiyel yağının aynı zamanda özellikle içeriğindeki beta mirsen bileşeninden kaynaklı ağrı kesici etkisi de vardır. Ayrıca portakal yağının güta perkanın yumuşamasında halotan ve kloroform gibi geleneksel çözücülerden daha etkili olduğu görülmüştür (43).

SONUÇ

Antimikrobiyal, antiinflamatuvar, antiseptik, antifungal ve antikaryojenik özelliklerinden dolayı diş hekimliğinde diş macunu, jel ve gargara formülasyonlarda yer alan esansiyel yağların diş ve diş eti hastalıklarında önemli terapötik etkinliğe sahip olduğunu gösteren çalışmalar literatürde yer almaktadır. Günümüzde esansiyel yağların periodontal hastalıklar üzerindeki teröpatik etklerinin daha iyi anlaşılması ve esansiyel yağ bazlı yeni formülasyonların geliştirilmesi adına in vitro,in vivo çalışmalar ve hayvan deneyleri yapılmaya devam edilmektedir (44-50). Tüm bu bilgiler ışığında esansiyel yağların periodontal hastalıkların tedavisinde kullanımı araştırmaya hala açık olan bir konudur. Literatürdeki çalışma sonuçlarının kıyaslanabileceği yeni klinik çalışmalara ihtiyaç vardır.

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Review / Derleme

MEDICINE PALLIATIVE CARE

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Relationship between periodontal disease and vitamin D

Periodontal hastalık ve D vitamini ilişkisi

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ABSTRACT

Vitamin D is a hormone synthesized by human skin cells or consumed through diet with immunomodulatory, anti-inflammatory, and antiproliferative effects. Vitamin D deficiency may increase the risk of periodontal disease by causing decreased bone mineral density, osteoporosis, progression of periodontal diseases, and resorption of the jawbone. In addition, vitamin D is important for bone metabolism, alveolar bone resorption, and the prevention of tooth loss. It increases the antibacterial defense of gingival epithelial cells, reduces gingival inflammation, accelerates postoperative wound healing after periodontal surgery, and is a key supplement functioning as a prophylaxis in periodontology. The present review study aims to highlight the role of vitamin D in periodontal disease.

Keywords: Periodontititis, vitamin D, 25(OH)D3, periodontal treatment, 1.25(OH)2D3

ÖZ

D vitamini, insan deri hücreleri tarafından sentezlenen veya diyet yoluyla tüketilen immünomodülatör, antienflamatuar, antiproliferatif etkilere sahip bir hormondur. D vitamini eksikliği kemik mineral yoğunluğunun azalmasına, osteoporoza, periodontal hastalıkların ilerlemesine ve çene kemiğinde rezorpsiyon oluşmasına neden olarak, periodontal hastalık riskini artırabilir. Ayrıca D vitamini kemik metabolizması, alveolar kemik rezorpsiyonu ve diş kayıplarının önlenmesi için de önemlidir. Diş eti epitel hücrelerinin antibakteriyel savunmasını arttırır ve dişeti enflamasyonunu azaltır, periodontal cerrahi sonrası postoperatif yara iyileşmesini hızlandırır ve periodontolojide profilaksi olarak kullanılan önemli bir takviyedir. Bu derlemenin amacı, periodontal hastalıkta D vitamininin rolünü vurgulamaktır.

Anahtar Kelimeler: Periodontititis, D vitamini, 25(OH)D3, periodontal tedavi, 1,25(OH)2D3

INTRODUCTION

Periodontal diseases are complex disorders resulting in the interaction of biofilm with the host immuno-inflammatory response and subsequent changes to soft and hard tissue hemostasis (1,2). Inıtial human and animal studies to explore the pathogenesis, prevention, and treatment of periodontal diseases in the 1960s concluded that bacteria assume a key role in initiating gingivitis and periodontitis (3,4). Accordingly, the final opinion is that "bacteria lead to periodontal disease." In this model, bacteria-secreted products and metabolism residues cause tissue destruction. Yet, the research in the 1980s revealed that the host immuno- inflammatory response plays a central role in the development of periodontal diseases. The products secreted by polymorphonuclear cells, the very first defense mechanism against bacteria and their products, also cause indirect tissue destruction (5,6). In 1997, it was shown that various genetic, environmental, and acquired risk factors with the bacteria-host relationship play a role in the pathogenesis of periodontitis (7). Among the fat-soluble vitamins, vitamin D is a steroid vitamin that can be synthesized endogenously with hormone-like functions. Vitamin D3 can be taken in two different ways through diet: ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3). Cholecalciferol is the primary dietary source of vitamin D and is mainly found in foods of animal origin. Ergocalciferol, on the other hand, is extracted from plant sterols. A significant portion of vitamin D3 (estimated to be about 80%) is produced endogenously in the skin from 7-dehydrocholesterol with the effects of UV rays. After reaching the liver together with vitamin D (D3 or D2) absorbed from food, skin-produced vitamin D3 is hydroxylated by the enzyme 25-hydroxylase and turns into its inactive form, 25(OH) D3, also known as calcidiol. Circulating to the kidneys,

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25(OH)D3 is metabolized by the enzyme 1α-hydroxylase to its active form, 1,25(OH)2D3, also known as calcitriol, or to its inactive metabolite, 24,25-dihydroxyvitamin D3, by the enzyme 24-hydroxylase (8, 9). It is a form of vitamin D with a concentration of about 1000 times that of 1,25(OH)2D3 (10).

Vitamin D deficiency is characterized by low calcium levels and is a stimulus that also elevates parathyroid hormone (PTH) levels. PTH is secreted while serum PTH concentration increases in response to low serum calcium levels. Calcium reabsorption from the kidneys and 1α-hydroxylase activity increase, but 24- hydroxylase activity decreases. Thus, intestinal calcium absorption is boosted with increased production of 1,25(OH)2D3. Along with elevated vitamin D levels, high levels of calcium suppress PTH production. While PTH increases in hypophosphatemia and hypocalcemia, it is inhibited by 1,25(OH)2D3 and FGF-23 (11). Along with PTH, 1,25(OH)2D3 stimulates osteoclasts by osteoblasts and induces the release of calcium from bones to blood (12). Nevertheless, 1,25(OH)2D3 does not robustly inform about vitamin D levels due to its short half-life. With a half-life of 12-19 days, 25(OH)D3 is considered the most accurate indicator of vitamin D in serum.

It was reported that about one billion people worldwide suffer from vitamin D deficiency or insufficiency (13). The 2019 guideline by the Turkish Society of Endocrinology and Metabolism (TEMD) suggests measuring serum 25(OH)D3 levels to assess vitamin D status. In this measurement, serum 25(OH)D3 level > 30 ng/mL is accepted as adequate vitamin D level, 20-30 ng/mL as vitamin D inadequacy, < 20 ng/mL as vitamin D deficiency, and < 10 ng/mL as severe vitamin D deficiency. The TEMD Osteoporosis and Metabolic Bone Diseases Working Party determines the minimum daily vitamin D requirement for bone and muscle health of adults (19-70 years) as 600 IU and the need to keep the serum 25(OH) D3 level at 30 ng/ml as 1500-2000 IU. Satisfying daily vitamin D needs requires food consumption and sun exposure, as well as vitamin D supplementation. People at risk for vitamin D deficiency need to be supplemented with vitamin D at the recommended doses. The safe upper limit of vitamin D is known to be 4000 IU per day, and every 100 IU (2.5 micrograms) of vitamin D increases serum 25(OH)D3 level by 0.7-1 ng/ml (14). Sufficient vitamin D levels allow the formation of the appropriate calcium-phosphorus compound, resulting in adequate bone mineralization. Yet, low vitamin D levels are associated with type 2 diabetes mellitus (T2DM), insulin resistance, hypertension, and endothelial dysfunction. In addition to its role in bone mineralization and calcium balance, vitamin D has antioxidant, anti-inflammatory, antiangiogenic, immunomodulatory, and antiproliferative properties. Vitamin D level is key in bone development since boosting the absorption of magnesium, calcium, and phosphate. Osteomalacia, a severe metabolic end-stage disease, may develop in adults due to low (< 4-10 ng/ml) vitamin D levels. Renal 1-alpha hydroxylation has strict control mechanisms in the synthesis of vitamin D. When being sufficient, vitamin D allows intestinal calcium absorption to reach 30-40% of dietary intake; however, vitamin D deficiency may lead to the inability to absorb more than 10-15% of dietary calcium (15,16).

Current evidence demonstrates the immunomodulatory effect of 1,25(OH)2D3, particularly in innate immunity, can be acknowledged as anti-inflammatory and immunomodulatory, including up-regulation of expression of antimicrobial peptides, promotion of phagocytic killing of pathogenic microorganisms, down-regulation of inflammatory factor release, and reduction of inflammation (15,17). Thanks to its key role in calcium/phosphorus homeostasis and bone physiology, vitamin D also holds a central place in the optimal functioning of the cardiovascular, endocrine, and immune systems. It also helps reduce the risk of many chronic diseases (e.g., cancer, autoimmune disease, infectious disease, hypertension, and cardiovascular diseases). Moreover, vitamin D supports immune regulation and function by controlling more than 200 genes responsible for cellular proliferation, differentiation, and apoptosis (18, 19, 16).

Relationship between Vitamin D and Periodontal Disease

Previous research reported that periodontal ligament cells and human gingival fibroblasts have the ability to synthesize vitamin D (20). It was also found that both 1,25(OH)D3 and 25(OH)D3 regulate inflammatory responses in periodontal ligament cells through the VDR and may affect inflammatory processes in periodontal disease (21). Moreover, it was shown that 25(OH)D3 suppresses the expression of IL-1ß, IL-6, and TNF-α and improves alveolar bone loss (22, 23). The "perio protective" effects of vitamin D were documented to be related to human gingival fibroblasts' ability to regulate inflammatory cytokine production following the AGE-RAGE interaction (24). In vitro studies showed that vitamin D can reduce the number of Porphyromonas gingivalis through active autophagy (25) and the inflammatory burden of periodontitis in rodent models (26, 27). Vitamin D may affect periodontal disease through both its immunomodulatory effects and its effects on bone mineral density. A meta-analysis study concluded an association between specific VDR polymorphisms and susceptibility to periodontitis in humans (28). It was also shown that there are significant relationships between vitamin D and calcium and

periodontal diseases (29). Another study reported a negative correlation between serum vitamin D levels and attachment loss, suggesting that increased vitamin D levels have a positive effect on periodontitis (30). It was previously found that low serum 25(OH)D3 levels are associated with periodontitis and gingival inflammation (31). In another study, high serum 25(OH)D3 level was associated with a lower prevalence of periodontal disease (32). It was also reported that daily calcium and vitamin D supplementation of more than 800-1000 IU can reduce the severity of periodontal disease (33). In addition, it was discovered that 25(OH)D3 levels increase in patients with chronic periodontitis following a dental cleaning and root surface straightening (34). In the literature, periodontal treatment with vitamin D supplementation was reported to improve periodontal health; therefore, vitamin D can be used as a supplement in the treatment of moderate and severe periodontitis (35).

A previous study identified defects in dental and mandibular bone mineralization In mice deficient in 1,25(OH)D3 and reported that vitamin D assumes a dominant role in hard tissue formation than PTH (36). In an animal study, it was found that mice deficient in 1,25(OH)D3 had greater alveolar bone loss, that gene expression levels of IL-1β, TNF-α, MMP-3, and MMP-8 markedly increased, and bone mineral density decreased significantly independent of extracellular calcium and phosphorus levels and age (37). In the same study, it was shown that the reduced bone volume in vitamin D-deficient mice was due to decreased formation rather than increased resorption, as the number and surface of TRAP-positive osteoclasts did not change between groups, and that vitamin D exhibited an anabolic effect. In addition, it was stated that the impact of vitamin D on alveolar bone is directly intrinsic regardless of diet. In another study, 1,25(OH)D3 deficiency induced a higher inflammatory response in gingival tissues with greater numbers of NF-κB p65 and CD3+ cells, which is consistent with reports showing the anti-inflammatory effect of 1,25(OH)D3 by regulating the biosynthesis of pro-inflammatory molecules via NF-κB, which mediates oral infections and periodontitis (38, 39). As a result, 1,25(OH)D3 deficiency accelerated bone loss by inhibiting the osteoblastic bone formation and boosting periodontal tissue degeneration regardless of phosphorus and age. The above- mentioned findings bring novel insights into the deleterious effects of vitamin D deficiency on the periodontium, thereby promoting the idea that vitamin D plays a protective role in periodontal tissues (37). Possible underlying biological mechanisms are that vitamin D has the function of regulating calcium maintenance, which is key in bone metabolism, and its anti-inflammatory or antimicrobial effects (40). Despite increased scholarly interest in the relationship between vitamin D and the development and progression of periodontal diseases, the literature hosts inconsistent findings on uncertainties about whether vitamin D deficiency contributes to the severity of periodontitis (31,32,41-44). In their randomized, double-blind, placebo-controlled clinical study comparing systemic vitamin D and calcium administration with calcium-only administration, Schulze-Spate et al. (2016) found no difference between the groups by graft resorption or bone formation following the maxillary sinus augmentation procedure and reported a higher bone remodeling activity associated with higher vitamin D levels (45). Supplementation with vitamin D was shown to have a dose-dependent anti-inflammatory impact on gingivitis (46). Following periodontal treatment, the healing of intraosseous defects was found to be better in patients with adequate 25(OH)D3 levels compared to those with insufficient 25(OH)D3 levels (47). It was also shown that the use of vitamin D3 in diabetic mice significantly reduces the destruction of periodontal tissues and is a convenient and effective method in modulating immune function thanks to its effect of promoting cathelicidin production (48). The literature documented that patients with chronic periodontitis have lower 25(OH)D3 levels compared to healthy periodontal individuals (49). Recently, low serum vitamin D concentrations have been demonstrated in T1DM and T2DM patients (50, 51) and found to be associated with an increased risk of cardiovascular mortality. In addition, serum 1,25(OH) D3 levels were found to be significantly increased following anti-infective periodontal therapy in T1DM patients (52). Moreover, the previous studies uncovered an increase in PTH after periodontal treatment in T1DM patients with moderate or severe periodontitis and that the increase in serum 1,25(OH)D3 is largely independent of serum PTH (53). Some studies also suggested that vitamin D is inversely related to gingival bleeding and probing depth rather than tooth and alveolar bone loss (32) and that patients with low 25(OH)D3 levels can be kept periodontally stable for five years, which may imply no relationship between vitamin D and tooth loss (43,44).

CONCLUSION

Assuming significant functions in the bodily systems, Vitamin D is essential for adequate calcium absorption in bones. Vitamin D deficiency is often shown to be associated with periodontal disease. Vitamin D supplementation can improve periodontal health in periodontal therapy, and it can be utilized as a supplement in the treatment of moderate to severe periodontitis. In periodontal diseases, vitamin D levels should be checked and supplemented if deficient considering that vitamin D level is related to periodontal health.

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Review / Derleme

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Platelet-rich fibrin and its use in dentistry

Trombositten zengin fibrin ve diş hekimliğinde kullanımı

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ABSTRACT

PRF is often defined as an autogenous fibrin biomaterial rich in leukocytes and platelets and is clinically easy to obtain and use. Various methods are available to prepare platelet concentrates, albeit the contents of platelet concentrates obtained by different methods also vary. Accordingly, they are divided into P-PRF, L-PRF, i-PRF, A-PRF, and A-PRF+, considering the thrombocyte leukocyte concentrates and fibrin contents. PRF is widely adopted in dentistry as promoting angiogenesis, immunity, and epithelial proliferation.

Keywords: PRF, P-PRF, L-PRF, i-PRF, A-PRF, A-PRF+

ÖZ

TZF, lökositten ve trombositten zengin otojen bir fibrin biyomateryali olarak tanımlanmıştır . TZF'nin elde eldilmesi ve klinik kullanımı kolaydır. Trombosit konsantrelerinin hazırlanmasında değişik yöntemler mevcuttur. Farklı yöntemlerle elde edilen trombosit konsantrelerinin içeriği de farklıdır. Buna göre trombosit lökosit konsantrelerinin ve fibrin içerikleri göz önünde bulundurularak S-TZF, L-TZF, E-TZF, G-TZF ve G-TZF+ olarak gruplara ayrılmaktadır. TZF, anjiojenez, bağışıklık ve epitel proliferasyonu desteklediği için diş hekimliğinde yaygın bir şekilde kullanılmaktadır.

Anahtar Kelimeler: TZF, S-TZF, L-TZF, E-TZF, G-TZF, G-TZF+

INTRODUCTION

The use of platelet concentrations in medicine was initiated in the 1990s and has expanded until today. Platelets are cells that initiate and promote wound healing by releasing various growth factors. Such growth factors create signals stimulating cell proliferation and affect connective tissue healing, bone regeneration and repair, increase in mitogenesis of fibroblasts and angiogenesis of the wound site, and macrophage activation (29). The use of growth factors to contribute to wound healing has been found to be rather interesting, and thus, many platelet-derived blood products have been developed using different techniques. Yet, the literature has conceptual confusion since different platelet-derived blood products, in other words, platelet-derived blood concentrations, are called by similar names. All available platelet-rich plasma (PRP) methods bear some common aspects. Blood is drawn with anticoagulant just before surgery and immediately centrifuged. Platelet concentration preparation time is variable but is always accomplished within an hour. The first centrifugation step separates the blood into three layers: while red blood cells are at the very bottom layer, acellular plasma (platelet-poor plasma) occupies the top layer. The thrombocyte-rich buffy coat is found between these two layers. Finally, the platelet concentrate is administered to the surgical site through an injector with thrombin and/or calcium chloride (or similar factors) to trigger platelet activation and fibrin polymerization (13).

PRF, on the other hand, is the latest developed of these protocols. In this protocol, blood is drawn without any anticoagulant and immediately centrifuged. A natural coagulation process is allowed, and L-PRF is easily collected without the intervention of any biochemical agent in the blood (i.e., without the need for anticoagulants, thrombin, or calcium chloride) (12). This open-intervention method is considered the simplest and lowest-cost one ever developed (15).

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Choukroun's Platelet-rich Fibrin

The PRF protocol was first described by Choukroun in France in 2001 and introduced in the review series published by Dohan et al. (7) in 2006. PRF is a second-generation platelet concentrate that allows for obtaining a membrane rich in platelets and growth factors. The protocol is not dependent on a medical device or specialized machine and can be easily adopted. Unlike fibrin glue or PRP, it is not a blood-derived product. Venous blood is collected into dry glass tubes and centrifuged at a low speed [about 400g: 3000 rpm-10 min. or 2700 rpm-12 min.]. Since no anticoagulant is given to the blood in PRF, clotting begins as soon as the blood contacts the tube (10). Platelet activation and fibrin polymerization are promptly triggered in the absence of anticoagulants. Fibrinogen is initially formed at the neck of the tube before circulating thrombin converts it to fibrin and then gathers in the middle. Platelets are theoretically trapped in the fibrin mesh; therefore, three layers are formed after centrifugation: red blood cells at the bottom, acellular plasma at the top, and PRF clot in the middle. PRF clot generates a strong fibrin matrix with a complex three-dimensional structure in which most of the clot, leukocytes, and platelets are concentrated (11).

The success of the method relies entirely on the rate of collection and centrifugation of blood since the only way to achieve a clinically usable PRF is to act quickly. If not treated quickly enough, the fibrin will likely polymerize, and the resulting product will contain negligible fibrin mesh. A clinically usable PRF has serum and platelets trapped in the fibrin mesh. When serum from the fibrin clot is removed, a highly resistant autologous fibrin membrane will remain between two sponges. The previous research reported the use of this autologous biomaterial in maxillofacial and plastic surgery and implant surgery (31).

In this method, the fibrin mesh obtained by slow centrifugation of blood is ensured to be three-dimensional and flexible, allowing cytokine and cell migration (12).

Unlike PRP, PRF does not dissolve immediately after administration and forms slowly, similar to a natural blood clot. This method allows for the collection of platelets and leukocytes with high efficiency and preservation of leukocytes. In addition, platelets are activated during the process, which helps platelet and leukocyte growth factors to be absorbed into the fibrin matrix (12). This method ensures obtaining high volumes of PRF for more extensive operations using an eight-tube centrifuge or any modified laboratory centrifuge. The method is also low-cost and convenient; therefore, it becomes advantageous for widespread use in daily practice (15).

PRF Content

PRF obtained by centrifugation of blood taken with a standard 10 ml syringe contains all the components found in 10 ml blood:

- Platelets
- Platelet growth factors
- Leukocytes
- Cytokines
- Fibrin
- Circulating stem cells.

Platelets are discoidal and anucleated cells with a lifespan of 8-10 days, and their cytoplasm has granules to be released into the environment when activated. β-granules contain specific (such as β-thrombomodulin) and non-specific (fibronectin, thrombospondin, fibrinogen, other coagulation factors, growth factors, fibrinolysis inhibitors, and immunoglobulins) products. They need to be activated to initiate and support hemostasis in the wound area. As a result of their degranulation, they also provide the release of cytokines and growth factors that initiate the first phase of wound healing within the fibrin matrix. Following centrifugation, platelets are only found in the region of the PRF clot. The previous research demonstrated that platelets are particularly dense at the junction of the PRF and the red clot where the red blood cells are concentrated. The absence of anticoagulants in the blood during PRF formation allows for intense platelet activation in the glass tube, resulting in the release of platelet cytokines and growth factors. These cytokines are then trapped in the flexible fibrin mesh emerging due to slow polymerization. Glycosaminoglycans (heparin, hyaluronic acid) are also embedded in the PRF matrix; they are histologically bound to the fibrillar structure of fibrin. The binding power of glycosaminoglycans to small circulating peptides is relatively strong, and their capacity to support cell migration and healing is pretty high (12). Choukroun, a developer of PRF, further modified it to an advanced form (A-PRF), which is expected to contain a relatively greater number of white blood cells (WBC). Because of low-speed centrifugation, this fibrin clot is softer than that of the original PRF. On the other hand, concentrated growth factors (CGF), another modified form of PRF, are prepared by repeatedly switching the centrifugation speed and are characterized as a relatively stiffer fibrin clot. Therefore, it has been anticipated that the difference in mechanical characteristics may produce a difference in the growth factor content (40).

PLATELET GROWTH FACTORS

Transforming Growth Factor - β1 (TGF-β1)

TGF-β is a very large superfamily with more than 30 members, and its most produced isoform is TGF-β1.

TGF-β1 is produced not only from the α granules of platelets but also in intercellular communication. Its effects vary by the amount applied, matrix circumference, and cell type. For example, it can easily inhibit the proliferation of osteoblasts as well as boosts them. It is considered the most potent fibrosis agent among all cytokines (5). It contributes to collagen-1 production in osteoblasts and fibroblasts (fibrosis) and is considered an inflammatory regulator thanks to its capacity to induce fibrous healing.

Platelet-derived Growth Factor (PDGF)

PDGFs are highly needed for the migration, proliferation, and survival of mesenchymal cells. Depending on the distribution of their specific receptors, they can either stimulate or inhibit the growth of these cells. They play a role in embryonic development and regeneration mechanisms in all tissues; therefore, they assume a key role in physiological recovery and pathogenesis of atherosclerosis and many other fibroproliferative diseases (e.g., neoplasms, pulmonary and renal fibrosis) (35).

Insulin-like Growth Factor (IGF)

It is knowns as a cell protective agent. IGFs are positive regulatory agents for the differentiation and proliferation of many cells, including tumor cells. Despite being proliferation mediators for cells, they are the most important cytokines regulating apoptosis by generating signals that protect cells from many apoptotic stimuli in the matrix. IGFs are found in high levels in the circulating blood, although they are secreted by platelets. A previous study revealed that IGF in PRF is not caused by platelet activation and that the highest concentration of IGF is found in plasma. In an in vitro study, TGF-β1, PDGF-BB, and IGF-1 concentrations in PRF were found to be 6.634 ng/ml, 1.419 ng/ml, and 209.68 ng/ml, respectively (13).

LEUKOCYTES

The literature on platelets often overlooks the influence of fibrin and leukocytes, two key parameters in classification. Some scholars recommend the removal of leukocytes despite the lack of scientific evidence (1). Some others, on the other hand, emphasize leukocytes in platelet concentrations because of their essential role as anti-infectious agents and in immune regulation (19).

CYTOKINES

Inflammatory Cytokines

The number of cytokines involved in inflammation is quite large. The most prominent of these are known to be IL-1β, IL-6, and TNF-α. IL-1β has a vital role in the control of inflammation. T-Helper provides lymphocyte stimulation. It also prevents the bone formation and increases its destruction together with TNF-α. TNF-α increases inflammatory cell phagocytosis and cytotoxicity capacity and the synthesis of IL-1 and IL-6. IL-6 is a differentiation factor for B lymphocytes and an activator for T lymphocytes and stimulates the release of antibodies (10).

Wound-healing Cytokines

Healing can be regarded from two aspects:

- Neutralization of the inflammatory signaling pathway by inhibiting its amplifications, an IL-4 function.
- Regulating and enhancing the development of initial healing structures (e.g., vasculature), a VEGF function.

The primary task of IL-4 is to support healing in inflammation. It increases collagen synthesis from fibroblasts and prevents the stimulation of MMP-1 and MMP-3 by IL-1β. It also inhibits all inflammatory signaling pathways mediated by IL-1β (23). Besides, VEGF is known to be the most potent and common vascular growth trigger. The endothelium holds a key role in cell behavior (e.g., proliferation, migration, specialization, and cell survival); even its presence is sufficient to initiate angiogenesis (22).

Like platelets, these cytokines are trapped in the fibrin mesh and released slowly during polymerization. These slow-release cytokines may suggest that PRF may be a key point in immune regulation. The cytokines in PRF also can control their own amount. A previous study investigated the amounts of IL-1β, IL-4, IL-6, TNF-α, and VEGF in the same amount of serum, PRF, and platelet-poor plasma (Dohan et al., 2006). The findings revealed that all parameters except VEGF were found in the highest amount in PRF, which refers to that slow blood activation in PRF leads to leukocyte degranulation. The increase in the number of immune cytokines indicates the defense capacity of PRF (12).

FIBRIN

Substances in PRF promote the three phenomena of soft tissue healing and maturation: angiogenesis, immunity, and epithelial closure. Angiogenesis is indeed the formation of new blood vessels in the wound. Fibrin is a natural guide for angiogenesis, and the fibrin matrix was previously shown to direct angiogenesis (10). The angiogenesis feature of the fibrin matrix can be explained by the three-dimensional structure of the fibrin gel and the activities of the cytokines trapped in the mesh. In addition, fibrin gel hosts basic fibroblast growth factor (b-FGF), VEGF, angiopoietin, and PDGF, the primary soluble factors of angiogenesis. Some studies previously documented that b-FGF and PDGF have a high affinity for fibrin (20). The binding of fibrin to some growth

factors may explain the effect of angiogenesis. An essential phase of angiogenesis is the production of αvβ3 integrin from endothelial cells. This molecule enables endothelial cells to bind to fibrin, fibronectin, and vitronectin. Fibrin increases the expression of this molecule (20).

The fibrin matrix covers the wound area by affecting epithelial cells and fibroblasts. At the wound margins, epithelial cells lose their basal and apical load and enlarge in the basal and apical direction, covering the wound. Cell migration is regulated by fibrinogen, fibronectin, tenascin, and vitronectin. The presence of fibrin, fibronectin, PDGF, and TGF-β is required to regulate integrin expression and fibroblast proliferation and migration to the wound area. Thus, PRF can be considered a fibrin-based natural biomaterial that promotes micro vascularization development and directs epithelial cell migration. It is evident that such a membrane is important to protect open wounds and accelerate healing. It also contains leukocytes, which encourage the migration of these substances. The density and content of the fibrin matrix are important parameters for any platelet concentration. A plethora of studies addressing the biological impact of platelet concentrations focus on platelet growth factors and ignore the influence of the fibrin matrix or cytokines in their environment affecting their release (11).

CIRCULATING STEM CELLS

Mesenchymal cells originating from the bone marrow participate in the regeneration of many tissues. These undifferentiated cells gather at the wound site and differentiate into different cell types. This initial differentiation occurs in the temporary wound matrix by fibrin and fibronectin; therefore, fibrin is used as a supporting matrix in the transplantation of these cells (4).

Various methods are available for preparing platelet concentrates; thus, the contents of platelet concentrates obtained by different methods are also different. Accordingly, considering the leukocyte and fibrin contents of platelet concentrates, the current classification is as follows (34):

1. Platelet-Rich Plasma (PRP)
   a. Pure Platelet-Rich Plasma (P-PRP)
   b. Leukocytes and Platelet-Rich Plasma (L-PRP)
2. Platelet-Rich Fibrin (PRF)
   a. Pure Platelet-Rich Fibrin (P-PRF)
   b. Leukocyte and Platelet-Rich Fibrin (L-PRF)
   c. Injectable PRF (i-PRF)

Pure Platelet-rich Plasma (P-PRP)

It was first developed by Anitua in 1999 (2). To obtain P-PRP, the entire cell-poor plasma layer at the top of the tube and the part of the yellowish layer in the middle section facing the cell-poor plasma are extracted through a pipette and transferred to a different tube following the very first centrifugation of the blood containing the anticoagulant agent. After the second centrifugation at a higher speed compared to the first, the cell-poor plasma layer is removed by pipetting. Then, calcium chloride is added to the remaining material in the tube to coagulate. Using only the upper part of the yellowish layer to prevent leukocytes in the product to be obtained may cause the platelet content of the material to be low. This technique of getting P-PRP is a cost-effective application to be adopted in the clinic; however, its handicap is that it is a bit challenging to prepare (15).

Leukocytes and Platelet-rich Plasma (L-PRP)

To be able to obtain L-PRP, the entire cell-poor plasma and yellowish layer and a part of the layer containing red blood cells are transferred to a new tube after the first centrifugation of the blood without the anticoagulant agent. After the second centrifugation at a higher speed compared to the first, the cell-poor plasma layer is removed by pipetting. Coagulation is ensured by adding bovine thrombin or calcium chloride to the product obtained. The amount of L-PRP obtained following these manual and time-consuming procedures is often low and quickly disappears in the tissue during healing since containing a low-density fibrin matrix. The reproducibility of the results is not reliable because the success of the technique highly relies on the person performing it (13). L-PRP was obtained differently by changing the centrifuge time and speed in the basic protocol in many studies, most of which could not introduce an explicit content of L-PRP. For example, not taking the entire yellowish layer into the second tube following the first centrifugation definitely affects the cell content and may cause P-PRP to be obtained instead of L-PRP (10).

Pure Platelet-rich Fibrin (P-PRF)

Although obtaining P-PRF is similar to getting L-PRP, the only difference is that the coagulant is added to the tube before the second centrifugation during P-PRF preparation. In this way, a denser product is obtained compared to L-PRP. Nevertheless, it is costly to obtain a sufficient amount of P-PRF to be used in the clinic with this technique, and its clinical efficacy has not yet been proven (15).

Leukocyte and Platelet-rich Fibrin (Choukroun's PRF) (L-PRF)

L-PRF is a platelet concentration involved in wound healing and immunity and includes all components of the blood (11). For the first time, it was developed

by Choukroun et al. (6) in France in 2001. Since no anticoagulant agent is needed while preparing L-PRF, it can also be considered a second-generation platelet concentrate (12). To obtain L-PRF, the blood is collected in 10 ml tubes without anticoagulant and immediately centrifuged for 10-12 minutes at about 400 g. Following centrifugation, the fibrin clot is formed in the middle of the tube. While cell-free plasma emerges at the top of the tube, red blood cells occupy the bottom. The success of the technique depends on the time spanning between collecting the blood sample and placing it in the centrifuge. Since no anticoagulant is involved when the platelets in the blood come into contact with the tube wall, platelet activation and fibrin polymerization are rapidly initiated. If the time taken for blood collection and transfer to the centrifuge is prolonged, the fibrin polymerizes dispersedly, and a small amount of non-consistent blood clot is observed (11).

L-PRF becomes a strong membrane when crushed between two hard floors, and this blood-derived biomaterial is often utilized used in oral (11), maxillofacial, otolaryngology, and plastic surgery (8) . L-PRF has the property of polymerizing naturally and slowly during centrifugation. In this technique, platelets and leukocytes are obtained in high yield, and leucocytes are preserved at every stage. Activation of platelets during the production of L-PRF ensures that platelet and leukocyte growth factors are embedded in the fibrin matrix (12). In a study, it was discovered that L-PRF contains almost all of the platelet count in the blood, the platelets are not homogeneously distributed in L-PRF, and these cells are concentrated on the fibrin side adjacent to the substrate where red blood cells accumulate in the tube (14). Dohan et al. (14) reported that growth factors (e.g., TGF-β, VEGF, and PDGF-AB) were slowly released from L-PRF for seven days. The presence of growth factors in high concentrations in the medium, therefore, allows L-PRF to stimulate the environment of wound healing. The products in this natural fibrin material bear a high potential for effect during wound healing. The key role of leukocytes in platelet concentrations was previously reported to be associated with anti-infective activity and immunomodulatory properties (17). Dohan et al. (13) investigated the amounts of IL-1b, IL-4, IL-6, TNF-α, and VEGF in platelet-poor plasma and serum with L-PRF. Accordingly, they reported that all parameters except VEGF were at the highest level in L-PRF, provided by leukocyte degranulation in L-PRF. Such an increase in cytokine levels was suggested to indicate the defense capacity of L-PRF.

L-PRF is a fibrin-based natural biomaterial that promotes micro vascularization development and directs epithelial cell migration. The relevant literature demonstrated that the fibrin matrix leads to angiogenesis (10). This feature of the fibrin matrix is explained by the three-dimensional structure of fibrin and the activities of cytokines trapped in the matrix. It was stated that b-FGF, VEGF, and PDGF show a high affinity for fibrin. On the other hand, it was suggested that fibrin acts as a supporting matrix for mesenchymal stem cells (3).

Advanced Platelets-rich Fibrin (A-PRF)

Recent years have witnessed a new protocol for PRF to further improve tissue regeneration thanks to the modification of centrifugation procedures. While standard PRF is centrifuged at 2700 rpm for 12 min., A-PRF is centrifuged at a lower rate (1500 rpm, 14 min.). This change in the centrifugation protocol was shown to increase platelet cell count and monocyte/macrophage behavior (21).

Advanced Platelet-rich Fibrin Plus (A-PRF+)

The initial procedure for PRF preparation, including a centrifugation step at 708 g relative centrifugal force-max ×12 min., is called L-PRF (11). This protocol was actually developed to activate the ex vivo coagulation process. Then, the produced fibrin matrix has a solid consistency and a dense structure with minimal space between fibrin fibers (11). There are few inflammatory cells in the matrix, but histologically they are located in the distal part of the clot. Recently, protocols for the preparation of platelet fibrin concentrates have been modified according to the "Low-speed centrifugation concept." The newest of these protocols is the A-PRF+ method (RCF-max: 208 g × 8 min.). The previous research showed that the A-PRF+ preparation gives better results; it was discovered that the number of platelets and leukocytes in the fibrin mesh is higher. Moreover, compared to L-PRF, the produced A-PRF+ fibrin matrix is more porous, providing more space for trapped platelets and immune cells and greater release of growth factors (16).

Titanium-prepared Platelet-rich Fibrin (T-PRF)

T-PRF is a novel platelet concentrate developed by Tunalı et al. (32) and utilizes titanium tubes to prevent adverse effects by the glass or glass-coated plastic tubes used in the Choukroun method to activate the platelets more. Activation of platelets with titanium compared to activation with silica particles brings many distinguishing features to T-PRF, including increased biocompatibility. Compared to the fibrin mesh in T-PRF, it was previously observed that PRF has a more robust mesh structure and longer in vivo solubility time. Thicker and tighter T-PRF is thought to cause a more polymerized fibrin formation; thus, it can stay in the tissue for a longer time (32). The T-PRF collection protocol is as follows: a blood sample is collected in 10 ml titanium tubes without anticoagulant and immediately centrifuged at 2800 rpm for 12 min.

The absence of anticoagulant leads most of the platelets to be activated within a few minutes after contact with the wall of the titanium tube, thus initiating the coagulation phase. Before circulating thrombin converts fibrinogen to fibrin, fibrinogen is accumulated at the top of the tube, and a fibrin clot forms in the middle (10). Unfortunately, the literature offers a limited number of studies on T-PRF.

Injectable PRF (i-PRF)

The way of utilizing i-PRF is often similar to PRF, but i-PRF is an injectable type. It can be used alone or in combination with other biomaterials (26), and no additives are required to produce i-PRF. It forms a small clot thanks to the presence of fibrin (26) and releases dynamic gel-containing cells and additional growth factors. i-PRF is also believed to contain stem and endothelial cells.

Areas of Use of Platelet-Rich Fibrin in Dentistry

Recent years have enjoyed increased reconstructive jaw bone surgeries thanks to the development of dental implant applications. PRF often provides convenience to the dentist and patient in pre-implant protection of extraction sockets, sinus operations, and horizontal and vertical bone augmentation applications (25). When placed in the socket following a tooth extraction, PRF accelerates healing with increased circulation and epithelialization and relatively prevents complications (e.g., alveolitis, pain, and inflammation). PRF may be advantagıus in extraction sockets as a filling material, in infected areas for new capillary vascularization and tissue reconstruction, or in systemic conditions delaying wound healing (e.g., diabetes, the use of immunosuppressants). PRF also facilitates coagulation and wound closure among patients using anticoagulants (9). Following cyst enucleation, healing is accelerated thanks to the growth factors it contains; a healing process of 6-12 months due to a blood clot is reduced to as little as two months. Together with graft materials, PRF can be used to reconstruct bone defects. In a study on rabbit parietal bone, the researchers applied no material to the defect in the control group but silk fibroin and PRF together in the experimental group. The findings revealed significantly more total new bone in the experimental group at the end of 12 weeks (27). In a study with sinus augmentation, freeze-dried bone allograft was used alone or in combination with T-PRF (29). In the group augmented with bone graft only, implants were placed at eight months, but at four months in the group with T-PRF supplement. Histomorphometric analyses revealed that the new bone formation was the same in both groups and that T-PRF could accelerate the formation of new bone. It was stated that the rich leukocytes and growth hormones in T-PRF may increase angiogenesis and contribute to the revascularization of the graft. In the same study, it was shown that the sinus membrane perforation could be permanently closed with T-PRF. Accordingly, it was proposed that the autogenous and strong fibrin matrix structure of PRF minimizes the risk of infection in perforations during healing thanks to its rich immunological structure (7). In another study, Tunalı et al. (18) documented clinical and radiographic improvement as a result of the 3-month follow-up of the autogenous bone graft and PRF applied to a tooth with an endo-perio lesion. It has been stated that the recovery is accelerated by the growth factors secreted by the platelets isolated from the blood. T-PRF was utilized as a carrier with antibiotics (e.g., high-capacity doxycycline), showing higher absorption capacity with 7-day stable activity and unique long-acting local antibacterial effect compared to collagen. Therefore, it can be confirmed that T-PRF/Doxy is a promising therapeutic agent in the treatment of periodontitis and peri-implantitis. Besides, recent research demonstrated that i-PRF has a positive and curative effect on erosive lichen planus (30). In another study, Johns et al. (36) documented that pulp revascularization shows disinfection with photodynamic therapy combined with platelet-rich fibrin leads to satisfactory root development in necrotic immature teeth. In another systematic review suggested that PRF can improve alveolar cleft reconstruction and orthodontic tooth movement (37). Pulp-capping agents such as $Ca(OH)_2$, MTA, and PRF yielded similar success rate when used in teeth with irreversible pulpitis (38). i-PRF-facilitated orthodontics is an effective and safe treatment modality to accelerate tooth movement, and this method can help shorten orthodontic treatment duration (39).

CONCLUSION

PRF demonstrated the ability to release high concentrations of various growth factors and induced high fibroblast migration. The use of PRF in dentistry is very common and successful.

ETHICAL DECLARATIONS

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Review / Derleme

MEDICINE PALLIATIVE CARE

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End-of-life care in pediatric palliative care

Pediatrik palyatif bakımda yaşam sonu bakım kavramı

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ABSTRACT

The problem of EOL care of a child is very important because the recovery of a family from grief over a child's death depends on that manner. For improving the quality of this specific care, it would be useful to assess the life expectancy/survival of congenital anomalies, life-threatening diseases, conditions that may shorten a child's life, and the outcomes of palliative care units regarding mortality. Besides, there is an urgent need for more data on what families define as 'good death' and how to cope with the loss. Not only caregivers but also siblings, grandparents, relatives, and healthcare professionals are impacted by a child's death and their needs must be explored. Pediatric palliative care staff in low/middle-income countries need educational assistance for skills of multidisciplinary training about end-of-life care to improve appropriate care for dying children and their families. It is important to provide sensitive and empathetic end-of-life care to children in a family-centered manner helping them to find comfort, meaning, and support while enhancing the quality of a child's life and death. Many attending physicians felt inexperienced when communicating with dying patients and their families while discussing the transition to palliative care and resuscitation status. Also, the good death of a child is an emerging concept in this research domain to improve end-of-life care for dying children and their families. The goal of this review was to provide pediatric healthcare professionals and physicians with an overview of palliative care regarding end-of-life issues.

Keywords: Care, child, end of life, palliative, pediatric

ÖZ

Bir çocuğun yaşam sonu bakımı sorunu çok önemlidir, çünkü bir ailenin ölümle ilgili sıkıntılarından ve kederinden kurtulması tamamen buna bağlıdır. Bu özellikli bakımın kalitesinin iyileştirilmesi için konjenital anomaliler, yaşamı tehdit eden hastalıklar ve yaşamı kısıtlayan durumlarda palyatif bakım birimlerinde beklenen yaşam süresinin ve mortalitenin belirlenmesi yararlı olacaktır. Sadece primer bakım verenler değil, aynı zamanda kardeşler, büyükanne/büyükbabalar, akrabalar ve sağlık profesyonelleri de çocuğun ölümünden etkilenmektedir ve onların ihtiyaçları da önemlidir. Ayrıca günümüzde ailelerin 'güzel ölüm' tabirini nasıl tanımladıkları ve bu kayıpla nasıl başa çıkılacağı konusunda daha fazla veriye ihtiyaç vardır. Gelişmekte olan ülkelerdeki pediatrik palyatif bakım personelinin, ölmekte olan çocuk ve ailelerine uygun bakımı verebilmek için yaşam sonu bakımı hakkında disiplinli bir eğitim almaya ihtiyacı vardır. Bir çocuğun hem yaşam hem de ölüm kalitesini artırırken, bununla birlikte konfor, anlam ve destek bulmalarına yardımcı olan aile merkezli bir yaşam sonu bakım sağlamak önemlidir. Pek çok hekim ve sağlık profeyoneli, ölmekte olan hasta ve aileleriyle iletişim kurarken, canlandırma işlemi ve çocuk palyatif bakıma geçiş noktasında deneyimsiz hissetmektedir. Bir çocuğun başına gelebilecek 'güzel ölüm/saygın ölüm', yaşam sonu bakımı iyileştirmek için ortaya çıkan bir kavramdır. Bu derlemenin amacı, sağlık bakım hizmetleri profesyonellerine ve hekimlere pediyatrik palyatif bakımda yaşam sonu bakım kavramıyla ilgili farkındalık oluşturmak ve daha geniş bir bakış açısı sağlamaktır.

Anahtar Kelimeler: Bakım, çocuk, palyatif, pediatrik, yaşam sonu

INTRODUCTION

Palliative care is a developing pediatric specialty that focuses on the quality of life and symptom management for children who have life-limiting/threatening diseases that have no hope of recovery (1,2). Optimizing and achieving the quality of this care and treating the physical, psychosocial, and spiritual needs of patients and their families is an important healthcare goal (3). There has been a decrease in the children mortality rate, but meanwhile, technological and medical evolution led to an increase in life-limiting and life-threatening diseases. The global under-five mortality rate declined from 93 deaths per 1,000 live births in 1990 to 38 in 2019, by 59 percent.

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Despite this progress, approximately 14,000 under-five deaths occurred every day, in 2019. In addition, chronic conditions like cancer or cardiovascular disease, account for more than 15,000 deaths per year (4). Children who would not have survived their chronic conditions previously are now living longer with very different death courses with medical and technological advancements (5). Pediatric palliative care is defined by The World Health Organization as "aiming to improve the quality of life of patients facing life-threatening illnesses and their families through the prevention and relief of suffering by early identification and treatment of pain and other physical, psychosocial, or spiritual problems." It begins when the illness is diagnosed and continues until the end of life (6). Therefore, it is important to provide sensitive and empathetic end-of-life care to children in a family-centered manner helping them to find comfort, meaning, and support while enhancing the quality of a child's life and death (7,8). Many attending physicians felt inexperienced when communicating with dying patients and their families while discussing the transition to palliative care and resuscitation status (9). Besides, the good death of a child is an emerging concept in this research domain to improve end-of-life care for dying children and their families. The goal of this review was to provide pediatric healthcare professionals and physicians with an overview of palliative care regarding end-of-life issues.

Perinatal Palliative Care As An Emerging Speciality

Meanwhile, there is good evidence in the literature that, pediatric palliative care starts during pregnancy (10). Parents may have information from a prenatal ultrasound about their baby's life-threatening condition and after gathering information they can decide whether to go forward with the pregnancy or not. Perinatal palliative care patients are mainly divided into three clinical groups: (1) extremely premature (<23 gestational weeks) at the limits of viability, (2) diagnosis of life-limiting/threatening diseases with poor prognosis incompatible with life, (3) severe/critical clinical conditions without possible improvement requiring complex care and intensive support (11). After the delivery of the baby, the parents may want to take the baby home if the baby lived (12). In this instance, the perinatal palliative care team provides information and support to parents and family members after postdelivery. As soon as discharged from the hospital, the baby is cared for and loved by family members, neighbors, friends, and the team provides support to the family in terms of arrangements for funeral visits, and spiritual needs. The baby should not experience any pain or distress and should take the last breath in the parents' arms at home in a few days. Good examples of such an experience are available in the literature (12). Recent medical experience of the healthcare providers offers different strategies for the treatment of perinatal palliative care patients, according to their condition and the diagnosis of life-limiting disease (11). Specific training and collecting dedicated resources are necessary in this regard. To establish proper perinatal palliative care training programs, we must increase the recognition and social awareness of the deficiency of this setting. Clinical, ethical, organizational, and communicational skills can maintain the best interest of the newborn with a life-limiting/life-threatening disease. The collection of shared data and new research is essential in finding novel tools applicable in different centers (11).

Location of Death of a Child

Dying at home may be the choice of many parents, where children die and a child's location of death may be more important than it is claimed. In a cross-sectional study of 140 parents who lost their child to cancer at tertiary-level pediatric hospitals, it was reported that the chance to plan the location of death was related to outcomes consistent with high-quality palliative care. Most parents were reported to choose a home for the child's place of death and when non-home deaths were evaluated, parental planning was associated with more deaths occurring in the ward than in the pediatric intensive care unit, and fewer children were intubated. Good communication with physician and home health care services increase the possibility of planning a child's death location (13). Parental preparedness was also connected with planning the location of death and was a key contributing factor for high-quality EOL care (14). Besides, the parents who planned were more likely to prefer less invasive care at the time of death.

Good Death Concept of a Child

'Good death' is a phrase used for persons near the end of life which is not usually used for dying infants and children (12). A child's death cannot be normalized compared to the death of the elderly, even in nature. Children are considered innocent, and their death raises questions about the meaning of life. Throughout the time in literature, the death of a child led to the questioning of faith in God and harming the belief in the fairness and balance of the universe spiritually (5). Hence, it is a tough question for a person to ask 'how can the death of a child be good? '. It can simply be defined as; a peaceful death that is free of pain and avoidable distress (12). It must accord with patients' and caregivers' wishes and their cultural and ethical standards since cultural-specific differences towards dying children are expected. Designing the dying process is required to optimize EOL care for a child. Most of the deaths occur in the PICU with planned withdrawals, but in our country, the order of 'do not resuscitate' is not legal, therefore the withdrawal of treatments is forbidden by laws, even when approval of the family exists.

A good death could be identified as being free from distress, dying in a favorite place; having good relationships with family members and medical staff; feeling that life is complete, maintaining dignity, and preparing for death. However, this identification in adult studies, cannot be applied to children completely (14). For the peace of death of a child, environmental regulations of details are important to be fulfilled upon the families' decision (5). Preferred time of day, family members/staff who wants to be present at the time of death, the noise and lighting (alarms must be tolerable), the lines/tubes, machines/monitors, and pumps might be removed for the comfort of the patient. The family may want to perform cultural and religious practices before withdrawing in accordance with their beliefs. Besides, the preferred position of the parents (laying with the child in bed or holding the child in arms), the position of the child in the room (eg, near windows, etc.), and other special requests like playing the child's favorite song or reading the child's much-loved book, ensure the quality of death during his/her last hours (5).

In a comprehensive study, components of a good death for children with cancer were identified as; adequate opportunities to play freely, peer support, continued access to their common activities, assurance of privacy, respect for their decisions and preferences, a sense that others acknowledge and respect their childhood, comfort to minimize distressing symptoms, hope, not being aware of their forthcoming death, constant dignity, strong family relationships, no sense of being a burden to family members and good relationships with medical staff (15). It is necessary to provide a healthy social environment for terminally ill oncology patients such as normal school life with optimal palliative care focusing on patients' physical and psychological distress. Individually tailored care should be provided depending on each patient's age and developmental period to provide high-quality pediatric palliative care (15).

In addition, healthcare workers who are most affected by witnessing and participating in the death of a child, seek good death for their dying patients for improved EOL care since they are an important piece of the support structure. Physicians and healthcare staff are defenseless to the effects of EOL care delivery. Some studies report that providers who have inadequate training and experience in the delivery of this care are vulnerable to feelings of "burnout," insufficiency, and discomfort. Hence, lack of support for staff who provide this care is crucial since it can lead to depression, emotional abandonment, and regression at work (16, 17).

Controversies in Pediatric End-of-Life Care

The prolonged and variable dying process is characteristic of children with chronic conditions complicating their end-of-life care. Medical technology transformed medicine by widening the distinction between death and dying. The death of a child can occur after a few different trajectories. Common four routes encountered in the ICUs are; sudden/unexpected death, death from a lethal congenital anomaly, death from a possibly curable disease, and death from a chronic/terminal disease (5). Therefore, preparation of the family and child for the end of life is necessary to make decisions in their child's interest. As a child proceeds toward death, care goals shift from cure to supportive care and bereavement (5). The honesty and comprehensiveness of information, effect when delivering news, withholding of data, provision of false hope, linguistic complexity (many Syrian refugees are living in our country), speed of providing information, conflicting information, and physician's body language is troublesome communication-related factors which effects the parents' perceptions about adequate care. Parents state that they are "better prepared" with open and honest information because it helped them to know what to expect (5, 18). Moreover, most of the parents want to see the "big picture," and ask for all the information and the truth, no matter what the truth may be (19).

A pediatric survey suggested that concerns about excessively burdensome treatment were greater in pediatric end-of-life care than in adults. Attending physicians were worried 10 times and nurses worried 20 times more across all specialties about "saving children who should not be saved" as about giving up early (20). Physicians like intensivists probably have concerns of conscience about providing excessively burdensome treatments because in neurologically devastated patients restoration to a meaningful existence seems hopeless. On the other hand, hematology/oncology clinicians have concerns of conscience because prognostic uncertainty for pediatric cancer is high and hence cure-oriented interventions are excusable. They usually have longer-term relationships with patients' families and these emotional bonds may weaken their ability to provide objective counseling and advice (20). Pediatric palliative care specialists' thoughts and approaches are probably the same way. Most physicians usually overestimate survival when confronted with an uncertain prognosis. A study has reported that a minimum 3-month gap existed between the time that a physician recognized that the child had no chance of survival and the time that the parents recognized the same (21). Also, there is a belief that families are not ready to recognize an incurable condition besides the fear of anger or blame

from parents. In mass media, stories of miraculous recoveries lead people to rely on the endless possibility of medical technology and physicians feel guilty for this, not being certain (22). Families frequently use denial as a coping mechanism and the absence of a consistent and clear message from residents complexes the problem. Using sensitive, caring and honest dialogue between parents and healthcare staff regarding a child's terminal condition assists in the preparation for the dying process (14). Overall, families prepared for death by healthcare workers who were honest, compassionate, and available; feel more comfortable that everything that could have been done for their children was done (5, 23). Hence compassionate and consistent EOL care affects the recovery of a family after a child's death.

The Training About End-of-Life Care

At present, the training in EOL care is not satisfactory in many countries. In a study, 89% of the residents don't feel ready to face EOL management (24). Pediatric palliative care requires specific training, uncharacteristic competencies, and skills along with continuing treatments together with the children and their families for an unpredictable time, probably some years. Children suffer from many symptoms and multiple diseases which require interdisciplinary expertise and in contrast to the stated experience of adult-oriented palliative care services, most children live more than a year after initiating pediatric palliative care (2). Hence, the recent palliative care model supports the administration of curative and supportive treatments simultaneously from a multidisciplinary team that includes nurses, physicians, social workers, child life/ development specialists, pharmacists, dieticians, spiritual care specialists, and physical/occupational therapists (3). Initiative for Pediatric Palliative Care identifies goals for high-quality family-centered pediatric palliative care through six domains. These consist of; 1) communication about treatment goals and plans, 2) ethics and shared decision-making, 3) relief of pain and symptoms, 4) continuity of care, 5) support of the family and, 6) grief/ bereavement support (20,21). With this point of view; key topics for palliative care are communication, pain, physical, psychosocial, spiritual considerations, and ethical/legal concerns (3, 25). The absence of knowledge and skills in this specific expertise area may create hesitation in caring for children. Personal reactions of healthcare professionals include fears and concerns when confronted with death (24).

Declaration of death is also another complex experience. In a tertiary children's hospital study, 44 residents and 52 fellows stated that they desire formal training in three specific areas; which are pain control, delivering bad news, and discussing prognosis (26).

In a study in which pediatric residents were taught how to manage withdrawal or limitation of life-sustaining treatment, how to declare death, complete a death certificate, and have a follow-up with families; it was found that they have limited experience with end-of-life care. Their educational experiences varied and they didn't feel sufficiently trained to perform the responsibilities related to providing EOL care for children. (27). However, in another study, the authors reported that education boosted healthcare professionals' confidence regarding personal knowledge, skills, communication abilities, and ethical/ legal concerns. Besides, providing emotional support to dying children and their families increases after appropriate training (28). Therefore additional and urgent efforts are needed to reach comprehensive and multidisciplinary training for residents of pediatric palliative care and it should regularly be provided with the optimization of a concise and clear methodology. Unfortunately, the awareness of low or middle-income country residents on this issue is not adequate and at the same time, there is a lack of formalized education/ training in the approach and management of end-of-life care. Pediatric university hospitals, children's hospitals, and research hospitals must include their residency programs with a sufficient number of hours devoted to training, not only for pediatric palliative care but also for pediatric EOL care immediately. Therewithal, training courses, conferences, and conventions on these topics may also help to compensate for this deficiency a little bit.

CONCLUSION

The problem of EOL care of a child is very important because the recovery of a family from grief over a child's death depends on that manner. For improving the quality of this specific care, it would be useful to assess the life expectancy/survival of congenital anomalies, life-threatening diseases, conditions that may shorten a child's life, and the outcomes of palliative care units regarding mortality. There is an urgent need for more data on what families define as a good death and how to cope with the loss. Not only caregivers but also siblings, grandparents, relatives, and healthcare professionals are impacted by a child's death and their needs must be explored. Development in the healthcare system must include hospice policies for those with a life expectancy of 6 months or less. Pediatric palliative care staff in low/ middle-income countries need educational assistance for skills of multidisciplinary training about end-of-life care to improve appropriate care for dying children and their families.

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Title: There should be a short and clear title. It should not contain abbreviations and should be written in Turkish and English. Abstract: Turkish and English abstracts should be written. In research articles; It should be divided into sections of Aim/Introduction, Material and Method, Results/Findings and Conclusion and should not exceed 400 words. In the review, case reports and the like, Öz; it should be short and one paragraph, and should not exceed 300 words in reviews and 250 words in case reports.

Keywords: Turkish Abstract and English should be found at the end of the abstract. A minimum of 3 and a maximum of 6 should be written. Words should be separated by semicolons. Keywords should be submitted in accordance with Subject **Medical Subject Headings (MESH)** (www.nlm.nih.gov/mesh/MBrowser.html). Turkish Keywords "Turkey Science Terms' what should be in accordance with (www.bilimterimleri.com). If not, a one-to-one Turkish translation should be provided.

Figures, Photographs, Tables and Graphics: It should be indicated at the end of the sentence where it is mentioned in the text, should not be placed in the text, and should be added to the end of the text after the references. Abbreviations used should be indicated in the description below. If previously printed figures, pictures, tables and graphics are used, written permission must be obtained and this permission should be stated in the description of figures, pictures, tables and graphics. The article should be passed by the authors for academic plagiarism prevention program. The picture/photo should be in jpeg and at least 300 dpi resolution.

Text Sections: The text samples to be sent for publication are as follows.

Editorial Comment/Discussion: It is the evaluation of the original research articles published by the expert other than the authors. It is published before the articles in the journal.

Research Article: Prospective-retrospective and all kinds of experimental studies can be published. Abstract (approximately 400 words; aim/introduction, material and method, results/findings and conclusion sections in Turkish and English), Introduction, Material and Method, Results, Discussion, Conclusion, References.

Review: Can be prepared by invited authors or directly. It can be prepared to include the latest medical literature for any subject that has medical characteristics. Abstract (about 300 words, unpartitioned, Turkish and English), titles, references.

Case Report: These are rare or different articles in diagnosis and treatment. It should be supported with sufficient number of photographs and diagrams. Abstract (about 250 words; no section; Turkish and English), Introduction, case report, discussion, conclusion.

Letter to the Editor: The articles that are published in the journal within the last year include a maximum of 500 words containing various opinions, experiences and questions of the readers. There are no Title and Abstract sections. The number of references is limited to 5 (max. 10). It should be indicated which article (number, date) is dedicated and at the end there should be the name, institution and address of the author. The answer to the letter is given by the editor or the author (s) of the article and published in the journal.

Education: Scientific articles supported by the latest clinical and laboratory applications that send messages to readers on current issues within the scope of the journal. Abstract (about 250 words; no section; Turkish and English), related titles, references.

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ETHICAL DECLERATIONS

Ethics Committee Approval: The study was carried out with the permission of ..... Ethics Committee (Date:....., Decision No. .....).

Informed Consent: Written informed consent was obtained from all participants who participated in this ....study (If study retrospective: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

Acknowledgements: If any, it should be written before references.

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Excerpt from journals;

Cesur S, Aslan T, Hoca NT, Cimen F, Tarhan G, Cifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (not 15-18).

Excerpt from the book;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Excerpt from the book, which is the only author and editor;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams & Wilkins; 1996: 46-60.

Excerpt from the book with multiple authors and editors;

Schulz JE, Parran T Jr.: Principles of identification and intervention. In: Principles of Addicton Medicine, Graem AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams & Wilkins; 1998: 1-10.

If the editor is also the author of the chapter in the book;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Excerpt from PhD/Undergraduate Thesis;

Kilic C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Excerpt from an internet site;

Site name, URL address, author names, access date should be given in detail.

Giving a Doi number;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into the family market in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi: 10.1093/ecam/nep019).

For other reference styles, see "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References".

Eder I hereby declare that all or part of the material in this study has not previously been published in any place and is not currently being evaluated elsewhere for publication. electronic submissions and all kinds of pre-declarations.

Sponsorship Statement

Authors should declare, if any, the roles of sponsors of the study:

1. Design of the study 2. Data collection, analysis and interpretation of the results 3. Writing the report

CHECKLIST/CONTROL LIST

The checklist must be complete.

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- Ethical Status,
- "Conflict of Interest"
- Orcid numbers and author information should be on this page.

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12. **Copyright Transfer Form:** Must be filled in the original language of the manuscript. It must be signed by all authors. In the absence of the signature of all authors, the **Corresponding Author** may take responsibility and sign on behalf of all authors.

YAYIN KURALLARI, YAYIN POLİTİKASI, GENEL İLKELER VE GÖNDERME KURALLARI

YAZARLARA BİLGİ

Journal of Medicine and Palliative Care (JOMPAC) hakemli, açık erişimli, periyodik olarak çıkan bir dergidir. Dergi yazım kurallarına göre düzenlenmiş makaleler **DergiPark** sistemi üzerinden kabul edilmektedir. https://dergipark.org.tr/tr/pub/jompac/archive web adresinden ve **Dergipark** web sayfasından tüm sayılara ücretsiz olarak erişilebilmektedir. Amacımız uluslararası bir tabanda hastalıkların teşhis ve tedavisinde yenilikler içeren yüksek kalitede bilimsel makaleler yayımlamak ve bilime katkı sağlamaktır. Yılda dört kez (**Mart, Haziran, Eylül, Aralık**) yayımlanmaktadır. Hakemli bir dergi olarak gelen yazılar biyomedikal makalelere ait **Uluslararası Tıp Dergileri Editörleri Komitesi** (www.icmje.org) tarafından tanımlanan standart gereksinimler ile ilgili ortak kurallara uygunluğu açısından değerlendirilmektedir. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, **DergiPark** web sitemizden (https://dergipark.org.tr/en/pub/jompac) okuyabilir, indirebilirsiniz. Amacımız siz meslektaşlarımızın göndermiş olduğu yayınların karar ve yayımlanma sürecini en kısa sürede sonuca ulaştırmaktır. Dergimizin kalitesini yükseltmek için her zaman önerilere ve yapıcı eleştirilere açık olduğumuzu ve bu konudaki bildirimlere gereken hassasiyeti göstereceğimizi belirtmek isteriz. Makale işletim sisteminde ve atıflarda derginin İngilizce adı kullanılacaktır.

Journal of Medicine and Palliative Care (JOMPAC) kapsam olarak tıbbın ve tıpla ilgili sağlık bilimlerinin her branşı ile ilgili retrospektif/prospektif klinik ve laboratuvar çalışmaları, ilginç olgu sunumları, davet üzerine yazılan derlemeler, editöre mektuplar, orijinal görüntüler, kısa raporlar ve teknik yazıları yayımlayan bilimsel, hakemli bir dergidir. Derginin dili **İngilizce** ve **Türkçe**'dir. Makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe gönderilen makalelerde ayrıca İngilizce Başlık, Abstract, Keywords olmalı, İngilizce olarak gönderilen makalelerde de ayrıca Türkçe Başlık, Öz, Anahtar Kelimeler olmalıdır. Başka bir dergide yayımlanmış veya değerlendirilmek üzere gönderilmiş yazılar veya dergi kurallarına göre hazırlanmamış yazılar değerlendirme için kabul edilmez. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez. Dergimizde yayımlanmış makalelerin tamamına elektronik ortamdan ulaşabilir, https://dergipark.org.tr/tr/pub/jompac web sitemizden okuyabilir, indirebilirsiniz. Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir.

DERGİ ADI

Journal of Medicine and Palliative Care

DERGİ ADININ KISALTMASI

J Med Palliat Care/JOMPAC/jompac

YAZIŞMA ADRESİ

Yazılar e-posta yoluyla sorumlu yazar tarafından, **DergiPark**'a kayıt olunduktan sonra **DergiPark** üzerinden https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new linkine girilerek gönderilmelidir.

MAKALE GENEL YAZIM KURALLARI

Yazıların tüm bilimsel sorumluluğu yazar(lar)a aittir. Editör, yardımcı editör ve yayıncı dergide yayımlanan yazılar için herhangi bir sorumluluk kabul etmez.

EDİTÖRİYEL ÖN KONTROL DEĞERLENDİRMESİ

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen yazılar format ve intihal açısından değerlendirilir. Formata uygun olmayan yazılar değerlendirilmeden sorumlu yazara geri gönderilir. Bu tarz bir zaman kaybının olmaması için yazım kuralları gözden geçirilmelidir. Basım için gönderilen tüm yazılar iki veya daha fazla yerli/yabancı hakem tarafından değerlendirilir. Makalelerin değerlendirilmesi, bilimsel önemi, orijinalliği göz önüne alınarak yapılır. Yayıma kabul edilen yazılar editörler kurulu tarafından içerik değiştirilmeden yazarlara haber verilerek yeniden düzenlenebilir. Makalenin dergiye gönderilmesi veya yayıma kabul edilmesi sonrası isim sırası değiştirilemez, yazar ismi eklenip çıkartılamaz.

BİLİMSEL VE ETİK SORUMLULUK

Journal of Medicine and Palliative Care (JOMPAC)'in yayın ve yayın süreçleri, Dünya Tıbbi Editörler Derneği (World Association of Medical Editors (**WAME**)), Yayın Etiği Komitesi (Committee on Publication Ethics (**COPE**)), Uluslararası Tıbbi Dergi Editörleri Konseyi (International Council of Medical Journal Editors (**ICMJE**)), Bilim Editörleri Konseyi (Council of Science Editors (**CSE**)), Avrupa Bilim Editörleri Birliği (**EASE**) ve Ulusal Bilgi Standartları Organizasyonu (National Information Standards Organization (NISO)) kurallarına uygun olarak şekillendirilmiştir. Dergi, Bilimsel Yayıncılıkta Şeffaflık ve En İyi Uygulama İlkeleri'ne (Principles of Transparency and Best Practice in Scholarly Publishing (**doaj.org/bestpractice**)) uygundur.

Klinik araştırma makalelerinin protokolü Etik Komitesi tarafından onaylanmış olmalıdır. İnsanlar üzerinde yapılan tüm çalışmalarda "**Gereç ve Yöntem**" bölümünde çalışmanın ilgili komite tarafından onaylandığı veya çalışmanın **Helsinki İlkeler Deklarasyonu**'na (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**) uyularak gerçekleştirildiğine dair bir cümle yer almalıdır. Çalışmaya dahil edilen tüm kişilerin **Bilgilendirilmiş Onam Formu'**nu imzaladığı metin içinde belirtilmelidir. **Journal of Medicine and Palliative Care (JOMPAC)'**e gönderilen makalelerdeki çalışmaların **Helsinki İlkeler Deklarasyonu'**na uygun olarak yapıldığı, kurumsal etik ve yasal izinlerin alındığı varsayılacak ve bu konuda sorumluluk kabul edilmeyecektir. Çalışmada "Hayvan" öğesi kullanılmış ise yazarlar, makalenin Gereç ve Yöntem bölümünde hayvan haklarını **Guide for the Care and Use of Laboratory Animals** (**https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals**) prensipleri doğrultusunda koruduklarını, çalışmalarında ve kurumlarının etik kurullarından onay aldıklarını belirtmek zorundadır. Olgu sunumlarında hastanın kimliğinin ortaya çıkmasına bakılmaksızın hastalardan "Bilgilendirilmiş rıza" alınmalıdır. Makalede Etik Kurul Onayı alınması gerekli ise; alınan belge makale ile birlikte gönderilmelidir. Makale yazarlar tarafından **akademik intihal önleme programı**ndan geçirilmelidir. Makalenin etik kurallara uygunluğu yazarların sorumluluğundadır.

Tüm makale başvuruları intihal araştırılması için taranmalı ve sonrasında dergi sistemine yüklenmelidir. İntihal, atıf manipülasyonu ve gerçek olmayan verilerden şüphelenilmesi veya araştırmaların kötüye kullanılması durumunda, yayın kurulu **COPE** yönergelerine uygun olarak hareket eder. Bakınız: **Guidance from the Committee on Publication Ethics** (**COPE**).

Yazar olarak listelenen her bireyin **Uluslararası Tıp Dergisi Editörleri Komitesi** (**ICMJE - www.icmje.org**) tarafından önerilen yazarlık kriterlerini karşılaması gerekir. **ICMJE** yazarlığın aşağıdaki 4 kritere dayanmasını önerir: (1) Çalışmanın tasarımı, verilerin elde edilmesi, analizi veya yorumlanması (2) Dergiye gönderilecek kopyanın hazırlanması veya bu kopyanın içeriğini bilimsel olarak etkileyecek ve ileriye götürecek şekilde katkı sağlanması (3) Yayımlanacak kopyanın son onayı (4) Çalışmanın tüm bölümleri hakkında bilgi sahibi olma ve tüm bölümleri hakkında sorumluluğu alma.

Bir yazar, yaptığı çalışmanın bölümlerinden sorumlu olmanın yanı sıra, çalışmanın diğer belirli bölümlerinden hangi ortak yazarların sorumlu olduğunu bilmeli ayrıca yazarlar, ortak yazarlarının katkılarının bütünlüğüne güvenmelidir. Yazar olarak atananların tümü yazarlık için dört kriteri de karşılamalı ve dört kriteri karşılayanlar yazar olarak tanımlanmalıdır. Dört kriterin tümünü karşılamayanlara makalenin başlık sayfasında teşekkür edilmelidir. Yayın kurulu yazarlık şartlarını karşılamayan bir kişinin yazar olarak eklendiğinden şüphe ederse yazı daha fazla incelenmeksizin reddedilecektir.

Journal of Medicine and Palliative Care (JOMPAC)'e gönderilen bir çalışma için bireylerden veya kurumlardan alınan mali hibeler veya diğer destekler Editör Kurulu'na bildirilmelidir. Potansiyel bir çıkar çatışmasını bildirmek için, **ICMJE Potansiyel Çıkar Çatışması Bildirim Formu**, katkıda bulunan tüm yazarlar tarafından imzalanmalı ve gönderilmelidir. Editörlerin, yazarların veya hakemlerin çıkar çatışması olasılığı, derginin Editör Kurulu tarafından **COPE** ve **ICMJE** yönergeleri kapsamında çözümlenecektir. Derginin Editör Kurulu, tüm itiraz durumlarını **COPE** kılavuzları kapsamında ele almaktadır. Bu gibi durumlarda, yazarların itirazları ile ilgili olarak yazı işleri bürosu ile doğrudan temasa geçmeleri gerekmektedir. Gerektiğinde, dergi içinde çözülemeyen olayları çözmek için bir kamu denetçisi atanabilir. Baş editör itiraz durumlarında karar alma sürecinde alınacak kararlarla ilgili nihai otoritedir. Yazarlar, dergiye bir makale gönderirken, yazıların telif haklarını **Journal of Medicine and Palliative Care (JOMPAC)**'e devretmiş olmayı kabul ederler. Yazı yayımlanmamak üzere reddedilirse veya herhangi bir sebepten geri çekilirse telif hakkı yazarlara geri verilir.Şekiller, tablolar veya diğer basılı materyaller de dahil olmak üzere basılı ve elektronik formatta daha önce yayımlanmış içerik kullanılıyorsa yazarlar telif hakları sahiplerinden gerekli izinleri almalıdır. Bu konudaki hukuki, finansal ve cezai yükümlülükler yazarlara aittir. **Journal of Medicine and Palliative Care'de (JOMPAC)** yayımlanan makalelerde belirtilen ifade veya görüşler, editörlerin, yayın kurulunun veya yayıncının görüşlerini yansıtmaz; editörler, yayın kurulu ve yayıncı bu tür materyaller için herhangi bir sorumluluk veya yükümlülük kabul etmez. Yayınlanan içerikle ilgili nihai sorumluluk yazarlara aittir.

MAKALE "BAŞKA BİR YERDE YAYIMLANMAMIŞTIR" İBARESİ

Her yazar makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığını ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığını, editöre sunum sayfasında belirtmelidirler. Kongrelerde sunulan sözlü veya poster bildirilerin, başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmesi gereklidir. Dergide yayımlanan yazıların her türlü sorumluluğu (etik, bilimsel, yasal, vb.) yazarlara aittir.

YAYIN HAKKI DEVİR FORMU

Telif Hakkı Devir Formu (https://dergipark.org.tr/tr/journal/3258/file/3177/show) linkinden temin edilebilir. Makalenin ana dilinde (makalenin dili İngilizce ise, İngilizce olmalıdır, makalenin dili Türkçe ise, Türkçe olmalıdır) doldurulmalı, makale (https://dergipark.org.tr/tr/journal/3258/submission/step/manuscript/new) adresi üzerinden yüklenirken on-line olarak gönderilmelidir 1976 Copyright Act'e göre, yayımlanmak üzere kabul edilen yazıların her türlü yayın hakkı yayıncıya aittir.

YAZIM DİLİ KONTROLÜ

Derginin yayın dili **Türkçe** ve **İngilizce**'dir, makaleler hem Türkçe hem de İngilizce olarak kabul edilmektedir. Türkçe yazılan yazılarda düzgün bir Türkçe kullanımı önemlidir. Bu nedenle Türk Dil Kurumu'nun Türkçe sözlüğü veya www.tdk.org.tr adresi ayrıca Türk tıbbi derneklerinin kendi branşlarına ait terimler sözlüğü esas alınmalıdır. İngilizce makaleler ve İngilizce Abstract gönderilmeden önce profesyonel bir dil uzmanı tarafından kontrol edilmelidir. Yazıdaki yazım ve gramer hataları içerik değişmeyecek şekilde İngilizce dil danışmanımız ve redaksiyon komitemiz tarafından düzeltilmektedir.

İSTATİSTİK DEĞERLENDİRMESİ

Tüm prospektif, deneysel ve retrospektif araştırma makaleleri istatistik yönünden (gerekirse istatistik uzmanı tarafından) değerlendirilmeli ve uygun plan, analiz ve raporlama ile belirtilmelidir.

YAYIMA KABUL EDİLMESİ

Editör ve hakemlerin uygunluk vermesi sonrası makalenin gönderim tarihi esas alınarak yayım sırasına alınır. Her yazı için bir **Doi** numarası alınır.

MAKALE YAZIM KURALLARI

Yazılar Microsoft Word programı ile çift satır aralıklı ve başlık yazıları (Makale Adı, Öz, Abstract, Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Kaynaklar vs.) 12 punto olarak, makalenin diğer kısımları 11 punto olacak şekilde, her sayfanın iki yanında ve alt ve üst kısmında 2,5 cm boşluk bırakılarak yazılmalıdır. Yazı stili Times New Roman olmalıdır. "System International" (SI) unitler kullanılmalıdır. Şekil, tablo ve grafikler metin içinde refere edilmelidir. Kısaltmalar, kelimenin ilk geçtiği yerde parantez içinde verilmelidir. Türkçe makalelerde %50 bitişik yazılmalı, aynı şekilde İngilizcelerde de 50% bitişik olmalıdır. Türkçe'de ondalık sayılarda virgül kullanılmalı (55,78) İngilizce yazılarda nokta (55.78) kullanılmalıdır. Araştırma makalesi ve derleme 4000, olgu sunumu 2500, editöre mektup 500 kelimeyi (ABSTRACT/ÖZ ve REFERENCES/KAYNAKLAR hariç olmak üzere) geçmemelidir. Öz sayfasından itibaren sayfalar numaralandırılmalıdır.

Yazının Bölümleri

1. Editöre Sunum Sayfası

Journal of Medicine and Palliative Care (Tıp ve Palyatif Bakım Dergisi)'de yayımlanmak üzere değerlendirilmesi isteğinin belirtildiği, makalenin sorumlu yazarı tarafından dergi editörüne hitaben gönderdiği yazıdır. Bu kısımda makalenin bir bölümünün veya tamamının başka bir yerde yayımlanmadığı ve aynı anda bir diğer dergide değerlendirilme sürecinde olmadığı, "**Maddi Destek ve Çıkar İlişkisi**" durumu, dil ve istatistik kontrolünün yapıldığı belirtilmelidir.

2. Başlık Sayfası

Sayfa başında gönderilen makalenin kategorisi belirtilmedir (klinik analiz, araştırma makalesi, deneysel çalışma, olgu sunumu, derleme vs). Tüm yazarların ad ve soyadları yazıldıktan sonra üst simge ile 1'den itibaren numaralandırılıp, çalıştıkları kurum, klinik, şehir ve ülke yazar isimleri altına eklenmelidir. Başlık sayfasında her yazarın **Orcid no** bilgisi, **e-posta** adresi olmalıdır. Bu sayfada Sorumlu Yazar belirtilmeli isim, açık adres, telefon ve e-posta bilgileri eklenmelidir (Dergimizin formatı gereği adres bilgileri, kurumları makale dili Türkçe ise Türkçe olarak, İngilizce ise İngilizce olarak belirtilmelidir). Kongrelerde sunulan Sözlü veya Poster bildiriler başlık sayfasında kongre adı, yer ve tarih verilerek belirtilmelidir.

3. Makale Dosyası

Yazar ve kurum isimleri bulunmamalıdır, bu bilgiler sadece başlık sayfasında olmalıdır.

Başlık: Kısa ve net bir başlık olmalıdır. Kısaltma içermemeli, Türkçe ve İngilizce olarak yazılmalıdır. Öz: Türkçe ve İngilizce (Abstract) yazılmalıdır. Araştırma makalelerinde Öz; Amaç, Gereç, Yöntem, Bulgular ve Sonuç bölümlerine ayrılmalı ve 400 kelimeyi geçmemelidir. Derleme, olgu sunumları ve benzerlerinde Öz; kısa ve tek paragraflık olmalı, derlemelerde 300, olgu sunumlarında 250 kelimeyi geçmemelidir.

Anahtar Kelimeler: Türkçe Öz'ün ve İngilizce Abstract'ın sonlarında bulunmalıdır. En az 3 en fazla 6 adet yazılmalıdır. Kelimeler birbirlerinden noktalı virgül ile ayrılmalıdır. İngilizce Anahtar Kelimeler (Keywords) "**Medical Subject Headings (MESH)**"e uygun (www.nlm.nih.gov/mesh/MBrowser.html) olarak verilmelidir. Türkçe Anahtar Kelimeler "Türkiye Bilim Terimleri' ne uygun olarak verilmelidir (www.bilimterimleri.com). Bulunamaması durumunda bire bir Türkçe tercümesi verilmelidir.

Şekil, Fotoğraf, Tablo ve Grafikler: Metin içinde geçtiği yerlerde ilgili cümlenin sonunda belirtilmeli, metin içine yerleştirilmemeli, kaynaklardan sonra metin sonuna eklenmelidir. Kullanılan kısaltmalar altındaki açıklamada belirtilmelidir. Daha önce basılmış şekil, resim, tablo ve grafik kullanılmış ise yazılı izin alınmalıdır ve bu izin açıklama olarak şekil, resim, tablo ve grafik açıklamasında belirtilmelidir. Makale yazarlar tarafından akademik intihal önleme programından geçirilmelidir. Resim/fotoğraf jpeg ve en az 300 dpi çözünürlükte olmalıdır.

Metin Bölümleri: Yayımlanmak üzere gönderilecek yazı örnekleri şu şekildedir.

Editöriyel Yorum/Tartışma: Yayınlanan orijinal araştırma makaleleri ile ilgili, araştırmanın yazarları dışındaki, o konunun uzmanı tarafından değerlendirilmesidir. Dergide makalelerden önce yayımlanır.

Araştırma Makalesi: Prospektif-retrospektif ve her türlü deneysel çalışmalar yayımlanabilmektedir. Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç olarak düzenlenmelidir. Öz (yaklaşık 400 kelime; amaç, gereç ve yöntem, bulgular ve sonuç bölümlerinden oluşan Türkçe ve İngilizce), Giriş, Gereç ve Yöntem, Bulgular, Tartışma, Sonuç, Kaynaklar.

Derleme: Davet edilen yazarlar tarafından veya doğrudan hazırlanabilir. Tıbbi özellik gösteren her türlü konu için son tıp literatürünü de içine alacak şekilde hazırlanabilir. Öz (yaklaşık 300 kelime, bölümsüz, Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Olgu Sunumu: Tanı ve tedavide farklılık gösteren veya nadir görülen makalelerdir. Yeterli sayıda fotoğraflarla ve şemalarla desteklenmiş olmalıdır. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), Giriş, Olgu sunumu, Tartışma, Sonuç olarak düzenlenmelidir.

Editöre Mektup: Dergide son bir yıl içinde yayımlanan makaleler ile ilgili okuyucuların değişik görüş, tecrübe ve sorularını içeren en fazla 500 kelimelik yazılardır. Başlık ve Öz bölümleri yoktur. Kaynak sayısı 5 (en fazla 10) ile sınırlıdır. Hangi makaleye (sayı, tarih verilerek) ithaf olunduğu belirtilmeli ve sonunda yazarın ismi, kurumu, adresi bulunmalıdır. Mektuba cevap, editör veya makalenin yazar(lar)ı tarafından, yine dergide yayımlanarak verilir.

Eğitim: Derginin kapsamı içinde güncel konularda okuyucuya mesaj veren son klinik ve laboratuvar uygulamaların da desteklediği bilimsel makalelerdir. Öz (yaklaşık 250 kelime; bölümsüz; Türkçe ve İngilizce), konu ile ilgili Başlıklar, Kaynaklar.

Kitap Değerlendirmeleri: Derginin kapsamı içinde güncel değeri olan ulusal veya uluslararası kabul görmüş kitapların değerlendirmeleridir.

KAYNAKLARDAN HEMEN ÖNCE BELİRTİLMESİ GEREKENLER

ETİK BEYANLAR

Etik Kurul Onayı (Eğer gerekiyorsa): "Çalışma için …….. Etik Kurulu'ndan .....tarih ve ..... sayı /karar no ile etik kurul onayı alınmıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Aydınlatılmış Onam: Bu çalışmaya katılan hasta(lar)dan yazılı onam alınmıştır (Olgu sunumlarında ve kişilerle yapılan prospektif çalışmalarda mutlaka olmalıdır. Eğer çalışma retrospektif ise: "Aydınlatılmış Onam: Çalışma retrospektif olarak dizayn edildiği için hastalardan aydınlatılmış onam alınmamıştır." ifadesiyle yazarlar tarafından belirtilmelidir.

Hakem Değerlendirme Süreci: "Harici çift kör hakem değerlendirmesi" ifadesiyle yazarlar tarafından belirtilmelidir.

Çıkar Çatışması: "Yazarlar bu çalışmada herhangi bir çıkara dayalı ilişki olmadığını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Finansal Destek: "Yazarlar bu çalışmada finansal destek almadıklarını beyan etmişlerdir" ifadesiyle yazarlar tarafından belirtilmelidir.

Yazar Katkıları: "Yazarların tümü; makalenin tasarımına, yürütülmesine, analizine katıldığını ve son sürümünü onayladıklarını beyan etmişlerdir." ifadesiyle yazarlar tarafından belirtilmelidir.

Teşekkür Yazısı: Varsa kaynaklardan önce yazılmalıdır.

Kaynaklar: Kaynaklar makalede geliş sırasına göre yazılmalıdır. Kaynaktaki yazar sayısı 6 veya daha az ise tüm yazarlar (soyadı ve adının ilk harfi olacak şekilde olmalı, yazar isimleri birbirinden virgül ile ayırılmalı) belirtilmeli, 7 veya daha fazla ise ilk 3 isim yazılıp ve ark. ("et al") eklenmeli, makale ismi (Tümce şeklinde sadece cümlenin ilk harfi ve özel isimlerin ilk harfi büyük olacak), kısa dergi adı, yıl, cilt, kısa sayfa no (15-8. şeklinde olacak, 15-18 olmayacak) eklenmeli ve noktalama işaretleri arasında birer boşluk bırakılmalıdır. Kaynak yazımı için kullanılan format Index Medicus'ta belirtilen şekilde olmalıdır (www. icmje.org). Kaynak listesinde yalnızca yayınlanmış ya da yayınlanması kabul edilmiş veya Doi numarası almış çalışmalar yer almalıdır. Dergi kısaltmaları **Cumulated Index Medicus**'ta kullanılan stile uymalıdır (http://www2.bg.am.poznan.pl/czasopisma/ medicus.php?lang=eng.). Kaynak sayısının araştırma makalelerinde 40, derlemelerde 60, olgu sunumlarında 20, editöre mektupta 5 (en fazla 10) ile sınırlandırılmasına özen gösterilmelidir. Kaynaklar metinde cümle sonunda nokta işaretinden hemen önce parantez kullanılarak belirtilmelidir. Örneğin (4,5). Kaynakların doğruluğundan yazar(lar) sorumludur. Yerli ve yabancı kaynakların sentezine önem verilmelidir.

4. Şekil, Grafik, Resim ve Tablo Başlıkları

Başlıklar kaynaklardan sonra yazılmalıdır. Her biri ayrı bir görüntü dosyası (en az 300 dpi çözünürlükte, jpg) olarak gönderilmelidir.

Makalenin basıma kabulünden sonra Dizginin ilk düzeltme nüshası sorumlu yazara e-posta yoluyla gönderilecektir. Bu metinde sadece yazım hataları düzeltilecek, ekleme çıkartma yapılmayacaktır. Sorumlu yazar düzeltmeleri 2 gün içinde bir dosya halinde e-posta ile yayın idare merkezine bildirecektir.

Kaynak Yazım Örnekleri

Dergilerden yapılan alıntı;

Cesur S, Aslan T, Hoca NT, Çimen F, Tarhan G, Çifci A. Clinical importance of serum neopterin level in patients with pulmonary tuberculosis. Int J Mycobacteriol 2014; 3: 15-8 (15-18 değil).

Kitaptan yapılan alıntı;

Tos M. Cartilage tympanoplasty. 1st ed. Stuttgart-New York: Georg Thieme Verlag; 2009.

Tek yazar ve editörü olan kitaptan alıntı;

Neinstein LS. The office visit, interview techniques, and recommendations to parents. In: Neinstein LS (ed). Adolescent Health Care. A practical guide. 3rd ed. Baltimore: Williams&Wilkins; 1996: 46-60.

Çoklu yazar ve editörü olan kitaptan alıntı;

Schulz JE, Parran T Jr: Principles of identification and intervention. In:Principles of Addicton Medicine, Graham AW. Shultz TK (eds). American Society of Addiction Medicine, 3rd ed. Baltimore: Williams&Wilkins; 1998: 1-10.

Eğer editör aynı zamanda kitap içinde bölüm yazarı ise;

Diener HC, Wilkinson M (editors). Drug-induced headache. In: Headache. First ed., New York: Springer-Verlag; 1988: 45-67.

Doktora/lisans tezinden alıntı;

Kılıç C. General Health Survey: A Study of Reliability and Validity. phD Thesis, Hacettepe University Faculty of Medicine, Department of Psychiatrics, Ankara; 1992.

Bir internet sitesinden alıntı;

Sitenin adı, URL adresi, yazar adları, erişim tarihi detaylı olarak verilmelidir.

Doi numarası vermek;

Joos S, Musselmann B, Szecsenyi J. Integration of complementary and alternative medicine into family prac- tice in Germany: Result of National Survey. Evid Based Complement Alternat Med 2011 (doi:10.1093/ecam/nep019).

Diğer referans stilleri için "ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Sample References" sayfasını ziyaret ediniz.

"Bu çalışmanın içindeki materyalin tamamı ya da bir kısmının daha önce herhangi bir yerde yayımlanmadığını ve halihazırda da yayın için başka bir yerde değerlendirilmede olmadığını beyan ederim." Bu 400 kelimeye kadar olan özler hariç, sempozyumlar, bilgi aktarımları, kitaplar, davet üzerine yazılan makaleler, elektronik formatta gönderimler ve her türden ön bildirileri içerir.

Sponsorluk Beyanı

Yazarlar aşağıda belirtilen alanlarda, varsa çalışmaya sponsorluk edenlerin rollerini beyan etmelidirler:

1. Çalışmanın dizaynı 2. Veri toplanması, analizi ve sonuçların yorumlanması 3. Raporun yazılması

KONTROL LİSTESİ

Kontrol listesindekiler eksiksiz yapılmalıdır.

Makalede mutlaka olması gerekenler;

—Editöre Sunum Sayfası

—Başlık Sayfası

- Etik Durum,
- "Çıkar Çatışması Durumu" belirtir cümle,
- Orcid numaraları ve yazar bilgileri bu sayfada olmalıdır.

—Ana Metin

—Telif Hakkı Devri Formu

1. **Editöre Sunum Sayfası:** Sorumlu Yazar tarafından editöre hitaben yazılmış olmalıdır. Telefon ve E-posta eklenmelidir. Gönderilen makalenin adı, kısa adı, "Daha önceden yayımlanmamış, şu an herhangi bir dergiye değerlendirilmek üzere gönderilmemiştir ve yazarların kendi orijinal çalışmasıdır" ibaresi, "Çıkar Çatışması Beyanı" içermelidir.
2. **Başlık sayfası:** Türkçe ve İngilizce Makale başlıkları/Kısa başlıklar, Yazarlar ve Kurumları, Sorumlu Yazar posta adresi ve telefon, tüm yazarların **Orcid no** (2019 yılından itibaren zorunludur) ve **E-posta** adresleri. **Başlıkta özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**.
3. **Makalenin Ana Metin sayfaları:** Türkçe ve İngilizce Makale Başlıkları/Kısa Başlıklar, Türkçe ve İngilizce Öz/Abstract ve Anahtar Kelimeler/Keywords, Makale Metni, Kaynaklar, Tablo ve Şekil Başlıkları, Tablolar. **Bu sayfada yazar isimleri, kurum bilgileri olmayacaktır.**
4. **Yazı tipi:** Başlıklarda "Times New Roman" ve 12 punto olmalı, makalenin diğer kısımlarında 11 punto, çift boşluklu satır arası ve tüm alanlarda 2,5 cm girinti ayarıyla yazılmalıdır.
5. **Öz/Abstract:** Türkçe özet **ÖZ** ile başlamalı; "**Giriş/Amaç, Gereç ve Yöntem, Bulgular ve Sonuç**" kısımlarını içermelidir. İngilizce özet **ABSTRACT** başlığıyla başlamalı "**Introduction/Aim, Material and Method, Findings/Results, Conclusion**" kısımlarını içermelidir.
6. **Anahtar Kelimeler/Keywords:** Türkçe Öz kısmının altına "**Anahtar Kelimeler**", İngilizce "Abstract" kısmının altında "**Keywords**" (birleşik) halde eklenmelidir. Anahtar kelimeler en az 3, en çok 6 kelime/sözcük olmalı, birbirlerinden virgülle ayırılmalı ve MeSH'e uygun olmalıdır.
7. **G**ereç ve Yöntem kısmında **Etik Kurul Onayı** alındığı (Alındığı yer, tarih, etik kurul no olacak şekilde yazılması önerilir) belirtilmelidir. Etik Kurul Onayı gerektirmeyen makalelerde Kurum Onayı/İzni alındığı (Çıkar Çatışması olmaması için) belirtilmelidir. İlgili belgeler talep edildiğinde gönderilmelidir. Etik problemlerde sorumluluğun yazar(lar)da olduğu unutulmamalıdır.
8. **T**artışmada istatistiksel terimler (p, r, α gibi) **kullanılmamalıdır.**
9. **"Maddi Destek/Çıkar Çatışması Durumu"** kaynakçadan önce belirtilmeli, "***Teşekkür Yazısı***" varsa kaynakçadan önce yazılmalıdır.
10. **Kaynak Gösterimi;** yazım kurallarında detaylı anlatıldığı gibi olmalıdır. Derginin sayı numarası "(2)" parantez içinde olacak şekilde bizim kaynakça gösterimimizde **bulunmamaktadır.** Altı yazara kadar yazarı olan makalelerde bütün yazarların adı yazılmalı (Soyadı ve Adının ilk harfi olacak şekilde), yedi ve daha üstü yazarlı makalelerde ilk üç yazar, et al. (ve ark.) şeklinde kaynak gösterilmelidir. Makalenin adı Tümce kullanımı şeklinde (**özel isimler ve ilk harf dışında küçük harf kullanılmalıdır**) olmalıdır. **Derginin kısa adı verilmelidir.** Dergi adından sonraki noktalama işaretleri arasında birer boşluk bırakılmalıdır.
11. **T**ablo, Şekil ve Resimler ayrı bir başlık altında kaynakçadan sonra yerleştirilmelidir. **Şekil/Resim** (En az 300 dpi çözünürlükte, **jpeg** dosyası olmalıdır) ve **Tablo**lar ayrı bir veya daha fazla dosya halinde gönderilmelidir.
12. **Telif Hakkı Devri Formu:** Makalenin asıl dilinde doldurulmalıdır. Tüm yazarlar tarafından imzalanmalıdır. Tüm yazarların imzasının olmadığı durumlarda **Sorumlu Yazar** tüm yazarlar adına sorumluluğu alarak imzalayabilir.