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EDITORIAL

Dear readers,

We are publishing the third issue of our journal in 2022 with a total of 26 (25 research articles and 1 case report). In this issue of COVID-19 articles, which made up almost half of the articles in the previous issues, we see it decreasing. Our journal is now indexed in TR-Dizin TÜBİTAK ULAKBİM since Jun, and thanks to this situation, the number of articles is gradually increasing. To be close to our goal, to improve our final quality, to apply to ESCI and PubMed in the near future is to make SCIE close and closer to our goal. Our journal's EndNote style was made for plagiarism cuisine Used as Ithenticate with CrossRef. It continues on this path rapidly.

The expenditure required for our readers of this issue.

Yours truly,

Prof. Aydın ÇİFCİ, MD
Editor-in-Chief

EDİTÖRDEN

Değerli okuyucularımız,

Dergimizin 2022 yılı üçüncü sayısını toplamda 26 (25 araştırma makalesi ve 1 olgu sunumu) makale ile çıkartıyoruz. Önceki sayılarda neredeyse makalelerin yarısını oluşturan COVID-19 makalelerinin bu sayıda azaldığını görüyoruz. Dergimiz artık Haziran ayından itibaren TR-Dizin TÜBİTAK ULAKBİM'de ve bu durum sayesinde makale sayısı giderek artmaktadır. Amacımız yakın gelecekte birçok yeni dizine kabul edilerek bilimsel kalitemizi artırmak, ardından yakın bir zamanda ESCI ve PubMed müracaatı yaparak SCIE dergi olmak hedefimize biraz daha yaklaşmaktır. Dergimizin EndNote stili oluşturuldu, intihal taraması için CrossRef ile Ithenticate kullanım sözleşmesi yapıldı. Bu yolda çalışmalarımız hızla devam etmektedir.

Bu sayının okuyucularımız için faydalı olacağını umuyorum.

Saygılarımla,

Prof. Dr. Aydın ÇİFCİ
Baş Editor

Original Article / Özgün Makale

Original Article / Özgün Makale

Original Article / Özgün Makale

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MEDICINE PALLIATIVE CARE

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J Med Palliat Care 2022; 3(3): 135-141

Do high $PaCO_2$ levels during discharge from the hospital predict medium-term mortality in chronic respiratory failure patients without domiciliary non-invasive mechanical ventilator?

Hastaneden taburculuk sırasında yüksek $PaCO_2$ seviyeleri, evde non-invaziv mekanik ventilatörü olmayan kronik solunum yetmezliği hastalarında orta vadeli mortaliteyi öngörüyor mu?

Deniz Çelik[1], Murat Yıldız[2], Hasret Gizem Kurt[2], Zeynep Tilbe Saymaz[2]

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ABSTRACT

Aim: Long-term domiciliary use of a non-invasive mechanical ventilator (NIV) is a controversial form of therapy for patients with chronic obstructive pulmonary disease (COPD) and moderate hypercapnia. The present research attempted to examine hospital admissions, hospitalizations, and medium-term (6-8 months) mortality in a group of patients with compensated but moderate hypercapnia who were discharged from our clinic without a domiciliary NIV.

Material and Method: The sample of this retrospective, observation-based cohort study consisted of compensated hypercapnic cases that were hospitalized in our Pulmonology Intensive Care Unit (ICU) between 01.01.2019 and 12.31.2020.

Results: A total of 245 patients discharged with high partial pressure of carbon dioxide ($PaCO_2$) levels between 01.01.2019 and 12.31.2020 were included in the study. While 58% of the cases were males (n=142), we found the mean age of the patients to be 71.89±12.63 years. The findings yielded no significant differences between the groups by sex, use of NIV during hospitalization, number of days of NIV use during hospitalization, use of LTOT or Oxygen tube at home, and intubation history before ICU admission ($p>0.05$). Similarly, we could not conclude significant differences between the groups by hospitalization, discharge, and follow-up arterial blood gas (ABG) parameters. Yet, the rates of congestive heart failure, coronary artery disease, and atrial fibrillation were significantly higher in the mortality group ($p=0.017$, $p=0.032$, and $p=0.002$, respectively). Besides, high $PaCO_2$ levels versus mortality rates at 1, 3, 6, 8, and 12 months and in the entire follow-up period were subjected to the ROC analysis. Accordingly, when accepting 50.25 mmHg as the cut-off value for determining the 8-month mortality for discharge $PaCO_2$ levels, we calculated the sensitivity to be 78.6% and the specificity to be 43%.

Conclusion: Overall, it is highly convenient to consider the possible positive effects of NIV therapy on mortality among patients with heart-related diseases and with moderate hypercapnia ($PaCO_2$>50 mmHg) at discharge.

Keywords: Respiratory failure, hypercapnia, mortality, ventilation

ÖZ

Amaç: Uzun süreli evde NIV kullanımı, kompanse ılımlı hiperkapnik KOAH olan hastalar için tartışmalı bir tedavi şeklidir. Çalışmamızın amacı kliniğimizden taburcu edilen kompanse fakat ılımlı hiperkapnik hastalardan evde non-invaziv mekanik ventilatörü olmayan hasta grubunun taburculuk sonrası hastaneye başvuru sayıları, hastaneye yatış sayıları ve orta vadeli (6-8 ay) mortalite durumlarını incelemektir.

Gereç ve Yöntem: Çalışma grubunu oluşturan hastalar 01.01.2019 ve 31.12.2020 tarihleri arasında Göğüs Hastalıkları Yoğun Bakım Kliniğinde yatarak tetkik edilip taburcu edilmiş kompanse hiperkapnik olgulardan oluşmaktadır. Araştırmamız retrospektif gözleme dayalı kohort çalışma olarak planlanmıştır.

Bulgular: Çalışmaya 01.01.2019 ve 31.12.2020 tarihleri arasında yüksek $PaCO_2$ düzeyiyle taburcu edilmiş toplam 245 hasta dahil edildi. Olguların %58'i erkek (n=142) cinsiyette idi. Hastaların yaş ortalaması 71,89±12,63 idi. Her iki grup arasında cinsiyet, yatışları sırasında NIV kullanımı, yatışları sırasında NIV kullanım gün sayısı, evde USOT veya Oksijen tüpü kullanımı ve GYBÜ yatışı öncesinde entübasyon öyküsü bulunması açılarından istatistiksel olarak anlamlı farklılık bulunmamaktadır ($p>0,05$). Mortalite grubunda konjestif kalp yetmezliği, koroner arter hastalığı ve atriyal fibrilasyon bulunma oranları istatistiksel olarak anlamlı düzeyde daha yüksektir (sırasıyla $p=0,017$, $p=0,032$ ve $p=0,002$). Her iki grup arasında yatış, taburcu ve kontrol sonuçları açısından istatistiksel olarak anlamlı farklı izlenmemiştir. Yüksek $PaCO_2$ düzeyiyle taburcu olmuş olguların 1, 3, 6, 8, 12 aylık ve takip süresinin tamamındaki mortalite oranlarına karşılık taburculuk $PaCO_2$ düzeyleri ROC analizine tabi tutulmuştur. ROC analizi sonucunda, taburculuk $PaCO_2$ düzeyleri için 8. ay mortaliteyi belirlemede cut-off değeri 50,25 mmHg sınır değer kabul edildiğinde, duyarlılık %78,6 özgüllük %43 olarak hesaplanmıştır.

Sonuç: Taburculukta ılımlı hiperkapnisi ($PaCO_2$>50 mmHg) olan, kalp ilişkili hastalığı bulunan hasta grubunda evde NIV tedavisinin dikkatle değerlendirilmesi gerektiğini düşünüyoruz.

Anahtar Kelimeler: Solunum yetmezliği, hiperkapni, mortalite, ventilasyon

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INTRODUCTION

Respiratory failure is a syndrome resulting from inadequate oxygenation of mixed venous blood and/or carbon dioxide elimination and is often considered under two categories. On the one hand, hypoxemic respiratory failure is described as the arterial partial pressure of oxygen (PaO_2) less than 60 mmHg while breathing room air at rest. Hypercapnic respiratory failure, on the other hand, develops as a result of ventilation failure and is characterized by an increase in arterial partial pressure of carbon dioxide ($PaCO_2$) above 45 mmHg (1). The only physiopathological mechanism that specifies the $PaCO_2$ level is alveolar ventilation.

Diseases reducing minute ventilation or increasing dead space ventilation result in hypercapnia. Although the increase in $PaCO_2$ can be compensated by increasing alveolar ventilation, increased ventilation requirements cannot be met, which, in turn, may lead to hypercapnia with any underlying lung disease, respiratory muscle fatigue, or decreased $PaCO_2$ sensitivity of the respiratory center (2). Since its invention, non-invasive mechanical ventilation (NIV) has been growingly used for the treatment of patients with chronic obstructive pulmonary disease (COPD) and chronic stable hypercapnia. It is particularly utilized in respiratory failure developing during acute exacerbations of COPD because previous research consistently showed its positive impact on survival (3). However, few studies have addressed the domiciliary use of NIV for patients with stable hypercapnic COPD so far. Even most of these limited studies employed small numbers of patients and/or used a low pressure to normalize gas exchange, improve symptoms, and reduce morbidity and mortality (4).

Some studies concluded that long-term use of NIV improves physiological parameters (e.g., lung function or gas exchange), clinical symptoms (e.g., functional capacity, dyspnea, quality of life, and sleep quality), and patient-centered outcomes (e.g., hospital readmission and mortality rates) in stable patients with chronic hypercapnia (resting $PaCO_2$>45 mmHg and above; COPD in stable period) (5,6). On the other hand, there is still insufficient evidence that long-term NIV treatment increases life expectancy and reduces mortality (7). The long-term use of NIV is a controversial form of therapy for patients with moderate hypercapnic COPD. While there is no doubt that chronic nocturnal NIV administration improves outcomes in patients with restrictive lung diseases and neuromuscular diseases (8), there is conflicting evidence of its long-term benefits in COPD patients (9,10); thus, long-term NIV practice for COPD varies significantly across Europe (11).

Respiratory failure cases presenting with acute or chronic exacerbation are frequently hospitalized in the Pulmonary Intensive Care Unit (ICU) of tertiary hospitals for chest diseases (level II intensive care service is provided). Besides, COPD is blamed for respiratory failure in most patients.

Our study attempted to evaluate arterial blood gas (ABG) parameters of the patients, admissions to the hospital or emergency department, hospitalizations, and medium-term (6-8 months) mortality in a group of compensated but moderate hypercapnic patients who were discharged from our clinic without domiciliary NIV.

MATERIALS AND METHOD

Health Sciences University, Keçiören Training and Research Hospital, Clinical Research Ethics Committee granted ethical approval to our study (Date: 11.09.2021, Decision No: 2012-KAEK-15/2405). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The sample of this retrospective, observation-based cohort study consisted of compensated hypercapnic cases that were hospitalized in our Pulmonology ICU (PICU) between 01.01.2019 and 12.31.2020.

Patient Selection

The inclusion criteria included receiving inpatient treatment in a PICU, having available follow-up data, having a $PaCO_2$ value above 45 mmHg in ABG taken just before discharge, and not possessing a domiciliary NIV. Nevertheless, patients without available data, those with a $PaCO_2$ value of 45 mmHg and below in ABG before discharge, and patients who had a domiciliary NIV or had been prescribed an NIV at discharge were not included in the study.

We investigated readmissions to the emergency department after discharge with high carbon dioxide levels, intensive care admissions, numbers of outpatient visits, and mortality rates. The data included all admissions, hospitalizations, and mortality cases until 30.06.2021. In this respect, we extracted and analyzed a maximum of 19 months of follow-up data of the first discharged patient and a minimum 7-month follow-up data of the last discharged patient. We then statistically compared the data between the cases with mortality during the follow-up period constituted (mortality group) and others (survivor group).

Statistical Analysis

We analyzed the data using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The normality of data distribution was checked using the Kolmogorov

Smirnov test, while Levene's test was resorted to evaluate the homogeneity of variances in the data. We showed continuous data as mean±standard deviation and categorical data as number and percentage (n, %) unless stated otherwise. We then compared the groups using the independent samples t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Categorical variables were compared using the Pearson chi-square test or the Fisher exact test. Receiver operating characteristic curve (ROC) analysis was used to determine the threshold value of $PaCO_2$ associated with mortality risk. A p-value<0.05 was considered significant in all statistical analyses.

RESULTS

Of the 245 patients, discharged with high $PaCO_2$ levels, 58% were males (n=142), and 42% were females (n=103). The mean age of the patients was found to be 71.89±12.63 years. The findings revealed that the mortality group was significantly older than the survivors (p<0.001). Moreover, the mortality rates among those treated in a tertiary anesthesia intensive care unit (AICU) before being admitted to the PICU were found to be significantly higher (p=0.037). Yet, we could not reach significant differences between the groups by sex, NIV use during hospitalization, number of days of NIV use during hospitalization, long-term oxygen therapy at home (LTOT), and intubation history before PICU admission (p>0.05). The comparisons of the groups' demographic and other characteristics are given in **Table 1** and **Table 2**.

Table 1. Comparison of demographic and other characteristics between groups

	Mortality group (n=88)		Survivor group (n=157)		Total (n=245)		p
	n	%	n	%	n	%	
Sex (male)	51	58	91	58	142	58	0.999 β
Admission unit (to PICU)							0.037 β
Emergency department	30	34.1	76	48.4	106	43.3	
Ward	1	1.1	5	3.2	6	2.4	
AICU	57	64.8	76	48.4	133	54.3	
NIV use at PICU							0.478 β
No	26	29.5	53	34	79	32.4	
Yes	62	70.5	103	66	165	67.6	
LTOT at home							0.981 β
No	10	11.4	18	11.5	28	11.4	
Yes	78	88.6	139	88.5	217	88.6	
History of intubation							0.796 β
No	81	92	143	91.1	224	91.4	
Yes	7	8	14	8.9	21	8.6	

Categorical variables were expressed as frequency (percentage). Chi-square test β was performed, and p<0.05 was considered significant. PICU: Pulmonary intensive care unit, NIV: Non-invasive mechanical ventilation AICU: Anesthesia intensive care unit, LTOT: Long-term oxygen therapy

Table 2. Comparison of age and number of days of NIV use between groups

	Mortality group (n=88)		Survivor group (n=157)		Total (n=245)		p
	M	SD	M	SD	M	SD	
Age	76.61	10.70	69.24	12.89	71.89	12.63	<0.001*
Number of days of NIV use	4.77	3.68	4.58	3.37	4.65	3.48	0.733*

Continuous variables were expressed as mean (M)±standard deviation (SD). Independent samples t-test * was performed, and p<0.05 was considered significant. NIV: Non-invasive mechanical ventilation

Both groups were also compared by the presence of comorbidity, and the findings yielded that history of cardiac disease (congestive heart failure, coronary artery disease, and atrial fibrillation) was significantly higher in the mortality group (p=0.017, p=0.032, and p=0.002, respectively). Yet, the groups did not significantly differ by the presence of COPD, diabetes mellitus, hypertension, pulmonary thromboembolism, pneumonia, bronchiectasis, chronic kidney disease, lung cancer, interstitial lung disease, kyphoscoliosis, and obstructive sleep apnea syndrome (p>0.05) (**Table 3**).

Table 4 compares the ways of readmission and the rates of readmission in the first 30, 90, 180, and 360 days of discharge between the groups. Accordingly, we found that there were significantly more survivor patients readmitted through the mentioned channels (the emergency department, clinics, wards, and intensive care unit) than the patients with mortality (p<0.05). Similarly, the survivor group had significantly higher readmission rates in the first 90, 180, and 360 days of discharge (p<0.05). Yet, the groups did not significantly differ by readmission rate in the first 30 days of discharge (p=0.162).

The hospitalization, discharge, and follow-up ABG parameters between the groups are shown in **Table 5**. Our results did not yield significant differences between the mentioned ABG test results.

Discharge $PaCO_2$ levels versus mortality rates at 1, 3, 6, 8, and 12 months and in the entire follow-up period were subjected to ROC analysis. The results yielded an area under the procedure characteristic curve (AUC) to be 0.594 for determining the 8-month mortality for the discharge $PaCO_2$ levels, and it was statistically significant (p=0.034). To be able to define a cut-off value for this test, we examined sensitivity and specificity values and focused on the optimum points. Accordingly, when accepting 50.25 mmHg as the cut-off value for determining the 8-month mortality for discharge $PaCO_2$ levels, we calculated the sensitivity to be 78.6% and the specificity to be 43% (**Table 6**).

Table 3. Comparison of comorbidities between the groups

	Mortality group (n=88)		Survivor group (n=157)		Total (n=245)		p
	n	(%)	n	(%)	n	(%)	
Chronic obstructive pulmonary disease							0.957
No	11	12.5	20	12.7	31	12.7	
Yes	77	87.5	137	87.3	214	87.3	
Diabetes mellitus							0.620
No	67	76.1	115	73.2	182	74.3	
Yes	21	23.9	42	26.8	63	25.7	
Hypertension							0.136
No	35	39.8	78	49.7	113	46.1	
Yes	53	60.2	79	50.3	132	53.9	
Congestive heart failure							0.017
No	52	59.1	116	73.9	168	68.6	
Yes	36	40.9	41	26.1	77	31.4	
Coronary artery disease							0.032
No	66	75.0	135	86.0	201	82.0	
Yes	22	25.0	22	14.0	44	18.0	
Atrial fibrillation							0.002
No	77	87.5	153	97.5	230	93.9	
Yes	11	12.5	4	2.5	15	6.1	
Pulmonary thromboembolism							0.999
No	85	96.6	151	96.2	236	96.3	
Yes	3	3.4	6	3.8	9	3.7	
Pneumonia							0.499
No	81	92.0	148	94.3	229	93.5	
Yes	7	8.0	9	5.7	16	6.5	
Bronchiectasis							0.424
No	87	98.9	152	96.8	239	97.6	
Yes	1	1.1	5	3.2	6	2.4	
Chronic kidney disease							0.192
No	84	95.5	155	98.7	239	97.6	
Yes	4	4.5	2	1.3	6	2.4	
Lung cancer							0.657
No	87	98.9	153	97.5	240	98.0	
Yes	1	1.1	4	2.5	5	2.0	
Interstitial lung diseases							0.359
No	87	98.9	157	100.0	244	99.6	
Yes	1	1.1	-		1	0,4	
Kyphoscoliosis							0.999
No	87	98.9	154	98.1	241	98.4	
Yes	1	1.1	3	1.9	4	1.6	
Obstructive sleep apnea syndrome							0.265
No	87	98.9	150	95.5	237	96.7	
Yes	1	1.1	7	4.5	8	3.3	

*Chi-square test. p<0.05

Table 4. Readmissions to the hospital after discharge

	Mortality group (n=88)		Survivor group (n=157)		Total (n=245)		p
	n	(%)	n	(%)	n	(%)	
No readmission	38	48.1	39	25.2	77	32.9	0.004
Emergency department	19	24.1	44	28.4	63	26.9	
General ward	0	-	2	1.3	2	0.9	
Intensive care unit	0	-	1	0.6	1	0.4	
Outpatient clinic	22	27.8	69	44.5	91	38.9	
Readmission in the first 30 days	29	33	66	42	95	38.8	0.162
Readmission in the first 90 days	35	39.8	92	58.6	127	51.8	0.005
Readmission in the first 180 days	40	45.5	104	66.2	144	58.8	0.002
Readmission in the first 360 days	41	46.6	117	74.5	158	64.5	<0.001

*Chi-square test; p<0.05

Table 5. Hospitalization, discharge, and follow-up ABG values between the groups

ABG parameters	Mortality group (n=88)		Survivor group (n=157)		p
	M	SD	M	SD	
Hospitalization pH	7.37	0.08	7.39	0.08	0.226β
Discharge pH	7.46	0.08	7.46	0.05	0.196 β
Follow-up pH	7.42	0.07	7.42	0.06	0.870*
Hospitalization PaO_2	66.78	29.89	62.81	25.48	0.577 β
Discharge PaO_2	58.47	17.37	59.76	19.40	0.658 β
Follow-up PaO_2	64.66	31.38	58.73	21.98	0.430 β
Hospitalization $PaCO_2$	59.90	12.64	60.66	11.63	0.635*
Discharge $PaCO_2$	52.83	5.29	51.57	6.72	0.222 β
Follow-up $PaCO_2$	49.07	10.21	50.83	11.79	0.891 β
Hospitalization HCO_3	34.07	7.55	35.09	7.04	0.165 β
Discharge HCO_3	38.75	8.54	35.74	4.82	0.188 β
Follow-up HCO_3	30.65	5.23	31.81	6.26	0.403*
Hospitalization SaO_2	83.59	14.33	84.81	14.07	0.794 β
Discharge SaO_2	88.01	8.46	87.18	11.00	0.960 β
Follow-up SaO_2	88.09	9.75	83.36	16.28	0.338 β

Continuous variables were expressed as mean±standard deviation (SD). Independent samples t-test *, Mann-Whitney U Test β, p<0.05

Table 6. ROC analysis for discharge $PaCO_2$ levels and mortality periods

	n (%)	AUC	SE	p	95% CI
1-month mortality	17 (6.9)	0.630	0.066	0.073	(0.501-0.759)
3-month mortality	31 (12.7)	0.594	0.053	0.090	(0.491-0.698)
6-month mortality	46 (18.8)	0.585	0.045	0.074	(0.496-0.674)
8-month mortality	57 (23.3)	0.594	0.041	0.034	(0.512-0.675)
12-month mortality	68 (27.8)	0.561	0.040	0.140	(0.483-0.640)
General mortality	88 (35.9)	0.547	0.039	0.222	(0.471-0.623)

Test Result Variable(s): Discharge $PaCO_2$, AUC: Area, under the ROC Curve, SE: Standard Error, CI: Confidence interval

DISCUSSION

It is well-known that NIV use reduces dyspnea and dead space ventilation in patients presenting with COPD exacerbation, improves hypoventilation through increased minute ventilation, and, in turn, promotes gas exchange and regresses hypercapnia. NIV becomes the top-favored ventilator modality thanks to the mentioned positive impacts and since reducing the need for intubation and morbidity/mortality rates in patients with acute/chronic hypercapnia and acute/chronic respiratory failure (12).

The guideline by the 2020 Indian Society of Intensive Care (ISCCM) suggests robust evidence and strictly recommends NIV use in treating acute exacerbation of COPD in patients with acute or chronic acute respiratory acidosis (pH=7.25-7.35). However, it is not recommended to use NIV therapy routinely in normo-

or mildly hypercapnic patients with acute exacerbation of COPD without acidosis (pH>7.35) (13). Following the relevant guidelines, we did not administer NIV treatment to patients hospitalized in a GICU and those found to be hypercapnic without acidosis (n=79; 32.4%).

Arpağ et al. (14) evaluated the NIV response in acute hypercapnic respiratory failure and concluded that 41.7% of the patients whose hypercapnic acidosis rapidly improved with NIV treatment relapsed into respiratory acidosis shortly after switching to nasal oxygen. They also reported that acidosis status may vary depending on whether hypercapnia is acute or chronic and that patients need to be followed up in an ICU. Among our patients, those who were stable hypercapnic and were not given NIV were not included in the case group "who rapidly developed acidosis after switching to nasal oxygen," as determined by Arpağ et al. (14). In our center, NIV is often prescribed for home use to patients who rapidly develop acidosis.

In their study, Meservey et al. (15) examined readmission and mortality after discharge in patients with hypercapnic respiratory failure. The logistic regression analysis yielded that advanced age, active smoking, history of intubation at hospitalization, primary heart disease, congestive heart failure, peripheral vascular disease, history of malignancy, COPD, home oxygen use, low PaO_2 level, high serum HCO_3 level, and readmission in the first 30 days were found to be associated with mortality after discharge. They reported that the mortality risk increased by 1.39 for each unit increase in the Charlson comorbidity index (CI 1.09-1.76). The corrected mortality rates were high in those rehospitalized after discharge. In addition, mortality was found to be high in the first few months after discharge from the hospital.

We discovered that advanced age, congestive heart failure, coronary artery disease, and atrial fibrillation were significantly higher in the mortality group. Yet, the groups did not significantly differ by the presence of other comorbidities and clinical and laboratory findings. We also did not find a relationship between readmission to the hospital and mortality. On the contrary, we found that the readmission rate was higher in the survivor group probably since access to healthcare services in our country may be more convenient compared to other countries.

Baykal and Bulcun uttered that chronic hypoxemia in patients with COPD causes pulmonary vascular remodeling, leading to an increase in pulmonary artery pressure (16). Indeed, in our study, 88.5% (n=217) of the patients discharged with high partial carbon dioxide pressures were using home oxygen therapy. Thus, we may assert that the chronic hypoxemic and moderate hypercapnic clinical courses may have caused pulmonary hypertension, which can be explained by the significant divergence of mortality between the two groups due to heart-related diseases.

Borel et al. (17) found that cardiovascular comorbidities were the only independent factor associated with a higher risk of death in patients diagnosed with hypercapnic obesity hypoventilation syndrome and treated with long-term domiciliary NIV. In this study, we discovered no difference in $PaCO_2$ between the groups but a relationship between cardiac comorbidities and mortality. This finding may be related to the inability to meet the cardiac oxygen requirement due to hypoxemia. In their study, Şahan and Bulut (18) reported that hypoxia increases, pulmonary hypertension appears, and some changes occur in the right heart as the clinical severity of COPD progresses, which leads to atrial fibrillation.

Goedemans et al. (19) stated that the risk of acute myocardial infarction is increased in COPD patients due to similar pathophysiological mechanisms. They also reported that the risk of developing heart failure and cardiac arrhythmia is more common in COPD patients. In our study, we found that the rates of congestive heart failure, coronary artery disease, and atrial fibrillation were significantly higher in the mortality group.

Dretzke et al. (20) recruited thirty-one studies in their meta-analysis of the clinical outcomes of using domiciliary NIV in stable and newly discharged COPD patients. The findings showed no evidence of survival benefit of NIV use for stable patients, yet a possible trend to decrease hospitalization and improve quality of life. In our study, we found cardiac comorbidities to be factors affecting survival in stable and newly discharged hypercapnic patients who did not use domiciliary NIV and found the $PaCO_2$ cut-off value, showing a statistically significant difference in mortality at 8 months, to be 50.25 mmHg. Kohnlein et al. (21) proposed an algorithm for indications for long-term (domiciliary) NIV use, adapted from the German National Guidelines, in their systematic review. In this algorithm, long-term (domiciliary) NIV therapy is recommended:

- if the acute hypercapnic respiratory failure is developed in COPD exacerbation and NIV is utilized for treatment,
- if $PaCO_2$ level is >53 mmHg for 14 days, or diurnal $PaCO_2$ is >50 mmHg,
- if chronic respiratory failure symptoms are present, or nocturnal $PaCO_2$ is >50 mmHg, or diurnal $PaCO_2$ is between 45-50 mmHg, and nocturnal $PtcCO_2$ increases >10 mmHg.

Chu et al. (22) recruited 110 patients in their study, administered NIV therapy to those with COPD exacerbation and acute hypercapnic respiratory failure, and followed up survivors after discharge. The findings revealed the rate of readmission within a year to be 79.9%, the rate of life-threatening exacerbation to be 63.3%, and the overall mortality rate to be 49.1% . In our study, the rate of readmission in the first year was 64.5%, and the overall mortality rate was 35.9%.

Wilson et al. (23) reported that every 5 mmHg increase in $PaCO_2$ was associated with a significant increase in mortality from all causes in compensated hypercapnic patients. Suraj et al. (24) reported the effects of long-term use of domiciliary NIV use in their study. In their study consisting of patients hospitalized and discharged after more than three episodes of acute hypercapnic respiratory failure due to COPD in the last year, they showed that mortality, intensive care admissions, and hospitalizations decreased in the NIV group compared to the non-administered group. However, there were only 30 patients in the NIV group, and the follow-up period was only a year in this study.

In their meta-analysis, Xue He et al. (25) evaluated the efficacy of domiciliary NIV therapy in patients discharged after a COPD exacerbation. They reported that the frequency of exacerbations was significantly reduced in patients receiving domiciliary NIV. However, there were no significant differences in mortality, gas exchange (PaO_2, $PaCO_2$), and pH.

The relevant literature hosts conflicting data on the effect of long-term NIV use on mortality. However, there is a plethora of studies showing that hypercapnia increases the mortality rate, albeit moderately. In our study, we revealed that mortality increased especially among patients with heart-related disease accompanying mild hypercapnia, which is consistent with the literature.

Its retrospective design and the use of single-center data may be considered the major limitations of our study. In addition, the follow-up period can be counted among the limitations. We used exactly 24 months of patient data to avoid bias due to seasonal variability in COPD exacerbations and respiratory failure episodes.

CONCLUSION

We investigated the characteristics of the patients who were hospitalized with acute hypercapnic respiratory failure due to COPD exacerbation and discharged with moderate hypercapnia despite pH compensation (67.6%) or who were administered NIV in their treatment during the hospitalization. The findings uncovered the $PaCO_2$ cut-off level as 50.25 mmHg to predict 8-month mortality. While we could not reach significant differences between the groups by discharge $PaCO_2$ levels, the rates of heart-related diseases (e.g., congestive heart failure, coronary artery disease, and atrial fibrillation) were significantly higher in the mortality group. We assume that domiciliary NIV therapy needs to be considered among patients with mild hypercapnia ($PaCO_2$>50 mmHg) at discharge and with concomitant heart-related diseases. Further research may employ a larger sample size to engage in a more extensive investigation on the subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Keçiören Training and Research Hospital, Clinical Research Ethics Committee (Date: 11.09.2021, Decision No: 2012-KAEK-15/2405).

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.

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Laboratory changes in older patients using SGLT2 inhibitors

Yaşlı hastalarda SGLT2 inhibitörü kullanımı: laboratuvar değerlendirilmesi

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ABSTRACT

Aim: In this study, we aimed to investigate the results of laboratory parameters related to the use of sodium glucose cotransporter 2 (SGLT2) inhibitors in individuals over 65 years of age who were using empagliflozin or dapagliflozin for the treatment of type 2 diabetes mellitus (T2DM).

Material and Method: A total of 140 patients over 65 years of age who had empagliflozin (10 mg once daily) or dapagliflozin (10 mg once daily) added to their current treatment for T2DM were divided into two groups. Laboratory results at the beginning of treatment and at the 24th week of treatment and drug-related adverse events were noted. The study was retrospectively designed.

Results: Significant decreases in fasting blood glucose and HbA1c were observed in both groups. There was a significant decrease in lipid parameters in the dapagliflozin group. Phosphorus values were elevated in the empagliflozin group. In both groups, there was a significant increase in hemoglobin and calcium values. There was no significant difference in terms of adverse events.

Conclusion: We think that SGLT2 inhibitors, which have many positive effects other than blood sugar regulation with new mechanisms of action that continue to be discovered, can be administered as the primary treatment for appropriate patient groups.

Keywords: SGLT2 inhibitors, older patients, empagliflozin, dapagliflozin, diabetes mellitus

ÖZ

Amaç: Bu çalışmada Tip-2 Diabetes mellitus (T2DM) ile takipli, empagliflozin veya dapagliflozin kullanan 65 yaş üzeri bireylerde sodyum glukoz kotrasporter 2 (SGLT2) inhibitörü kullanımına bağlı laboratuar parametrelerinde ortaya çıkan sonuçları incelemeyi amaçladık.

Gereç ve Yöntem: 65 yaş üzeri T2DM ile takipli mevcut tedavisine empagliflozin (günde bir kez 10 mg) veya dapagliflozin (günde bir kez 10 mg) eklenmiş 140 hasta iki gruba ayrıldı. Tedavi başlangıcında ve tedavinin 24. haftasındaki laboratuar sonuçları, ilaca bağlı yan etkiler kaydedildi. Çalışma retrospektif olarak tasarlandı.

Bulgular: Her iki grupta da anlamlı açlık kan şekeri ve HbA1c düşüşleri gözlendi. Dapagliflozin grubunda lipid parametrelerinde anlamlı düşüş görüldü. Empagliflozin grubunda fosfor değerlerinde yükselme saptandı. Her iki grupta ise hemoglobin ve kalsiyum değerlerinde anlamlı artış meydana geldi. Toplam yan etkiler açısından anlamlı farklılık saptanmadı..

Sonuç: Kan şekeri regülasyonu dışında birçok olumlu etkileri olan ve yeni etki mekanizmaları keşfedilmeye devam edilen SGLT2 inhibitörleri uygun hasta gruplarında öncelikle tercih edilebilecek preperatlar olduğunu düşünüyoruz.

Anahtar Kelimeler: SGLT2 inhibitörleri, yaşlı hastalar, empagliflozin, dapagliflozin, diabetes mellitus

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic disease with increasing prevalence around the world, causing significant mortality and morbidity, especially in the elderly population (1).

It is very important to slow down the vascular complications accompanying T2DM, especially in older patient groups. However, treatment success may be limited due to drug side effects with fragility, multiple drug use, treatment incompatibility, and hypoglycemia in the elderly population (2-4).

SGLT2 inhibitors, which have been frequently used in recent years, are oral antidiabetic drugs that act by inhibiting glucose and sodium reabsorption in proximal tubules (**Table 1**) (5). Thanks to their natriuretic and glucosuric effects, they have a renoprotective effect and contribute to cardiovascular protection (6-8).

In older patients followed with T2DM, hypoglycemia and glycemic fluctuations are undesirable side effects. The risk of hypoglycemia is very low due to the fact that the decrease in glucose levels with SGLT2 inhibitor use is independent of insulin (9). In addition, reduced glucotoxicity improves beta cell function (10).

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In this study, we examine laboratory parameters before and after treatment in individuals over 65 years of age using SGLT2 inhibitors. In doing so, we hope to highlight the effects of these drugs other than blood sugar regulation, such as anti-inflammatory and vasculoprotective effects, to enrich the literature.

MATERIAL AND METHOD

This study was planned as a single-center retrospective study in June and July 2022. The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 22.06.2022, Decision No: E2-22-2035). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

The study included 147 patients over 65 years of age who were being followed with uncontrolled T2DM despite the maximum tolerable dose of metformin, sulfonylurea, dipeptidyl peptidase 4 inhibitor (DPP4), pioglitazone, glinide, or insulin. Laboratory data were recorded after 24 weeks for patients who had SGLT2 inhibitors added to their treatment regimens.

Patients under 65 years of age, with a history of gestational diabetes or type 1 diabetes, with a cancer or currently receiving anticancer treatment, with chronic pancreatitis, with a previous history of SGLT2 inhibitor use, with glomerular filtration rate of <45 mL/min, and with genitourinary tract infection or acute renal failure were excluded from the study.

Study Protocol

Clinical, demographic, and laboratory findings of the patients were recorded from the automation system of the hospital. Patients who received empagliflozin (10 mg once daily) or dapagliflozin (10 mg once daily) in addition to their current treatment constituted the study's two subgroups. Laboratory data were recorded at the start of treatment and after 24 weeks.

Laboratory Parameters

In the morning, fasting blood samples were drawn for the evaluation of biochemical parameters and other laboratory parameters. After the blood samples were centrifuged at 2500 × g for 10 minutes, plasma and serum samples were separated. All parameters were evaluated in the same laboratory. Serum glucose, serum electrolytes, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase, and alkaline phosphatase were measured with a Beckman Coulter AU 5800 autoanalyzer (Beckman Coulter Inc., Brea, CA, USA) by the enzymatic ultraviolet hexokinase method. HbA1c was measured by cation-exchange high-performance liquid chromatography method using the ARKRAY ADAMS A1c HA8180 automated glycohemoglobin analyzer (ARKRAY Global Business Inc., Kyoto, Japan). Albumin was measured by the bromocresol green method. Total cholesterol was measured by enzymatic colorimetric method and high-density lipoprotein cholesterol was measured by enzymatic colorimetric method with a Hitachi modular autoanalyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Low-density lipoprotein cholesterol level was calculated with the Friedewald formula for patients with triglyceride levels of <400 mg/dL (14). Patients with triglyceride of >400 mg/dL were evaluated by enzymatic colorimetric method with the second-generation LDL-C Plus Kit and the Hitachi Modular P800 (Roche Diagnostic Corp., Indianapolis, IN, USA).

Statistical Analysis

The STATA program (StataCorp LLC, College Station, TX, USA) was used for data analysis. Normality testing was performed with the Shapiro–Wilk test. Normal distributions were shown as mean ± standard deviation and non-normal distributions as median (interquartile range: 25th-75th percentile). Categorical variables were expressed as numbers and percentages. The Student t-test or Mann–Whitney U test was used to compare numerical variables between the SGLT2 inhibitor therapy groups. Chi-square, Yates correction, and Fisher exact chi-square tests were used for comparisons of categorical data. Changes of laboratory parameters at 24 weeks compared to baseline were evaluated by repeated measures for analysis of variance (ANOVA). Values of $p<0.05$ (*) were considered significant in statistical analysis.

RESULTS

The mean age of the study population was 69.0±3.6 years and the majority of patients were male (61.2%). Analysis of the SGLT2 inhibitor distribution revealed that 68.7% (n: 101) of the patients received empagliflozin and 31.3% (n: 46) received dapagliflozin. The male ratio was higher in the empagliflozin group compared to the dapagliflozin group (67.3% vs. 47.8%; p=0.029). Other demographic characteristics showed no significant differences between the SGLT2 inhibitor therapy groups (**Table 1**).

Table 1. Common SGLT2 inhibitors

	Empagliflozin	Dapagliflozin	Canagliflozin
Preparation	10 mg/25 mg	5 mg/10 mg	100 mg/300 mg
Dosage	10 mg daily, 25 mg max	5 mg daily, 10 mg max	100 mg daily, 300 mg max
Half-life	12.4 h	12.9 h	100 mg: 10.6 h 300 mg: 13.6 h
Time to reach peak plasma concentration	1.5 h	2 h	1-2 h
Oral bioavailability	70-90%	78%	65%
Excretion	54.4% urine, 41.2% feces	75% urine, 21% feces	51.7% feces, 33% urine

Source: Le Liu, Yu-Qing Ni, Jun-Kun Zhan, You-Shuo Liu. The Role of SGLT2 Inhibitors in Vascular Aging. Aging and Disease, Volume 12, Number 5; 1323-1336, August 2021. http://dx.doi.org/10.14336/AD.2020.1229.

At baseline, the mean uric acid level (5.5±1.4 vs. 4.7±1.1; p=0.014) was higher in the empagliflozin group compared to the dapagliflozin group, while the mean albumin (44.2±4.0 vs. 45.7±2.5; p=0.037) and mean phosphorus (3.6±0.5 vs. 3.9±0.7; p=0.007) levels were lower. Other baseline laboratory findings showed no significant differences between SGLT2 inhibitor therapy groups (**Table 2**).

The changes in short-term laboratory findings in patients receiving SGLT2 inhibitor therapy at 24 weeks of follow-up are shown in detail in Table 2. In both SGLT2 inhibitor therapy groups, mean urea levels and mean calcium levels were higher at 24 weeks compared to baseline, and mean fasting blood glucose, mean potassium, and mean HbA1c were lower (p<0.05). These changes were similar between the two SGLT2 inhibitor therapy groups (p>0.05).

In the dapagliflozin group, mean total cholesterol level (191.6±46.8 vs. 179.4±39.7; p<0.001) was lower at 24 weeks compared to baseline, while no significant difference was seen for other laboratory findings. In the empagliflozin group, mean creatinine level (0.9±0.2 vs. 1.0±0.3; p=0.007), mean phosphorus level (3.6±0.5 vs. 3.8±0.6; p<0.001), mean platelet count (242.0±63.8 vs. 252.4±68.6; p=0.019), and mean hemoglobin level (13.8±1.6 vs. 14.1±1.7; p=0.005) were higher at 24 weeks compared to baseline, while no significant difference was seen for other laboratory findings. In addition, the changes in creatinine, phosphorus, platelet count, and hemoglobin were higher in the empagliflozin group compared to the dapagliflozin group (**Table 2**).

The total incidence of adverse events, including urinary tract infection (8.8%) and dysuria (2.7%), was 10.2% (n: 15). Adverse events and their subtypes did not differ significantly between the SGLT2 inhibitor therapy groups (**Table 3**).

Table 2. Demographic characteristics of patients with type 2 diabetes mellitus

Variables	Whole population n=147	Empagliflozin n=101	Dapagliflozin n=46	p
Age, years	69.0±3.6	68.9±3.6	69.2±3.7	0.618
Gender, n (%)				
Female	57 (38.8)	33 (32.7)	24 (52.2)	0.029*
Male	90 (61.2)	68 (67.3)	22 (47.8)	
BMI, kg/m2	26.7±2.0	26.7±2.6	26.7±1.3	0.988
Comorbidity, n (%)				
Hypertension	110 (74.8)	76 (75.2)	34 (73.9)	0.841
CAD	97 (66.0)	68 (67.3)	29 (63.0)	0.708
Hyperlipidemia	116 (78.9)	80 (79.2)	36 (78.3)	0.999
Antihypertensive drugs, n (%)				
ACEI	48 (32.7)	38 (37.6)	10 (21.7)	0.061
ARB	48 (32.7)	33 (32.7)	15 (32.6)	0.999
CCB	48 (32.7)	36 (35.6)	12 (26.1)	0.343
Statin, n (%)	87 (59.2)	60 (59.4)	27 (58.7)	0.999
Oral antidiabetic drugs, n (%)				
Metformin	133 (90.5)	88 (87.1)	45 (97.8)	0.081
Sulfonylurea	36 (24.5)	23 (22.8)	13 (28.3)	0.536
DPP4	74 (50.3)	52 (51.5)	22 (47.8)	0.724
Glitazone	9 (6.1)	6 (5.9)	3 (6.5)	0.999
Glinide	3 (2.0)	1 (1.0)	2 (4.3)	0.480
Insulin	55 (37.4)	35 (34.7)	20 (43.5)	0.359

Data are mean±standard deviation, median (IQR), or number (%).
*: Considered statistically significant (p<0.05).
Abbreviations: BMI, body mass index; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; DPP4, dipeptidyl peptidase-4 inhibitor.

Table 3. Changes in short-term laboratory findings in patients receiving SGLT2 inhibitor therapy

Variables	Empagliflozin			Dapagliflozin		
	Baseline	24 weeks	p	Baseline	24 weeks	p
FBG, mg/dL	174.2±56.7	156±56.5	0.012*	172.8±43.1	145±51.4	0.002*
Urea, mg/dL	38.5±10.4	41.8±14.3	0.012*	36.9±10.5	43.4±13.8	0.043*
Creatinine, mg/dL	0.9±0.2	1.0±0.3	0.007*	0.9±0.2	0.9±0.3	0.266
Uric acid, mg/dL	5.5±1.4	5.7±1.8	0.173	4.7±1.1	5.3±1.5	0.653
Albumin, g/dL	44.2±4.0	45.4±4.6	0.089	45.7±2.5	45.3±3.8	0.804
AST, U/L	19 (16-24)	19 (15-23)	0.380	19 (15-28)	17 (15-22.5)	0.238
ALT, U/L	24 (18-31)	22 (18-29)	0.181	21 (18-29)	21 (17-27)	0.822
ALP, U/L	80 (69-100)	83 (71-94)	0.913	83 (64-99)	86 (71-101.5)	0.723
Total cholesterol, mg/dL	176.4±56.0	180.0±56.3	0.208	191.6±46.8	179.4±39.7	0.044*
HDL, mg/dL	42.5±10.4	42.5±9.4	0.985	46.0±11.4	46.7±10.6	0.463
LDL, mg/dL	98.3±39.7	101.2±40.8	0.323	111.1±37.7	101.2±30.1	0.060
Triglyceride, mg/dL	152 (110-198.5)	146.5 (106-232.5)	0.431	161 (108-242)	159 (105-190)	0.159
Calcium, mg/dL	9.4±0.5	9.7±0.5	0.005*	9.5±0.8	9.7±0.5	0.048*
Magnesium, mg/dL	1.8±0.2	1.9±0.2	0.109	1.8±0.3	1.9±0.3	0.535
Phosphorus, mg/dL	3.6±0.5	3.8±0.6	<0.001*	3.9±0.7	3.9±0.6	0.635
Sodium, mmol/L	139.1±2.7	139.4±2.9	0.175	139.3±2.7	139.7±3.7	0.490
Potassium, mmol/L	4.6±0.5	4.5±0.4	0.026*	4.7±0.4	4.6±0.4	0.049*
eGFR, mL/min/1.73 m2	76.8±15.5	74.6±16.0	0.091	78.3±13.9	75.0±18.7	0.252
HbA1c, %	8.7±1.6	8.0±1.4	<0.001*	8.8±1.2	7.8±1.1	<0.001*
TİT (+)	21 (20.8)	14 (13.9)	0.144	9 (19.6)	6 (13.0)	0.366
WBC, $\times 10^3$/mL	8.1±2.3	8.1±2.1	0.712	8.1±2.2	8.1±2.1	0.870
Neutrophils, $\times 10^3$/mL	4.7 (3.5-6.2)	4.8 (3.8-5.8)	0.999	4.4 (3.7-5.7)	4.6 (3.60-5.8)	0.856
Lymphocytes, $\times 10^3$/mL	2.2 (1.7-2.6)	2.2 (1.8-2.5)	0.149	2.2 (1.6-2.8)	2.0 (1.6-2.9)	0.429
Platelets, $\times 10^3$/mL	242.0±63.8	252.4±68.6	0.019*	263.1±68.1	251.7±66.8	0.060
NLR	2.2 (1.6-3.0)	2.2 (1.7-2.9)	0.268	2.1 (1.7-2.9)	2.1 (1.8-3.0)	0.646
Hemoglobin, g/dL	13.8±1.6	14.1±1.7	0.005*	13.2±1.6	13.5±1.7	0.158
RDW	14.4±1.5	14.6±1.4	0.139	14.6±1.3	14.8±1.6	0.195
MPV	8.7±1.0	8.7±1.8	0.965	8.5±1.0	8.6±1.1	0.131

Data are mean±standard deviation, median (IQR), or number (%). *: Considered statistically significant (p<0.05). Abbreviations: WBC, white blood cell count, FBG, fasting blood glucose; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; NLR, neutrophil/lymphocyte ratio; MPV, medium platelet volume; RDW, red cell distribution width.

Table 4. Adverse events in patients with type 2 diabetes mellitus receiving SGLT2 inhibitor therapy

Adverse events	Whole population n=310	Empagliflozin n=170	Dapagliflozin n=140	p
Dysuria, n (%)	4 (2.7)	2 (2.0)	2 (4.3)	0.786
Urinary tract infection, n (%)	13 (8.8)	9 (8.9)	4 (8.7)	0.999
Total adverse effects, n (%)	15 (10.2)	10 (9.9)	5 (10.9)	0.999

Data are number (%).

DISCUSSION

SGLT2 inhibitors are frequently used by many clinicians in fields including cardiology, endocrinology, nephrology, and internal medicine. However, as of 2021, data on the use of these drugs among elderly individuals, who constitute 9.8% of the world's population, were still very limited (11).

SGLT2 inhibitors have begun to appear in clinical guidelines for many diseases. In recent studies, the glucose-lowering, cardioprotective, and renoprotective effects of SGLT2 inhibitors were described. In addition, many positive effects such as delayed vascular aging have begun to be shown to occur with different mechanisms. Empagliflozin and dapagliflozin have been shown to increase nitric oxide bioavailability and reduce the formation of reactive oxygen radicals induced by tumor necrosis alpha (12). In this way, it is thought that it may exert its protective effect against vascular aging by reducing endothelial inflammation.

Studies have also shown that SGLT2 inhibitors increase hemoglobin and hematocrit values (13,14). Dapagliflozin has been shown to exert this effect by increasing hepcidin levels (15), while empagliflozin has been shown to increase erythropoiesis and increase hemoglobin and hematocrit values (16). Although this result is evaluated positively in some studies because it may increase myocardial oxygenation, patients should be closely monitored for thrombosis and stroke risk (17). In this study, similar to the literature, an increase in hemoglobin values was observed in older patients. It is thought that SGLT2 inhibitors may contribute positively to delayed vascular aging by increasing tissue perfusion, but further studies are needed on the different mechanisms of this increase.

Chronic inflammation has been shown to increase endothelial dysfunction, which causes age-related disorders, and to exacerbate atherosclerosis (18). There are studies showing that SGLT2 inhibitors have vasculoprotective efficacy in animal models of T2DM (19). We saw that, while there was a decrease in lipid parameters in the dapagliflozin group, the same effect was not achieved in the empagliflozin group. In an experimental study, it was determined that empagliflozin was associated with an increase in LDL-C levels via the reduction of catabolism (20). One possible explanation for this may be differences in pharmacokinetic properties and SGLT2/SGLT1 receptor selectivity.

In our study, we observed that serum calcium increased in both groups. There are studies showing that empagliflozin strongly reduces calcium calmodulin-dependent kinase (CaMKII) activity in ventricular myocytes in animal models. This results in reduced calcium release from the sarcoplasmic reticulum and improved myocardial contractility (21).

In our results, especially after the use of empagliflozin, there was an increase in phosphorus values. This increase can contribute to increased delivery of oxygen to tissues by shifting the oxygen-dissociation curve to the right. In this way, it can make a positive contribution to tissue perfusion in older patient groups. However, SGLT2 inhibition may cause secondary hyperparathyroidism as a result of increased phosphate uptake (22). As a result of SGLT2 inhibitors increasing renal tubular phosphate reuptake, the level of 1,25-dihydroxyvitamin D decreases, and it is reported that the risk of bone fractures may increase with reduced calcium absorption from the intestines (23). This is an undesirable effect, especially for older patients with higher risks of falls and fractures. According to a meta-analysis, however, there was no increase in the risk of bone fractures in patients taking SGLT2 inhibitors (24). There are also studies showing that empagliflozin binds to SGLT2 with more than 2500-fold affinity compared to SGLT1, while dapagliflozin binds with 1200-fold affinity (25). The high selectivity of SGLT2 may explain the differing results for empagliflozin.

There are studies suggesting that the mechanism underlying the arterial stiffness prevention effect of empagliflozin is independent of its antihypertensive activity and endothelial function. It can be assumed that it acts with the direct activation of specific receptor signaling pathways (26).

In our study, it was seen that despite the other maximum tolerable doses of treatment used by the patients, there was a significant decrease in HbA1c and fasting blood glucose. SGLT2 inhibitors appear to be important drugs that increase the treatment options of clinicians in appropriate patient groups of all ages. In addition, there were no side effects due to the SGLT2 inhibitors that would necessitate drug withdrawal. However, it is possible that some individuals in this older patient population were not able to describe their symptoms.

Lack of information about patients' blood pressure and weight changes can be considered as one of the limitations of our study. Especially in the population over 65 years of age, weight and muscle loss, sarcopenia, and frailty are important factors that can increase the risk of falling. The fact that the findings cannot be compared with those of the population under 65 years of age and the number of patients being low can be counted as other deficiencies of this study.

CONCLUSION

SGLT2 inhibitors have promising effects in improving vascular function together with their blood sugar-lowering effects. With natriuretic and glucosuric effects, they can reduce arterial hypertension, atherosclerosis, and arterial stiffness. It is thought that SGLT2 inhibitors may have many other potential effects that have not yet been fully demonstrated. Therefore, more prospective basic and clinical research on these drugs is needed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 22.06.2022, Decision No: E2-22-2035).

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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The relationship between extended D-dimer elevations and hereditary thrombophilia in COVID-19 patients

COVID-19 hastalarında uzamış D-dimer yüksekliği ve herediter trombofili arasındaki ilişki

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ABSTRACT

Aim: To compare the D-Dimer levels in patients with mild COVID-19 disease with and without hereditary thrombophilia.

Material and Method: Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G) and FXIII (V34L) gene mutations were examined in all patients included in the study for various reasons such as recurrent miscarriage and venous embolism. Patients with any mutation were included in the hereditary thrombophilia group, while patients without mutations were included in the control group. D-dimer levels of the patients were also analyzed for the second time at least 25 days after admission. All included patients had received previously at least two doses of the BioNTech-Pfizer or CoronaVac vaccines.

Results: A total of 158 patients, 46 (29.1%) male and 112 (70.9%) female, were included in the study. The mean age of the patients included in the study was 39.08 ± 9.09 years. A total of 121 patients, 33 (27.3%) men and 88 (72.7) women, with hereditary thrombophilia were in the first group. A total of 37 patients, 13 (35.1%) male and 24 (64.9%) female, who did not have any mutations, were taken as the control group. Of the patients with hereditary thrombophilia, 47 (38.8%) had Factor V Leiden, 63 (52.1%) had MTHFR gene mutations, 32 (26.4%) had PAI-1 and 12 (9.9%) had FXIII gene mutations. When the D-dimer values of both groups were examined 20-35 days after admission to the hospital, the D-dimer level of the hereditary thrombophilia group was 667.26 ±354.11 while the D-dimer level of the control group was 369.76±173.45 (P=0.031). The D-dimer level of 23 patients in the hereditary thrombophilia group and 2 patients without thrombophilia were found to be above 1000ng/ml when they came for control.

Conclusion: It should be kept in mind that if there is prolonged or newly emerging D-dimer elevation in patients who had COVID-19 disease with mild-moderate symptoms, these patients may have hereditary thrombophilia.

Keywords: COVID-19, Herediday thrombophilia, D-dimer

ÖZ

Amaç: Bu çalışmada herediter trombofili olan ve olmayan hafif Covid-19 hastalarında D-Dimer düzeylerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Tekrarlayan düşük ve venöz emboli gibi çeşitli nedenlerle daha önce Faktör V leiden (G1691A) mutasyonu, metilen tetrahidrofolat gen mutasyonu (C677T, A1298C), PAI-1 (4G-5G) ve FXIII (V34L) gen mutasyonları bakılmış olan hastalar çalışmaya alındı. Herhangi bir mutasyonu olan hastalar kalıtsal trombofili grubuna, mutasyonu olmayan hastalar kontrol grubuna alındı. Hastaların D-dimer düzeyleri başvurudan en az 25 gün sonra bir kez daha kontrol edilmişti. Çalışmaya dahil edilen tüm hastalar daha önce BioNTech-Pfizer veya CoronaVac aşılarından en az iki doz olmuştu.

Bulgular: Çalışmaya 46 (%29,1) erkek ve 112 (%70,9) kadın olmak üzere toplam 158 hasta dahil edildi. Hastaların yaş ortalaması 39,08±9,09 idi. Herediter trombofilisi olan 33 (%27,3) erkek, 88 (72,7) kadın toplam 121 hasta birinci grup olarak alındı. Herhangi bir mutasyonu olmayan 13 (%35,1) erkek ve 24 (%64,9) kadın toplam 37 hasta ise kotrol grubu olarak alındı. Kalıtsal trombofili hastalarının 47'sinde (%38,8) Faktör V Leiden, 63'ünde (%52,1) MTHFR gen mutasyonu, 32'sinde (%26,4) PAI-1 ve 12'sinde (%9,9) FXIII gen mutasyonu vardı. Hastaneye yatıştan 20-35 gün sonra her iki grubun D-dimer değerleri incelendiğinde, herediter trombofili grubunun D-dimer düzeyi 667,26 ±354,11, kontrol grubunun D-dimer düzeyi 369,76±3; 173,45 (P=0,031) olarak bulundu. Herediter trombofili grubundaki 23 hastanın ve trombofili olmayan 2 hastanın kontrole geldiklerinde D-dimer düzeyleri 1000ng/ml'nin üzerinde bulundu.

Sonuç: Hafif-orta semptomları olan COVID-19 hastalığında uzamış veya yeni ortaya çıkan D-dimer yüksekliği varsa bu hastalarda kalıtsal trombofili olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: COVID-19, hereiditer trombofili, D-dimer

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INTRODUCTION

COVID-19 disease, which is a SARS-CoV-2 virus infection, appeared in China in December 2019 and was declared a pandemic by the World Health Organization in March 2020. It may be asymptomatic, or may cause severe respiratory failure and even death (1). Since the beginning of the pandemic, SARS-CoV-2 is causing both deaths and complications, especially thrombotic events, all over the world. Although the number of confirmed cases and mortality rates vary according to countries and regions, it has led to nearly 500 million confirmed cases and over 6 million deaths by 2022 (2). While studies are continuing to predict which patient will have a severe course after signs of infection appear, patients are followed closely to predict complications.

Hereditary thrombophilia is a genetically inherited disease that can cause ischemic damage at young ages, recurrent infant loss in pregnant women, and sudden death due to acute thrombosis in the coronary or cerebral arteries. Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G), FXIII (V34L) gene mutation are common mutations and are often found as the underlying cause in patients with hereditary thrombophilia. There are very few studies on whether these mutations may cause increased prothrombotic activity in COVID-19 patients (3,4,5).

Many studies have shown that despite the prophylactic anticoagulant and antiaggregant use in COVID-19 patients, thrombotic events may occur in the venous, arterial and microvascular systems (6,7). Several studies showing complications related to hypercoagulability are based on studies in which COVID-19 disease has a severe course (8). On the other hand, it has been shown that patients with mild symptoms and who are not critically ill may still have thrombosis if they have pre-existing typical thrombotic risk factors or if they are elderly. Although venous embolisms are seen more frequently than arterial embolisms, there are studies showing that the frequency of venous thromboembolism has increased recently, especially in non-critical patients (9).

D-dimers are the protein fragments that occur as a result of the destruction of fibrin bonds that take place in the last stage of coagulation. D-dimer elevation at any given time means that the coagulation system and fibrinolytic system are active (10). Monitoring D-dimer and fibrinogen levels at the initial admission and follow-up of COVID-19 patients may be informative in terms of demonstrating coagulation-related complications (11).

The aim of this study is to compare the D-Dimer levels in patients with mild COVID-19 disease with and without hereditary thrombophilia.

MATERIAL AND METHOD

The study was carried out with the permission of Lokman Hekim University, Noninvasive Clinical Researches Ethics Committee (Date: 16.02.2021, Decision No:2021/018).All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was carried out retrospectively by scanning the files of patients who applied to the hematology and internal diseases outpatient clinic between February 2021 and January 2022. Hemogram, C-reactive protein, D-dimer, lactate dehydrogenase (LDH), Ferritin, Homocysteine, Vitamin B12, Foliate, and fibrinogen levels of all patients included in the study were analyzed at the time of admission. The diagnosis of COVID-19 of all patients included in the study was made by taking a nasopharyngeal swab and with real-time PCR method. Age, gender, smoking history, and medical history of the patients were recorded.

Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G) and FXIII (V34L) gene mutations were examined in all patients included in the study for various reasons such as recurrent miscarriage and venous embolism. Patients with any mutation were included in the hereditary thrombophilia group, while patients without mutations were included in the control group. D-dimer levels of the patients were also analyzed for the second time at least 25 days after admission. Patients under the age of 18, patients with active malignancy or a history of malignancy, patients who are pregnant, patients with systemic lupus erythematosus or similar autoimmune diseases, and patients with a negative COVID-19 PCR test at admission were excluded from the study. Low molecular weight heparin (enoxaparin 40mg/day) therapy was given to patients in both groups whose D-Dimer was above 1000 at the time of admission. Patients whose general condition deteriorated after admission to the outpatient clinic and who were hospitalized were excluded from the study. All included patients had received previously at least two doses of the BioNTech-Pfizer or CoronaVac vaccines.

Statistical Analyses

All analyzes were performed using Statistical Packace for Social Sciences 20.0 (SPSS) for Windows. Fisher's Exact test was used to analyze the demographic characteristics of the patients included in the study. Student's t-test was performed to compare the means. The difference between the groups for non-parametric values was compared with the Chi-Square test. Results are given as mean ± standard deviation. $P<0.05$ was considered statistically significant.

RESULTS

A total of 158 patients, 46 (29.1%) male and 112 (70.9%) female, were included in the study. The mean age of the patients included in the study was 39.08 ± 9.09 years. A total of 121 patients, 33 (27.3%) men and 88 (72.7) women, with hereditary thrombophilia were in the first group. A total of 37 patients, 13 (35.1%) male and 24 (64.9%) female, who did not have any mutations, were taken as the control group. Of the patients with hereditary thrombophilia, 47 (38.8%) had Factor V Leiden, 63 (52.1%) had MTHFR gene mutations, 32 (26.4%) had PAI-1 and 12 (9.9%) had FXIII gene mutations. The mean duration of symptoms in both groups was between 2-4 days. None of the patients had previous coronary artery disease or cerebrovascular accident. Totally 27 patients were excluded from the study, due to secondary malignancy (n:9), autoimmune diseases (n:4), or since they were under warfarin, heparin or low molecular weight heparin (n:14). The comparison of blood tests and demographic characteristics of the study groups at the time of admission is shown in **Table**.

Table. The comparison of blood tests and demographic characteristics of the study groups at the time of admission

Feature	Hereditary thrombophilia (n=121)	Control (n=37)	P value
Gender (M/F)	33/88	13/24	0.410
Age (years)	38.02?11.46	42.51?13.59	0.68
Smoking (+/-)	51/70	15/22	0.509
Homocysteine (μmol/L)	9.91±5.22	9.42±4.41	0.802
D-Dimer (ng/ml)	202.52±81.59	185.48±73.74	0.421
Fibrinogen (mg/dL)	204.26±83.12	200.95±57.82	0.409
WBC (10^3/mL)	7.70?2.32	6.82?1.90	0.328
Trombocyte (10^3/uL)	280?100	271±81	0.964
Vitamin B12 (pg/ml)	392?140	428?149	0.417
Folate (ng/ml)	7.94?3.58	8.84?3.01	0.395

When the D-dimer values of both groups were examined 20-35 days after admission to the hospital, the D-dimer level of the hereditary thrombophilia group was 667.26 ±354.11ng/ml while the D-dimer level of the control group was 369.76±173.45 ng/ml (P=0.031). The D-dimer level of 23 patients in the hereditary thrombophilia group and 2 patients without thrombophilia were found to be above 1000 ng/ml when they came for control. Low molecular weight heparin therapy (enoxaparin 40mg/day) was given to 12 patients from the hereditary thrombophilia group and 4 patients from the control group because D-dimer level was >1000 ng/ml until the second D-dimer level was checked. Only one patient from the hereditary tromobophilia group was hospitalized during follow-up due to coronary artery disease. Pulmonary embolism was seen in only one patient and long-term anticoagulant treatment was started. No thromboembolic complications were observed in any of the patients in the control group. In the control visits after admission to the hospital, 12 patients from the hereditary thrombophilia group and 3 patients from the control group complained of increased symptoms such as cough and shortness of breath. However, none of the patients had oxygen saturation below 91% and did not need oxygen support. In 29 patients included in the study, lupus anticoagulant was tested before and it was negative.

DISCUSSION

Thrombotic complications developed during and after COVID-19 disease continue to be a serious problem for patients and clinicians. For this reason, it is important that risky patients can be selected and followed more closely. Our study is the first to predict that the presence of hereditary thrombophilia in non-critical patients may pose a risk for thrombophilia in the subacute period in COVID-19 patients.

D-dimer levels are a good marker for demonstrating hypercoagulability in COVID-19 patients (12). The blood D-dimer level is one of the parameters used to evaluate the severity of the disease at the first admission of COVID-19 patients, and APTT and PTZ are usually found to be normal during the first admission to the hospital (13). Especially in severe COVID-19 patients, the possibility of coagulopathy increases with increasing cytokine levels. In one study, the probability of coagulopathy in severe COVID-19 patients was found to be approximately 20% (14). In a meta-analysis evaluating 1551 patients, the mean D-dimer level of the patients with moderate disease was 580 ng/ml, it was 3550 ng/ml in patients with severe disease (15). In this meta-analysis, in which a total of 54 studies were evaluated, a significant association was found between D-dimer levels and mortality. In our study, the mean D-dimer level of all patients at admission was 298.53 mg/dl. In hospitalized patients, D-dimer levels can be found to be high secondary to the onset of the thrombotic process due to hypoxia, continuous interventional procedures, or direct endothelial damage of COVID-19 (16). While a D-dimer elevation of 3 times or more at the first admission was considered risky for embolism, a 4-fold or higher D-dimer level during follow-up was found to be a good indicator for mortality in hospitalized patients (17). Similarly, if D-dimer elevation still persists after the 5th day, this may be an indicator for severe COVID-19 disease and mortality (18). In another study, higher mortality rates were found in patients with D-dimer levels above 2000 ng/ml compared to patients with D-dimer levels below 2000 ng/ml (19). The prolongation of the inflammatory process and the development of endothelial dysfunction due to cytokine storm may explain the formation of

microthrombi in critically ill patients and the secondary elevation of D-dimer levels (20). None of our patients were having severe disease and in parallel with these studies, D-dimer levels of all our patients were within normal limits at the time of admission.

In a recent study, it was shown that the PA1-1 mutation both contributes to thrombus formation and increases the secretion of proinflammatory cytokines in COVID-19 patients (3). However, there are also studies showing that the severity of COVID-19 disease worsens in patients with Factor V Leiden mutation and Factor XIII mutation (21). There are also studies with similar results regarding the MTHFR gene mutation. In fact, it has been suggested in one study that the MTHFR gene mutation may be a useful marker to show the severity of COVID-19 (22). MTHFR gene mutation may affect homocysteine metabolism, resulting in high homocysteine levels. This, in turn, may activate the angiotensin type 2 receptors, causing COVID-19 to reason more damage (24). However, in our study, there was no significant increase in homocysteine levels at the time of admission in both hereditary thrombophilia and control groups. In our study, patients with severe disease were not included in the study. However, it is useful to consider that there may be primary hereditary thrombophilia in patients with thrombotic complications such as heart attack, stroke, and deep vein thrombosis secondary to COVID-19, and further studies should be conducted to clarify this issue. Similarly, in patients with previously known homocysteine elevations, recurrent miscarriage, a history of atypical thrombosis, or a family history of hereditary thrombophilia, it may be beneficial to follow the patients more closely for thrombosis after COVID-19.

Limitations

All of the patients included in the study were vaccinated against COVID-19, at different time periods. Although studies on the vaccines continue, it should be kept in mind that prolonged D-dimer elevation in these patients may be secondary to the vaccine. In only some of the patients included, antiphospholipid antibodies were checked and this is the second limitation of the study. Since the number of patients included in the study was insufficient, a subgroup analysis could not be performed for each gene mutation. Therefore, larger prospective studies are warranted.

CONCLUSION

As a result, it should be kept in mind that if there is prolonged or newly emerging D-dimer elevation in patients who had COVID-19 disease with mild-moderate symptoms, these patients may have hereditary thrombophilia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Lokman Hekim University, Noninvasive Clinical Researches Ethics Committee (Date: 16.02.2021, Decision No:2021/018).

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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Evaluation of Bethesda IV-V thyroid nodules: clinical experience

Bethesda IV-V tiroid nodüllerinin değerlendirilmesi: klinik deneyim

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ABSTRACT

Introduction: The malignancy rate in cases operated for thyroid nodule is approximately 5-10%, and although this rate shows significant differences according to Bethesda categories, there is a high risk of malignancy in categories IV and V compared to other categories. In our study, we examined the clinicopathological factors affecting the success of cytological diagnosis in nodules diagnosed with Bethesda IV-V.

Material and Method: A total of 780 patients who were diagnosed with thyroid nodules and underwent surgery at our center between 2011 and 2021 were included in the study. The preoperative cytological diagnoses of the patients were categorized using the Bethesda classification system. The demographic data of the patients, Bethesda classification of the nodules, and postoperative histopathological examination results were evaluated in subgroups, and their significance was determined.

Results: The age group with the highest number of cases was 45-59 years, and the female/male ratio of the whole cohort was 3:1. The rate of palpable nodules was 41.8% for the malignant diagnosis group and 58.2% for the benign diagnosis group. In both malignant and benign groups, <20 mm nodules were found at statistically significantly higher rates compared to nodule groups of other diameters ($p<0.001$ for both). While 50% of those diagnosed with DC-IV have a diameter greater than 20 mm; It was observed that 43.5% of those diagnosed with DC-V were more intense in the 10-20 mm diameter range. When the FNAB cytological diagnoses of the cases are compared with the postoperative histopathological diagnoses, it is seen that 32.5% of the cases diagnosed with DC-IV and 78.3% of those diagnosed with DC-V were diagnosed as malignant. While 69.2% of the cases with a cytological diagnosis of DC-IV were PTC and 30.8% were OTC; 100% of the cases with DC-V diagnosis are PTC histopathologically.

Conclusion: Our study showed that the diagnostic success of FNAB was decreased in microcarcinoma and large-sized nodules, with 10-20-mm nodules being the most suitable size for the success of cytological diagnosis. The risk of malignancy was higher in the nodules smaller than 20 mm compared to those larger than 20 mm. OTC should be primarily considered in >20-mm nodules with a DC-V diagnosis and PTC in smaller nodules. While benign pathologies are considered in DC-IV diagnoses; If the diameter of DC-V cytologically diagnosed nodules is larger than 20 mm, OTC should be considered primarily, and if less than 20 mm, PTC should be considered.

Keywords: Thyroid neoplasms, thyroid nodule, fine-needle biopsy

ÖZ

Amaç: Tiroidde nodül nedeniyle opere edilen olgularda malignite oranı yaklaşık %5-10 olup, bu oran Bethesda kategorilerine göre önemli farklılıklar göstermekle birlikte diğer kategorilere göre kategori IV ve V'te yüksek malignite riski mevcuttur. Biz çalışmamızda Bethesda IV-V tanısı alan nodüllerde sitolojik tanı başarısını etkileyen klinikopatolojik etkenleri inceledik.

Gereç ve Yöntem: Çalışmaya merkezimizde 2016-2021 yılları arasında tiroid nodülü tanısı alan ve opere edilen 780 hasta dahil edildi. Hastaların preoperatif sitolojik tanıları Bethesda Sistemi kullanılarak sınıflandırıldı. Hastaların demografik verileri, nodüllerin Bethesda sınıflandırması ve postoperatif histopatolojik inceleme sonuçları alt gruplar halinde değerlendirilerek anlamlı sonuçlar raporlandı.

Bulgular: Olguların en yoğun olarak bulunduğu yaş grubu 45-59 olup, K/E oranın 3:1 olduğu görülmektedir. Malign tanı grubundaki nodüllerin %41,8'inin; benign tanı grubundakilerin %58,2'sinin palpabl olduğu görülmektedir. 20 mm<büyük nodüllerde hem malign hem benign grupta diğer çaptaki nodül gruplarına göre istatistiksel olarak anlamlı şekilde ($p<0,001$; $p<0,001$) daha yüksek oranda bulunmaktadır. DC-IV tanı alanların %50'i 20 mm<'den büyük çaplı iken; DC-V tanısı alanların %43,5'inin 10-20 mm çap aralığında daha yoğun olduğu görüldü. Olguların İİAB sitolojik tanıları ile postoperatif histopatolojik tanıları kıyaslandığında DC-IV tanısı konulan olguların %32,5'i ve DC-V tanı konulanların %78,3'ü malign tanı aldığı görülmektedir. DC-IV sitolojik tanılı olguların %69,2si PTK ve %30,8'i DTK iken; DC-V tanılı olguların %100 PTK histopatolojik tanılıdır.

Sonuç: Çalışmamız mikrokarsinom ve büyük çaplı nodüllerde İİAB tanı başarısının düştüğünü, sitolojik başarı açısından en uygun nodül boyutunun 10-20 mm nodüller olduğunu göstermektedir. Malignite riski 20 mm'den küçük nodüllerde 20 mm'den büyük nodüllere göre daha yüksektir. DC-IV tanılarda bening patolojiler ön planda düşünülürken; DC-V sitolojik tanılı nodüllerin çapı 20 mm'den büyük ise ön planda DTK, 20mm'den küçük ise PTK düşünülmelidir.

Anahtar Kelimeler: Tiroid neoplazmaları, tiroid nodülü, ince iğne biyopsisi

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INTRODUCTION

Most of the adult population has one or more thyroid nodules (TN). It has been shown that with the widespread use of ultrasonography (USG), the rate of nodule detection has increased, reaching 50-70% (1). Although the possibility of cancer development in the presence of a nodule is the most important concern, it is known that only 5% of nodules have malignant properties (2,3). Thyroid cancers (TCs) are the most common endocrine tumors, with an incidence ranging from 1.2 to 2.6 in men and 2.0 to 4.4 in women per 100,000 population (4,5). Studies have shown that there is a relationship between TN and Graves' disease, parathyroid diseases, and chronic lymphocytic thyroiditis (6-8). The Bethesda classification system is used in the cytological evaluation of cases based on the results of the fine-needle aspiration biopsy (FNAB) of the thyroid (9). Malignancy rates have been reported as 1-4% for diagnostic category (DC) I, 0-3% for DC-II, 5-15% for DC-III, 15-30% for DC-IV, 60-75% for DC-V, and 97-99% for DC-VI (10,11).

The relationship between thyroid nodules and malignancy has been discussed for a long time. In our study, we aimed to retrospectively evaluate patients who were diagnosed with Bethesda DC-IV and DC-V nodules and underwent surgical treatment at our hospital over the last 10 years in terms of their demographic and histopathological features.

MATERIAL AND METHOD

The study was carried out with the permission of Gülhane Training and Research Hospital Clinical Research Ethics Committee (Date: 15.12.2021, Decision No: 2021/89). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Cases for which the surgical treatment decision was taken by the Endocrine Council of our hospital over the last 10 years were included in the study, and their data were obtained from the electronic patient files. This retrospective study included a total of 780 patients with complete epidemiological data and surgical and pathological reports. Cases with missing data were excluded from the study.

Data Collected/Recorded

The six-tier Bethesda classification system was used in all FNABs to report thyroid cytopathology (12). Cytological diagnoses were made as follows: DC-I: non-diagnostic or inadequate; DC-II: benign; DC-III: atypia or follicular lesion of uncertain significance (AUS/FLUS); DC-IV: follicular neoplasm or suspected follicular neoplasm; DC-V: suspicious for malignancy, and DC-VI: malignant.

Statistical Analysis

The statistical analyses of the study were performed using SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). When making comparisons between the groups, the chi-Square or Fisher's exact chi-square test was used for discrete data, and Student's t-test or the Mann Whitney-U test for continuous data. Statistical significance was defined as a p value of less than 0.05.

RESULTS

In our study, the age group with the highest number of cases was 45-59 years, and the female/male ratio of the whole cohort was 3:1. Two cases of medullary thyroid carcinoma (MTC) and one case of Hurthle cell carcinoma (HCC) were evaluated under the heading of other thyroid carcinomas (OTC) together with follicular thyroid carcinoma (FTC) due to the insufficient number of these diagnoses for statistical analysis (**Table 1**).

Table 1. Descriptive features of the cases included in the study

Variable	Number	Percentage
Gender		
Female	592	75.90
Male	188	24.10
Age, years		
<19	8	1.03
20-45	272	34.87
45-59	388	49.74
≥60	112	14.36
Diagnostic Group		
Malignant	378	48.46
PTC	354	45.38
OTC	24	3.08
Benign	402	51.54
NG/NH	258	33.08
MNG	18	2.31
GD	40	5.13
BTN	86	11.02
Total	780	100.00

PTC: Papillary Thyroid Carcinoma; Other Thyroid Carcinomas (OTC): Follicular Carcinoma, Hurthle Cell Carcinoma, Medullary Thyroid Carcinoma; NG/NH: Nodular Goiter/Nodular Hyperplasia; MNG: Multinodular Goiter; Benign Thyroid Neoplasms (BTN): Hurthle Cell Adenoma, Follicular Adenoma

In the ultrasonographic examination of 780 patients, a total of 958 thyroid nodules were visualized. Although 684 dominant nodules were detected in the histopathological examinations, the physical examination of the patients showed that 41.8% of the nodules in the malignant diagnosis group and 58.2% of the benign diagnosis group were palpable. When evaluated according to the diameters of the dominant nodules, nodules larger than 20 mm were found in both the malignant and benign groups at statistically significantly higher rates compared to smaller nodules ($p<0.001$). In the nodule group smaller than 20 mm, benign diagnoses were found at a higher rate than malignant diagnoses (59.8% vs 34.8%, respectively), although this was not statistically significant ($p=0.173$) (**Table 2**).

Table 2. Evaluation of dominant nodule size and histopathological diagnostic features

	Malignant		Benign		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
Number of patients	378	48.5	402	51.5	780	100.0
Number of dominant nodules	316	46.2	368	53.8	684	100.0
Number of palpable nodules	210	41.8	292	58.2	502	100.0
Number of nodules detected by USG	440	45.9	518	54.1	958	100.0
Dominant nodule features	**Malignant**		**Benign**		**Total**	
	Number	**Percentage**	**Number**	**Percentage**	**Number**	**Percentage**
Number						
Single nodule	106	33.5	90	24.5	196	28.6
Multiple nodules	210	66.5	278	75.5	488	71.4
Size						
<5 mm	16	5.1	8	2.2	24	3.5
5-10 mm	80	25.3	58	15.8	138	20.2
10-20 mm	110	34.8	82	22.3	192	28.1
≥20 mm	110	34.8	220	59.8	330	48.2
Total nodules	316	46.2	368	53.8	684	100.0

USG: Ultrasonography

Considering the distribution of Bethesda categories according to the dominant nodule size on the ultrasonographic examination, 55% of those diagnosed with DCI-II-III and 50% of those diagnosed with DC-IV had a diameter greater than 20 mm; 43.5% of those diagnosed with DC-V and 48.1% of those diagnosed with DC-VI were in the 10-20 mm diameter range. While 23% of those diagnosed with DCI-II-III were in the 10-20 mm diameter range; 45% of those diagnosed with DC-IV are nodules with a diameter of 10-20 mm. The diagnosis of DC-II was found to be statistically significantly higher in the nodules larger than 20 mm compared to the smaller nodules ($p<0.001$). The cytological diagnosis of DC-IV was higher in the 10-20 mm and >20 mm groups compared to the nodules smaller than 10 mm ($p<0.05$). In addition, the diagnosis of DC-IV was made at a significantly higher rate in the 10-20 mm and >20 mm groups compared to DC-V ($p<0.05$). When DC-I was excluded from evaluation, the most common cytological diagnosis was DC-VI at a rate of 28.89%, and the nodules with this diagnosis were mostly in the range of 10-20 mm in diameter ($p<0.001$). DC-VI was observed at a significantly higher rate among the nodules smaller than 10 mm and in the range of 10-20 mm compared to those larger than 20 mm ($p<0.001$) (**Table 3**).

Table 5 compares the cytological diagnoses of FNAB and postoperative histopathological diagnoses of the cases. While 32.5% of the cases diagnosed with DC-IV were diagnosed with malignant histopathology; It is seen that 78.3% of the cases with DC-VI diagnosis are malignant. While 69.2% of the cases with a cytological diagnosis of DC-IV were PTC and 30.8% were OTC; 100% of the cases with DC-V diagnosis are PTC histopathologically. In the cytological examination of the biopsies taken, it was seen that postoperative malignant histopathological diagnosis were made in 17.14% of the operated cases that were evaluated as benign. When evaluated in terms of the success of cytological diagnosis, it was found that FNAB was more successful in the NG cases than in the MNGs ($p<0.05$). The malignancy rates were similar between the DC-III and DC-IV groups (34.48% and 32.5%, respectively). The rate of benign pathologies was higher among the DC-IV cases ($p<0.05$). In the OTC diagnosis group, which also included follicular carcinomas, there was a higher rate of DC-I and DC-IV nodules. However, when the DC-IV cases were evaluated within themselves, it was seen that the histopathological diagnosis of PTC was significantly higher than that of OTC ($p<0.001$). The malignancy rate was higher in the DC-V and DC-VI cases (78.26% and 71.15%). In the histopathological examination of the DC-V cytological diagnoses, 78.26% were PTCs, and the relationship between PTC and other diagnoses in the DC-V group was statistically significant ($p<0.05$). In addition, the diagnosis of PTC was observed at a higher rate in the DC-V cases than in OTCs ($p<0.001$).

DC-I was seen at a lower rate in the OTC cases than in the PTC cases (41.7% vs 56.5%), and there was no cytological diagnosis of DC-V and DC-VI among the OTC cases. Since benign-malignant distinction can be made by evaluating capsule/vascular invasion in BTN and OTC cases, the cytological diagnosis was postoperatively confirmed in 55% of the patients ($p<0.001$). In addition, the histopathological confirmation of the cytological diagnoses of NG and PTC was found to be similar (71.15% and 72.22, respectively; $p<0.001$).

When the relationship between the accuracy of cytological diagnosis and nodule diameter was evaluated,

it was determined that a DC-II diagnosis provided more accurate results in the 5-10 mm and >20 mm nodules compared to smaller nodules (p<0.05 and p<0.001, respectively). In the PTC cases with a DC-VI cytological diagnosis, the success of the diagnosis decreased if the nodule was smaller than 5 mm (p=0.122), but the success rate was significantly higher in all the larger nodules groups (p<0.05). When the nodule sizes of all the cases and the correlation of cytological and histopathological diagnoses were evaluated, it was seen that the nodule group with the most successful diagnosis rate was 10-20 mm, and the success rate decreased in the 5-mm and >20-mm nodules.

Table 3. Evaluation of FNAB diagnoses according to the nodule diameter on ultrasonography

Fine needle aspiration biopsy diagnoses	<10 mm		10-20 mm		≥20 mm		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
DC-I	102	26.8	92	24.2	186	49.0	380	100
DC-II	2	2.8	14	19.4	56	77.8	72	100
DC-III	8	13.8	12	20.7	38	65.5	58	100
DC-IV	4	5.0	36	45.0	40	50.0	80	100
DC-V	14	30.4	20	43.5	12	26.1	46	100
DC-VI	36	34.6	50	48.1	18	17.3	104	100
Total Nodules	166	22.4	224	30.3	350	47.3	740	100.0

*Percentage of rows are taken. DC Diagnostic Categories; DC-I: Non-diagnostic, DC-II: Benign, DC-III: Atypia of uncertain significance or follicular lesion of uncertain significance (AUS-FLUS), DC-IV: Follicular neoplasm (FN) or suspected FN, DC-V: Suspected malignancy, DC-VI: Malignant

Table 4. Evaluation of histopathological diagnoses according to the nodule diameter on ultrasonography

Histopathological diagnoses	<10 mm		10-20 mm		≥20 mm		Total	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
NG	48	28.9	54	24.1	156	44.6	258	34.86
MNG	0	0.0	2	0.9	16	4.6	18	2.43
BTN	6	3.6	34	15.2	46	13.1	86	11.62
OTC	2	1.2	4	1.8	18	5.1	24	3.24
PTC	110	66.3	130	58.0	114	32.6	354	47.84
Total	166	22.4	224	30.3	350	47.3	740	100.0
BTN	**<10 mm**		**10-20 mm**		**≥20 mm**		**Total**	
	Number	Percentage	Number	Percentage	Number	Percentage	Number	Percentage
FA	4	66.7	22	64.7	42	91.3	68	79.1
HCA	2	33.3	12	35.3	4	8.7	18	20.9
Total	6	6.9	34	39.5	46	53.5	86	100.0

*Forty cases diagnosed with Graves' disease were not included in the table. PTC: Papillary Thyroid Carcinoma, OTC: Other Thyroid Carcinomas, MNG: Multinodular Goiter, BTN: Benign Thyroid Neoplasms, FA: Follicular Adenoma, HHA: Hurthle Cell Adenoma

Table 5. Evaluation of FNAB cytological diagnoses and histopathological diagnoses

FNAB	Malignant		Benign		Total	
	Number	Percentage	Number	Percentage	Number	Percentage
DC-I	210	55.6	172	47.5	382	51.6
DC-II	12	3.2	58	16.0	70	9.5
DC-III	20	5.3	38	10.5	58	7.8
DC-IV	26	6.9	54	14.9	80	10.8
DC-V	36	9.5	10	2.8	46	6.2
DC-VI	74	19.6	30	8.3	104	14.0
Total	378	51.1	362	48.9	740	100.0
FNAB	**PTC**		**OTC**		**Total**	
	Number	Percent	Number	Percent	Number	Percent
DC-I	200	56.5	10	41.7	210	55.6
DC-II	8	2.3	4	16.7	12	3.2
DC-III	18	5.1	2	8.3	20	5.3
DC-IV	18	5.1	8	33.3	26	6.9
DC-V	36	10.2	0	0.0	36	9.5
DC-VI	74	20.9	0	0.0	74	19.6
Total	354	93.7	24	6.3	378	100.0

FNAB: Fine-Needle Aspiration Biopsy, PTC: Papillary Thyroid Carcinoma, OTC: Other Thyroid Carcinomas, DC Diagnostic Categories; DC-I: Non-diagnostic, DC-II: Benign, DC-III: Atypia of uncertain significance or follicular lesion of uncertain significance (AUS-FLUS), DC-IV: Follicular neoplasm (FN) or suspected FN, DC-V: Suspected malignancy, DC-VI: Malignant

DISCUSSION

The p revalence o f t hyroid n odules i ncreases w ith a ge, with most being detected after the age of 40 years, and only 5% of these nodules are reported to be malignant (13,14). Although female gender was dominant in our study, there was no difference between the benign and malignant diagnosis groups in terms of mean age. Consistent with the literature, the age group with the highest incidence of cases was 40-59 years, and the male patients were older.

Although more than 90% of TNs are small and non-palpable lesions, they can present with microcarcinomas (15,16). In our study, the cases with a benign diagnosis had a significantly higher rate of palpable nodules than those with a malignant diagnosis. We consider this to be due to the high rate of microcarcinomas in cases with a histopathological diagnosis of PTC. In a study conducted by Kamran et al. (17), it was shown that large nodules had increased malignancy rates, but the relationship between size and malignancy was not linear. In the same study, the threshold value for an increased malignancy risk was accepted as approximately 20 mm, and the malignancy rate did not increase in larger nodules. In our results, the rate of increased malignancy in nodules smaller than 20 mm was 58.2%; the malignancy rate is reduced by 33.3% in nodules larger than 20 mm, which is similar to the literature.

In a review including 13 studies, it was reported that the mean risk of malignancy for the cytological diagnosis of follicular neoplasm was in the range of 10-45% for Hurthle cell type (DC-IV) and the average value was 22% (18-20). In our results, the cytological diagnosis of DC-IV was significantly higher in the 10-20-mm and >20-mm nodule groups. Unlike the PTC cases, most of the OTC cases were found to have nodules larger than 20 mm (75% vs. 32.2%). In light of these data, OTC should be considered primarily if the suspicious nodule diameter is larger than 20 mm, and PTC otherwise.

In our study, the diameter of the nodules in which FNAB was most successful was in the 10-20 mm range, which is compatible with the literature. In addition, the rate of a DC-IV cytological diagnosis was significantly higher in the nodules of 10-20 mm and those larger than 20 mm compared to DC-V. This was considered to be due to the radiologically late manifestation of follicular and Hurthle cell neoplasms. The nodules with a cytological diagnosis of DC-V and DC-VI were found to be mostly in the 10-20-mm diameter range.

In previous studies, it is stated that cytology has its own limitations, and it may not be able to distinguish between follicular hyperplastic and adenomatoid nodules, follicular adenoma, and some follicular variants of PTC; however, for most PTCs and poorly differentiated or undifferentiated carcinomas, the cytology report usually provides diagnostic utility (21). Pagni et al. (22) found that while the sensitivity of FNAB was 67.7% in microcarcinomas, it was 85.7% in carcinomas larger than 10 mm in diameter, and the sensitivity of FNAB was lower (31.8%) in large PTCs (>20 mm) due to tumor heterogeneity, confirming that USG-FNAB sensitivity is strongly correlated with tumor size. Our results are also consistent with the data reported in the literature in that the highest cytological success was obtained from the nodule group of 10-20 mm in diameter. In our study, the histopathological diagnosis of OTC was lower in the cases without a successful cytological diagnosis (DC-I) than in the PTC cases (41.7% versus 56.5%). We consider that most of the cases were caused by microcarcinomas, which are difficult to diagnose cytologically.

CONCLUSION

Our study showed that nodule size directly affected histopathological diagnosis and cytological success. Diagnostic success decreased in microcarcinomas and larger-diameter nodules, and the 10-20-mm nodules constituted the group with the highest cytological diagnostic accuracy. The risk of malignancy was higher in the nodules smaller than 20 mm than in those larger than 20 mm. The rate of benign pathological diagnosis is higher in DC-IV cases compared to DC-V. Therefore, especially in nodules with a cytological diagnosis of DC-V, a diameter greater than 20 mm should be considered in favor of OTC, and smaller nodules should indicate the presence of PTC.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gülhane Training and Research Hospital Clinical Research Ethics Committee (Date: 15.12.2021, Decision No: 2021/89).

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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Retrospective evaluation of pediatric trauma patients: a single-center experience of a tertiary pediatric intensive care unit

Pediatrik travma hastalarının retrospektif değerlendirilmesi: üçüncü basamak pediatrik yoğun bakım ünitesinin tek merkez deneyimi

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ABSTRACT

Aim: Due to the rapid development in pediatric critical care medicine, some past studies suggested that pediatric trauma patients have better outcomes such as lower mortality and lower length of hospital stay in the pediatric intensive care unit (PICU). In this study, we aim to describe the demographic, clinical features, mechanisms of injury, and outcomes of children hospitalized in our pediatric intensive care unit due to trauma.

Material and Method: We performed a retrospective evaluation of 60 pediatric trauma patients (between 0 and16 years of age) admitted to the PICU at University of Health Science, Sancaktepe Sehit Prof. Dr. İlhan Varank Training and Research Hospital from August 2020 to February 2022.

Results: A total of 60 pediatric trauma patients were followed up in our PICU. The median age of patients was 17 (0-724) months with a preponderance of male cases (n:38, 63.3%). The median duration of hospitalization in PICU was 6 (1-46) days. According to the trauma type, the majority of the injuries were falling from a height (n:37, 61.7%).

Conclusion: We would like to draw attention to the fact that head traumas due to falling were so common and also affect mortality. The lactate and the lactate/albumin ratio of patients who developed mortality were significantly higher. Although there are studies on the association of lactate/albumin ratio with mortality in critically ill pediatric patients, we could not find any data on this issue in pediatric trauma patients in the literature. Our study will contribute to the literature on the relationship between lactate/albumin ratio and mortality in pediatric trauma patients. We suggest that the relationship between lactate/albumin ratio and mortality should be investigated in pediatric trauma patients with larger case numbers.

Keywords: Pediatric intensive care unit, pediatric trauma, lactate/albumin ratio

ÖZ

Amaç: Pediatrik kritik bakım tıbbındaki hızlı gelişme nedeniyle, geçmişteki bazı araştırmalar, pediatrik travma hastalarının daha düşük mortalite ve daha kısa hastanede kalış süresi gibi daha iyi sonuçlara sahip olduğunu ileri sürmüştür. Bununla birlikte, çoğu gelişmekte olan ülkede, pediatrik travma merkezleri çok azdır veya hiç yoktur. Bu çalışmada travma nedeniyle çocuk yoğun bakım ünitemizde (ÇYBÜ) yatan çocukların demografik, klinik özellikleri, yaralanma mekanizmaları ve sonuçlarını tanımlamayı amaçladık.

Gereç ve Yöntem :Ağustos 2020 - Şubat 2022 tarihleri arasında Sağlık Bilimleri Üniversitesi, Sancaktepe Şehit Prof. Dr. İlhan Varank Eğitim ve Araştırma Hastanesi ÇYBÜ'ne başvuran 60 pediatrik travma hastası (0-16 yaş arası) retrospektif olarak değerlendirildi.

Bulgular :ÇYBB'mizde toplam 60 çocuk travma hastası takip edildi. Hastaların medyan yaşı 17 (0-724) aydı ve erkek olgular çoğunluktaydı (n:38, %63,3). ÇYBÜ'de medyan yatış süresi 6 (1-46) gündü. Travma tipine göre yaralanmanın büyük kısmı yüksekten düşme (n:37, %61,7) idi. Travmaya bağlı genel ölüm oranı %13.3 idi.

Sonuç: Düşmeye bağlı kafa travmalarının çok yaygın olduğuna ve mortaliteyi etkilediğine dikkat çekmek isteriz. Mortalite ile laktat, laktat/albümin oranı arasında anlamlı bir ilişki bulduk. Kritik hasta pediatrik hastalarda laktat/albümin oranının mortalite ile ilişkisine yönelik çalışmalar olmasına rağmen literatürde pediatrik travma hastalarında bu konuda herhangi bir veri bulamadık. Çalışmamız pediatrik travma hastalarında laktat/albümin oranı ile mortalite arasındaki ilişki ile ilgili literatüre katkı sağlayacaktır. Vaka sayısı fazla olan pediatrik travma hastalarında laktat/albümin oranı ile mortalite arasındaki ilişkinin araştırılmasını öneriyoruz.

Anahtar Kelimeler: Çocuk yoğun bakım ünitesi, çocuk travması, laktat/albümin oranı

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INTRODUCTION

Pediatric trauma is the leading cause of admission to the pediatric emergency departments (1). Blunt traumas are the most common injury in childhood and account for 85% of the cases (2). Injury takes an important place among the most common causes of death in children older than 1 year of age, and the majority of these deaths occur in developing countries (3). Mortality due to pediatric trauma was reported as 40% at the time of the accident, 30% in the early period, and 30% in the late period, respectively (2). While the mortality in the early period is due to hypoxia, hypovolemia, and severe head trauma, SIRS (Systemic Inflammatory Response Syndrome), MOFS (Multiple Organ Failure Syndrome), sepsis, and ARDS (Acute Respiratory Distress Syndrome) are the most common causes that increase mortality in the late period (2).

According to the American College of Surgeons National Trauma Databank 2014 data, 42% of pediatric trauma patients are admitted to an intensive care unit (4). In addition, head trauma ranks first among patients requiring intensive care hospitalization with a rate of 57%. Since there are significant physiological and anatomical differences in childhood compared to adult patients, susceptibility to trauma increases, injury mechanisms change, and there are differences in the evaluation/ treatment of pediatric trauma patients (2). Due to the rapid development in pediatric critical care medicine, some past studies suggested that pediatric trauma patients have better outcomes such as lower mortality and lower length of hospital stay by the treatment in the pediatric intensive care unit (5). However, in most developing countries, pediatric trauma centers are few or not present at all. On the other hand, it was reported that the outcomes of severely injured patients who were admitted to trauma centers were better compared to non-trauma centers (6).

Mechanisms and types of accidents also change depending on age. The most common causes of trauma in children are falling, in-vehicle or out-of-vehicle traffic accidents, bicycle accidents,water drowning, burns, and child abuse (7).

In this study, we aim to describe the demographics, clinical features, mechanisms of injury, and outcomes of children who were admitted to our pediatric intensive care unit (PICU) following trauma.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Science, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Scientific Researches Ethics Committee (Date: 15.06.2022, Decision No: E-46059653-020-552). This study was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki Principles.

Study Population

We performed a retrospective evaluation of 60 pediatric trauma patients (between 0 and16 years of age) admitted to the PICU at University of Health Science, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital from August 2020 to February 2022. Informed consent was obtained from all parents before hospitalization and during all procedures.

Patient Characteristics

Data was collected using a detailed form regarding the patient's age, gender, type of trauma, cause of trauma, length of stay in PICU, duration of mechanical ventilation, the requirement of surgical intervention, cranial CT findings, the requirement of the catheter, the requirement of transfusion, treatment options, treatment outcomes, and mortality. Lactate value in blood gas analysis and the serum albumin level on admission was recorded. Glasgow Coma Scale (GCS) is used to assess the level of consciousness and to predict the severity and early period of mortality due to neurological function disorders and is scored between 3 and 15 based on visual, verbal, and motor responses given to various types stimuli (8). Vasoactive Inotropic Score (VIS) is used to assess the amount of cardiovascular support required by trauma patients and includes dopamine, dobutamine, epinephrine, milrinone, vasopressin, and norepinephrine (9). For the calculation of the Pediatric Risk of Mortality III (PRISM III) Score, data for the following 16 variables were collected within 24 h of PICU admission: temperature, systolic blood pressure, heart rate, partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), GCS), pupillary reaction, prothrombin time (PT) and activated partial thromboplastin time (APTT), serum creatinine, serum urea nitrogen, serum potassium, blood glucose, and serum bicarbonate levels, white blood cell and platelet counts (10).

The patients were defined as multisystem trauma if they had injuries including two or more organs in different cavities or damage to internal organs and the musculoskeletal system including the face and the pelvis.

Statistical Analysis

Statistical analyses were done by using SPSS statistical software for Windows, 20.0. Numbers, frequencies [%], ratio, medians, and standard deviation values were used in the descriptive statistics of the data. The distribution of variables was checked with the Kolmogorov Smirnov test. During the analysis of quantitative data t-tests and Mann-Whitney, u-tests were used. The $\chi 2$ test was used

to compare categorical variables, and the Fischer test was used when chi-square conditions could not be met. PRISM score and lactate/albumin ratio were further evaluated for their predictivity of mortality by ROC curve analysis. According to the estimated cut-off, PRISM score values and lactate/albumin ratio were transformed to binary variables. Consequently, odds ratios are calculated for observed frequencies.

RESULTS

We evaluated 60 pediatric trauma patients followed up in our PICU. The median age of patients was 17 (0-724) months with a preponderance of male cases (n:38, 63.3%). The median duration of hospitalization in PICU was 6 (1-46) days. While accidents (n:52, 86.7%) were the most common cause of trauma, it was followed by child neglect-abuse (n:6, 10%) and suicide (n:2, 3.3%). When injuries were evaluated, it was determined that most of them were falling from a height (n:37, 61.7%), vehicle accidents, cutting injuries, and drowning. Among 60 patients 33 (55%) required invasive mechanical ventilation, and 13 (21.7%) required non-invasive mechanical ventilation. The median duration of invasive mechanical ventilation was 2 (0-4) days. The median PRISM score of the patients was 7 (0-39). The mortality rate due to trauma was (n:8, 13.3%)(**Table 1**).

Table 1. Clinical features of trauma patients

Features (n=60)	
Age (months), median (min-max)	17 (0-724)
Sex (n,%)	
Male	38 (63.3)
Female	22 (36.7)
Total	60 (100)
Cause of trauma (n,%)	
Suicide	2 (3.3)
Accident	52 (86.7)
Neglect and abuse	6 (10.0)
Total	60 (100)
Type of trauma (n,%)	
Motor vehicle accident (vehicle occupant)	4 (6.7)
Motor vehicle accident (pedesterian)	14 (23.3)
Fall	37 (61.7)
Injury by a sharp object	1 (1.7)
Drowning	4 (6.7)
Total	60 (100)
Mortality (n,%)	
Yes	8 (13.3)
No	52 (86.7)
Total	60 (100)
Duration of Hospital Stay (day), median (min-max)	6 (1-46)
Duration of Invasive Mechanical Ventilation (day), median (min-max)	2 (0-46)
Duration non-invasiveive ventilation (day), median (min-max)	0 (0-10)
PRISM score, median (min-max)	7 (0-39)
VIS score, median (min-max)	0 (0-98)

PRISM III: Pediatric risk of mortality III Score, VIS: Vasoactive inotropic score

When our trauma patients were evaluated according to the affected body parts, most of the patients (n:32, 53,3 %) were in the head trauma group. There were 12 (20%) patients in the multisystem trauma group and 8 (13.3%) of them had head trauma. In 16 (26.7%) patients, there were signs of trauma in one of the body parts other than the head. While 24 of 60 patients had normal CT images, the most frequent abnormal cranial CT finding was subdural hemorrhage (n:14, 23.3%) and subarachnoid hemorrhage (n:10, 16.7%). Other radiological findings were epidural hemorrhage and cerebral edema. Ten patients (16,7%) required surgical intervention and the most common type of surgery in these patients was neurosurgery (n:9, 90%). One patient required orthopedic surgery in addition to neurosurgery. Mannitol was given to 5 (8.3%) patients in addition to 3% hypertonic saline due to cerebral edema (**Table 2**).

Table 2: Clinical Features of Trauma Patients

Features	
Surgical intervention (n,%)	
Yes	10 (16.7)
No	50 (83.3)
Total	60 (100)
Type of surgery (n,%)	
Multisystem	1 (10.0)
Cranial	8 (80.0)
Extracranial	1 (10.0)
Total	10 (100)
CT findings (n,%)	
Normal	24 (40.0)
Subdural hemorrhage	14 (23.3)
Subarachnoid hemorrhage	10 (16.7)
Epidural hemorrhage	6 (10.0)
Cerebral edema	6 (10.0)
Total	60 (100)
Transfusion (n,%)	
Yes	39 (65)
PRBC (n)	35
FFP (n)	34
PS (n)	5
No	21 (35)
Total	60 (100)
Mannitol use (n,%)	
Yes	5 (8.3)
No	55 (91.7)
Total	60 (100)
Sedative medication use (n,%)	
Use of 2 or more drugs	12 (30.8)
Single drug use	27 (69.2)
Total	39 (100)
Analgesic medication use (n,%)	
Continuous infusion	40 (66.7)
Intermittent	20 (33.3)
Total	
Catheter sites (n,%)	
Jugular	16 (48.5)
Femoral	16 (48.5)
Subclavian	1 (3.0)
Total	33 (100)

PRBC: Packed red blood cell, FFP: Fresh frozen plasma, PS: Platelet suspension

While the need for transfusion developed in approximately two-thirds of the patients, the total number of blood product replacements was 74. The most commonly administered blood product (35 times) was packed red blood cell (PRBC), followed by 34 times fresh frozen plasma (FPP) and 5 times platelet suspension (PS). In total, 39 (65%) patients were sedated. While single sedation was the most preferred sedation strategy for 27 (69.2%) patients, 12 (30.8%) patients required more than one sedative agent. Of the 60 patients, 40 (66.7%) patients required intravenous analgesic infusion, other patients received intermittent analgesic medication. Jugular (n:16, %48,5), femoral (n: 16, 48,5%), or subclavian (n:1, 3%) central venous catheters were inserted in 33 patients (**Table 2**).

Although there is not a significant difference, the majority of cases were falling from a height with 23 (62.2%) patients in the head trauma group and 8 (21.6%) patients in the multisystem trauma group, respectively (**Table 3**).

When all parameters were evaluated according to the affected system, there was a positive correlation between only lactate value in the brain and one other system (thorax, abdomen, locomotor, etc.) and one and more than one system. There was not a statistically significant difference in duration of invasive/non-invasive mechanical ventilation, duration of PICU stay, PRISM III score, VIS score, and mortality between patients according to the affected body part (**Table 3**).

The need for mechanical ventilation, the need for PRBC transfusion, PRISM score, and VIS score of patients who developed mortality were significantly higher. Also, the lactate/albumin ratio of patients who developed mortality was significantly higher (**Table 4**).

ROC analysis is used for PRISM score and lactate/albumin ratio. According to ROC analysis, cut-off values are found as 13.50 and 0.9853 respectively (**Figure 1**, **Figure 2**). Cases were classified as positive and negative referred to as estimated cut-off values by ROC curve analysis. It would be estimated that possibility of being positive in the lactate/albumin ratio is 38.50 times more than being negative in cases of death (OR=38.50 (95% CI: 4.154-356.83). However, we could not estimate any defined odds ratio for PRISM cut-off due to any case that resulted in death having negative values (**Table 4**).

Table3. Clinical characteristics of trauma patient according to the affected organ

Features	Affected Organ			P value
	Cranial (n=32)	Multisystem (n=12)	Other (n=16)	
Hospitalization day, median (min-max)	5 (1-46)	8 (2-21)	7 (1-25)	0.376
Invasive mechanical ventilation (n,%)				0.081
Yes (n=33)	20 (60.6)	8 (24.2)	5 (15.2)	
No (n=27)	12 (44.4)	4 (14.8)	11 (40.7)	
Noninvasive mechanical ventilation (n,%)				0.841
Yes (n=13)	8 (61.5)	2 (15.4)	3 (23.1)	
No (n=47)	24 (51.1)	10 (21.3)	13 (27.7)	
Cause of trauma (n,%)				0.672
Suicide (n=2)	1 (50)	0 (0)	1 (50)	
Accident (n=52)	29 (55.8)	10 (19.2)	13 (25)	
Neglect and abuse (n=6)	2 (33.3)	2 (33.3)	2 (33.3)	
Type of trauma (n,%)				0.053
Motor vehicle accident (vehicle occupant) (n=4)	2 (50)	2 (50)	0 (0)	
Motor vehicle accident (pedesterian) (n=14)	5 (35.7)	2 (14.3)	7 (50)	
Fall (n=37)	23 (62.2)	8 (21.6)	6 (16.2)	
Injury of sharp object (n=1)	1 (100)	0 (0)	0 (0)	
Drowning (n=4)	1 (25)	0 (0)	3 (75)	
Mortality (n,%)				0.111
Yes (n=8)	5 (62.5)	3 (37.5)	0 (0)	
No (n=52)	27 (51.9)	9 (17.3)	16 (30.8)	
PRISM score, median (min-max)	8 (0-32)	8 (0-39)	4 (0-21)	0.094
VIS score, median (min-max)	0 (0-98)	0 (0-35)	0 (0-6)	0.440
Lactate, median (min-max)	1.95 (0.4-19.0)	1.7 (0.7-9.4)	0.95 (0.56-3.30)	0.017 *

PRISM III: Pediatric Risk of Mortality III Score, VIS: Vasoactive Inotropic Score *Significance for lactate value is between cranial and other and multisystem and other

Table 4. Comparison of survivors and non-survivors

Features	Mortality			p value	OR (95%CI)
	No (n=52)	Yes (n=8)	Total		
Hospitalization day, median (min-max)	6 (1-46)	2 (2-21)	8	0.076	N/A
Mechanical ventilation (n,%)				0.008	N/A
Yes (n=34)	26 (76.5)	8 (23.5)	34 26		
No (n=26)	26 (100)	0 (0)			
PRBC transfusion (n,%)				0.016	N/A
Yes (n=35)	27 (77.1)	8 (22.9)	35		
No (n=25)	25 (100)	0 (0)	25		
GKS, median (min-max)	12 (3-15)	3 (3-4)	15	<0.001	N/A
PRISM score, median (min-max)	6 (0-22)	24 (15-39)	30	<0.001	N/A
VIS score, median (min-max)	0 (0-30)	20 (0-98)	20	<0.001	N/A
PRISM score				<0.001	N/A
<13.50	44	0	44		
≥13.50	7	7	14		
Total	51	7	58		
Laboratory Findings				0.002	N/A
Lactate, median (min-max)	1.5 (0.4-9.4)	3.20 (1.7-9.0)			
Lactate/albumin ratio, median (min-max)	0.38 (0.17-2.30)	1.04 (0.54-0.42)		<0.001	38.50 (4.154-356.83)
Lactate/albumin ratio				<0.001	38.50 (4.154-356.83)
<0,985	44	1	45		
≥0,985	8	7	15		
Total	52	8	60		

PRBC: Packed red blood cell, GCS: Glasgow Coma Scale, PRISM III: Pediatric Risk of Mortality III Score, VIS: Vasoactive Inotropic Score, OR: Odds ratio

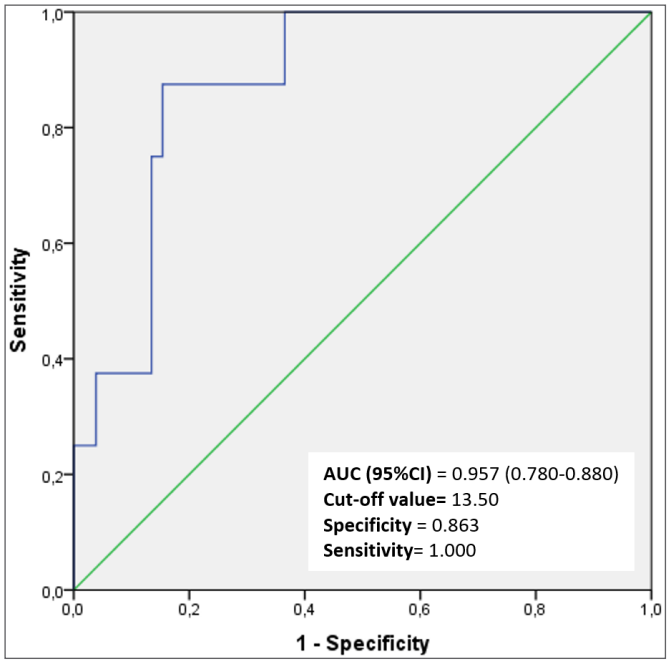

Figure 1. ROC Curve for the lactate/albümin ratio

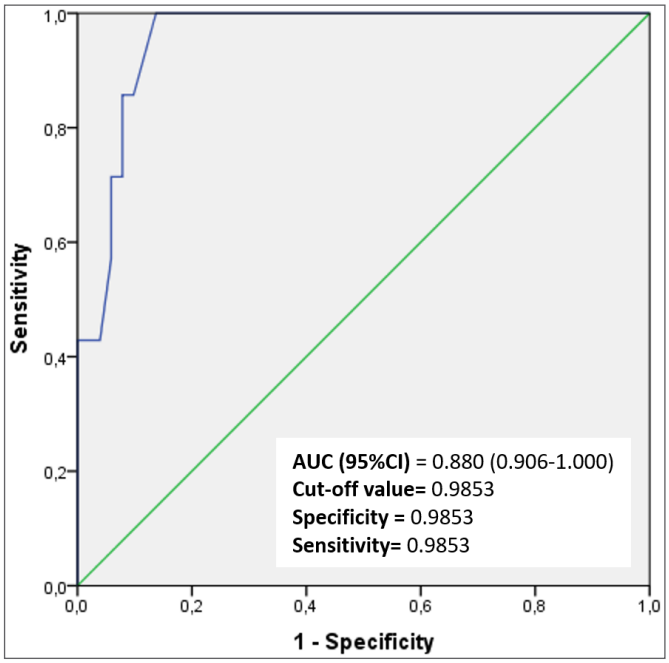

Figure 2. ROC Curve for PRISM score value

DISCUSSION

There are different results in the literature regarding the median age of pediatric trauma patients. Previously, Densmore et al. (5) reported that the median age of pediatric trauma patients was 12.2±6.2 years and in another study, Voth et al. (11) found that the median age of the pediatric patients was 8 years. In a study from Turkey, it was seen that the mean age of the patient was 77 months (3). Compared with other studies, a study in Brazil has a closer resultin which the mean age was 33 months (12). In some studies, the average age is reported to be between 33 and 77 months and boys were more frequently injured than girls (3,7,12,14). The main findings of this our study were such as; the median age of our pediatric patients admitted to the PICU was 17 months and most of them were male. In this study, boys were more frequently injured than girls as reported in other studies (1,3,7,13,14).However, the median age in our patients was found to be lower compared to previous studies. In our opinion, this result is related to the fact that younger children are more exposed to home accidents such as falling from a height due to the longer stay at home during the pandemic.

In the literature, there are studies in which the length of hospital stay varies between 4 and 11 days (3,13). In accordance with these results, the median duration of PICU stays in our study.

The mechanism of injury can differ by country related to their high or low-middle income. In the USA, motor vehicle accidents had been found as the most common mechanism of injury in injury-related deaths among 1–20 years aged patients, while the study by Herbert et al. (15) from South Africa which is covering 10 years, found that falls were among the most frequent mechanism type of injury compromising 39.8% (3). Studies from Turkey generally demonstrated that falling cases are more common than other trauma types which are similar to this study (1).

Although previous studies reported a wide range of mortality rates, from 3% to 17%, in general opinion, trauma patients have the highest mortality and morbidity among patients admitted to the PICU (3,13,16,17). The mortality rate in this study was 13.3 %. We attribute the high mortality rate in our study to the fact that the majority of our trauma patients were caused by head trauma, which is the highest-risk patient group.

PRISM score is one of the main indicators used in the pediatric intensive care unit (12,18). In a study performed in Sao Paulo, 54 (15%) of 359 patients died. The median mortality-associated PRISM score in dead patients was higher (median 8 points; min4-max14) compared to a lower score in patients who survived (median 7; min 3-max 12) (12). Similarly, in our study, 8 (3.3 %) of 60 patients died and the PRISM score was higher (median 7; min 0-max 39). In the light of this result, we think that the PRISM score is quite reliable in predicting mortality in trauma patients.

Head trauma is the most common form of pediatric trauma and is the most common cause of trauma-related mortality and morbidity (19,20). Mayer et al. (21) revealed that head trauma is the most common type of injury (78.8%) in the pediatric population. A study from Turkey reported that 73.5% of the patients had head trauma (19). In another study from our country by Emeksiz et al. (22), it was shown that the most common cause of trauma was falling and all the patients who followed up had head trauma. In our study, 66.6% of trauma patients had head trauma and subdural hemorrhage was the most common finding in CT. As in previous studies, we would like to draw attention to the fact that head trauma due to falling is very common and affects mortality.

Transfusion is an important part of trauma resuscitation (23). Hassan et al. (23) compare the characteristics and outcomes of children admitted to the ICU after traumatic injury, who did or did not receive PRBC transfusions. Transfused patients had greater PICU length of stay (LOS) and mortality. PRBC-transfused patients had a significantly greater requirement for mechanical ventilation and a longer duration of mechanical ventilation. We found that all 8 patients who can not survive, received PRBC transfusions and the transfusion requirement was significantly higher when compared to the survivor patients. Also, the duration of mechanical ventilation was significantly higher in non-survivor patients.

Many predictive biomarkers such as lactate (24,25) and albümin (26) have been developed to assess the prognosis and mortality in critically ill children. Lately, it was reported that the combination of lactate and albumin is a better predictor of mortality in critically ill patients (27-29). As each of the two parameters independently predicts mortality, a combination of both was meant to further increase the predictive value (29). In an adult trauma study, lactate and glucose levels were significantly higher, on the other hand, albumin and PaO_2/FiO_2 levels were significantly lower in non-survivor patients (30). Another adult trauma study showed that non-survivor patients had significantly higher MV duration, ICU length of stay, CRP and lactate level, higher lactate/albumin ratio, and significantly lower albumin level compared to surviving patients (31). But there are only a few studies that examined the lactate/albümin ratio in critically ill children. Most of the pediatric studies were designed to evaluate the prognostic value of the serum lactate/albumin ratio in septic patients. However, we could not find any study in the literature on the relationship between lactate/albumin ratio and mortality in pediatric trauma patients. Previously it was evaluated that the mortality in pediatric septic shock patients with underlying chronic disease was %26.7, and the albumin level was lower in non-survivors than in survivors. Additionally, the lactate/albumin ratio was 0.9±0.8 in survivors and 3.2±2.4 in non-survivors ($p<0.001$) (32). In our study, the lactate/albumin ratio of patients who developed mortality was significantly higher andthe lactate/albumin ratio above the cut-off value of 0.880 increased the mortality rate 38.50 times. In our opinion, this study will contribute to the literature on the relationship between lactate/albumin ratio and mortality in pediatric trauma patients.

CONCLUSION

In our opinion, our data will contribute to the literature since there is limited data in the literature regarding the follow-up of pediatric trauma patients in the PICU. We suggest that the relationship between lactate/albumin ratio and mortality should be investigated in pediatric trauma patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Science, Prof. İlhan Varank Sancaktepe Training and Research Hospital Scientific Researches Ethics Committee (Date: 15.06.2022, Decision No: E-46059653-020-552).

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.

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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

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Comparison of intrahepatic cholestasis incidence and maternal perinatal outcomes in fresh and frozen embryo transfers

Taze ve dondurulmuş embriyo transferlerinde intrahepatik kolestaz insidansı ve maternal perinatal sonuçların karşılaştırılması

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ABSTRACT

Objective: To compare the perinatal and maternal results of intrahepatic cholestasis (ICP) in fresh and frozen-thawed embryo transfer (ET) pregnancies.

Material and Method: This research was performed retrospectively, including fourty-five pregnant women applied to our hospital between October 2010 and January 2021. Two groups have been determined, group:1 (Frozen thawed; n:21) and group:2 (Fresh; n:24). Common pruritus in the body and high fasting bile acids (FBA) levels (greater than 10 mmol/L) were accepted as diagnostic criteria. The exclusion criteria were spontaneous pregnancies, multiple pregnancies, chronic liver disease history. SPSS, version 26 was used for statistical analysis.

Results: Statistically significant difference could not be associated between the two groups regarding age, maternal body mass index (BMI), smoking status, number of trials, gestational diabetes mellitus (GDM), types of infertility and polycystic ovary syndrome (PCOS) incidence (p-value >0.05). The way of birth, gender, congenital anomaly, need for meconium aspiration syndrome (MAS), weight of newborn at birth, neonatal intensive care unit (NICU), gestational age at birth and 5 min Apgar score also compared and significantly difference could not be associated between two groups (p-value > 0.05).

Conclusion: This study supports the fact that frozen-thawed and fresh in vitro fertilization (IVF) pregnancies in terms of maternal characteristics and perinatal results have no difference.

Keywords: Intrahepatic cholestasis of pregnancy, fresh embryo transfer, frozen-thawed embryo transfer, perinatal outcomes

ÖZ

Amaç: Taze ve dondurulmuş çözülmüş embriyo transferi (ET) gebeliklerinde intrahepatik kolestazın perinatal ve maternal sonuçlarını karşılaştırmak.

Gereç ve Yöntem: Bu araştırma, Ekim 2010-Ocak 2021 tarihleri arasında hastanemize başvuran 45 gebe kadın ile retrospektif olarak yapılmıştır. Grup:1 (Dondurulmuş çözülmüş; n:21) ve Grup:2 (Taze: n:24) olmak üzere iki grup belirlenmiştir. Vücutta yaygın kaşıntı ve yüksek açlık safra asitleri (FBA) seviyeleri (10 mmol/L'den fazla) tanı kriteri olarak kabul edildi. Dışlama kriterleri spontan gebelikler, çoğul gebelikler, kronik karaciğer hastalığı öyküsü idi. İstatistiksel analiz için SPSS, versiyon 26 kullanıldı.

Bulgular: Yaş, vücut kitle indeksi (VKİ), sigara içme durumu, deneme sayısı, gestasyonel diabetes mellitus (GDM), infertilite türleri ve polikistik over sendromu (PCOS) insidansı açısından iki grup arasında istatistiksel olarak anlamlı bir fark bulunmamıştır (p >0.05). Doğum şekli, cinsiyet, konjenital anomali, mekonyum aspirasyon sendromu (MAS), doğumdaki yenidoğan ağırlığı, yenidoğan yoğun bakım ünitesi (YYBB), doğumdaki gebelik yaşı ve 5 dk Apgar skoru da karşılaştırılmış ve anlamlı fark bulunamamıştır (p>0.05).

Sonuç: Bu çalışma, donmuş çözülmüş ve fresh tüp bebek gebeliklerinin maternal özellikler ve perinatal sonuçlar açısından farklılık göstermediğini desteklemektedir.

Anahtar Kelimeler: Gebeliğin intrahepatik kolestazı, taze embriyo transferi, donmuş çözülmüş embriyo transferi, perinatal sonuçlar

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INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in the pregnancy (1). During the pregnancy period, women experience several diseases and concerns (2-5). ICP is a disorder which is specifically seen in pregnancy, which has been reported to be prevalent by 0.3-5.6%. This disease is more common in advanced age pregnants, women using contraceptives, and multiparous women (6). Pruritus is one of the major symptoms of ICP. When the bile acid level is more than 10 mmol/L, pruritus will occur. This is observed in the second and third trimesters. Other symptoms such as jaundice, nausea, and appetite loss have been also reported in patients (7,8). At present, this disease has unknown causes but hormone, environmental and genetic factors interfere in the outbreak of this disease (9). The hormone factors are more important than other factors. Family history in mothers, sisters, or daughters of the patients is among the important warning factors. This disease is more prevalent in some special tribal groups (10). To prevent this disease, estrogen levels should be controlled. High estrogen level causes reduced biliary excretion and finally increase biliary acids, liver enzymes, and bilirubin. It is important to prevent high estrogen levels to prevent ICP (11). High estrogen levels are associated with women's liver, reducing biliary excretion and increasing biliary acids, elevated liver enzymes, and bilirubin levels (12). ICP is a benign illness for women, however it has severe perinatal consequences. Timely diagnosis of ICP is highly important for the neonate. Clinical investigations and timely diagnosis of the disease can prevent stillbirth or preterm labor. Therefore, early diagnosis is vital for curing this disease (9). ICP has no meaningful effects for the mother, but stillbirth, meconium-stained amniotic fluid, preterm labor, respiratory distress syndrome have been noted in pregnancies with ICP (13). The disease risks for the fetus are directly associated with biliary acids level. Increasing the biliary acids level threatens the fetus (14).

The frequency of ICP was compared between in vitro fertilization (IVF) and spontaneous pregnancies in many studies. But there is no study in the literature comparing increased ICP risk concerning embryo transfer way fresh or frozen-thawed. This study compares the laboratory, perinatal characteristics, and maternal of fresh and frozen-thawed embryo transfer pregnancies.

MATERIAL AND METHOD

The study was carried out with the permission of Doğu Akdeniz University Clinical Researches Ethics Committee (Date: 24.05.2022, Decision No: 2022-0148). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study was performed retrospectively including forty-five pregnant women between October 2010 and January 2021 at a private hospital. The data was collected from the data processing system records. When the fasting bile acids (FBA) levels more than 10mmol/L and common pruritus in the body diagnose can be done. The exclusion criteria were spontaneous pregnancies, multiple pregnancies, chronic liver disease history. Also, women with comorbidity like hypothyroidism, chronic renal failure, chronic hypertension, hyperthyroidism, hematological or rheumatologic disease, and heart disease were excluded from the analysis. Two patient groups have been determined according to their embryo transfer method as fresh and frozen-thawed. The maternal data of the patients in fresh and frozen-thawed groups were analyzed. Maternal data included smoking status, body mass index (BMI: kg/m2), age, number of trials, polycystic ovary syndrome (PCOS) status, Gestational Diabetes Mellitus (GDM) and types of infertility of the patients (primer and secondary). Perinatal outcomes included way of birth, gender, congenital anomaly status, necessity for neonatal intensive care unit, birth weight, meconium aspiration syndrome (MAS), gestational age at birth, and the 5-min APGAR score. To calculate the sample size with the GPower program, the total mean of the two compared groups with the power of 70%, effect size of 80%, and 0.05 type 1 error was at least 42 patients (15).

Statistical Analysis

Data were analyzed, tabulated, and subjected to using the SPSS, version 26. A p-value of < 0.05 was accepted as statistically significant. The continuous data were displayed as mean±SD. At the same time, categorical data were illustrated as numbers and percentages. The Kolmogorov-Smirnov test of normality was utilized to test the normality hypothesis. Based on the test results, proper parametric (Independent t-test) and nonparametric tests (Mann Whitney and Chi-square test) were used.

RESULTS

The sample consisted of 45 women, including 21 women with frozen-thawed and 24 women with fresh method aged 22 to 43 years (33.22±4.08). **Table 1** shows maternal characteristics of study groups. We evaluated the patients' maternal characteristics; maternal age at transfer was 33.19±3.45 years in the frozen-thawed group and 33.26±4.66 years in the fresh group (p-value>.05). There was no statistically significant difference between the two groups regarding BMI (frozen-thawed: 24.66±1.85 vs. fresh: 24.87±1.62, p-value>0.05). There was not a statistically significant difference between frozen-thawed group and fresh in terms of smoking status (p-value >0.05), number of trials (frozen-thawed: 1.85±0.79 vs. fresh: 1.87±1.26, p-value>0.05), types of infertility (p-value=0.923), PCOS (p-value>0.05), and GDM (p-value>0.05).

Table 1. Maternal characteristics of study groups

Variable	Categories	Frozen-thawed (n=21) (Mean±SD) or n (%)	Fresh (n=24) (Mean±SD) or n (%)	P-value
Age(yr)		33.19±3.45	33.26±4.66	0.955*
BMI		24.66±1.85	24.87±1.62	0.692*
Smoking				0.482***
	Yes	19 (90)	20 (83)	
	No	2 (10)	4 (17)	
Number of trials		1.85±0.79	1.87±1.26	0.474**
Types				0.923**
	Primer	20 (95)	23 (96)	
	Secondary	1 (5)	1 (4)	
PCOS				0.153***
	No	16 (76)	22 (92)	
	Yes	5 (24)	2 (8)	
GDM				0.153***
	No	16 (76)	22 (92)	
	Yes	5 (24)	2 (8)	

* Independent-Samples t-test ** Mann–Whitney U test ***Pearson Chi-Square Test
"PCOS; polycystic ovary syndrome", "GDM; gestational diabetes mellitus"

Table 2 shows perinatal characteristics of study groups. Statistically significant difference could not be shown between frozen-thawed group and fresh in terms of way of birth (p-value>0.05), gender (p-value>0.05), congenital anomaly (p-value>0.05), need for neonatal intensive care unit (NICU) (p-value>0.05), and MAS (p-value >0 .05). There was no statistically significant difference between the two groups in terms of birth weight (frozen-thawed 3030.95±360 vs. fresh: 2928.57±311, p-value >0.05), gestational age at birth (frozen-thawed: 37.19±0.60 vs. fresh: 37.20±0.50, p-value >0.05) and 5 min APGAR score (frozen-thawed: 8.09±0.88 vs. fresh: 8.19±0.98, p-value >0 .05). When comparing the two groups in terms of perinatal results, no statistically significant difference was found between them.

Table 2. Perinatal results of study groups

Variable	Categories	Frozen-thawed (n=21) (Mean±SD) or n (%)	Fresh (n=24) (Mean±SD) or n (%)	P-value
Way of birth				0.751***
	C/S	19 (90)	21 (87)	
	Vaginal delivery	2 (10)	3 (13)	
Gender				0.688***
	Male	11 (52)	14 (58)	
	Female	10 (48)	10 (42)	
Congenital anomaly				0.889***
	No	19 (90)	22 (92)	
	Yes	2 (10)	2 (8)	
Need for NICU				0.751***
	No	19 (90)	21 (87)	
	Yes	2 (10)	3 (13)	
Mass				0.923***
	No	20 (95)	23 (96)	
	Yes	1 (5)	1 (4)	
Birth weight (gr)		3030.95±360	2928.57±311	0.331*
Gestational age at birth (weeks)		37.19±0.60	37.20±0.50	0.967**
5 min Apgar score		8.09±0.88	8.19±0.98	0.765**

* Independent-Samples t-test ** Mann–Whitney U test ***Pearson Chi-Square Test
"C/S: caeserian section" "NICU: neonatal intensive care unit"

DISCUSSION

A raised incidence of ICP and fetal danger during pregnancy behind IVF has been documented in several kinds of research (16). In this study, in which frozen and frozen-thawed IVF pregnancies were assessed, the demographic and perinatal characteristics of the two groups were compared by retrospective analysis of 45 pregnancies with ICP.

In this study, there were no differences between the frozen-thawed group and fresh group in terms of maternal characteristics. Although there is a difference in maternal characteristics between healthy pregnant women and with ICP, there is no difference in maternal characteristics between pregnant women with ICP by various fertilization methods (16-18).

Providing, maintaining, and promoting the health of infants as a vulnerable group has a remarkable place in health services. ICP is associated with increased perinatal risks such as a higher rate of newborn intensive care admissions, the 5-min APGAR score increases, birth weight, and stillbirth. In line with other studies' results, in this study, there were no differences in perinatal results, and there was no difference between the frozen-thawed group and fresh in terms of gestational age at birth, birth types, congenital anomaly, gender, NICU admission rate, birth weight, and the 5-min APGAR score. The effect of fertilization methods such as IVF and spontaneous on perinatal results has been studied in many research, and no significant difference has been observed between fertilization methods and perinatal results (16-18). However, in twin pregnancies, the IVF method increases risks of ICP perinatal results (19-21). Birth weight is one of the most critical health indicators for evaluating newborns and infant health indexes (22). According to research, the birth weight of pregnant women with ICP is lower than that of normal pregnancies (23). There was no significant relationship between birth weight in the fresh and frozen-thawed groups, but the average birth weight in the frozen-thawed method was about 100 grams higher than the fresh method. The gestational age at birth and 5-min APGAR scores in both groups were very close.

The entire study implementation process, including IVF, follow-up, and delivery, was performed in our hospital. In order to avoid bias in recalling and interviewing participants, all participants' data were collected from their electronic medical records in the hospital system. On the one hand, this nature of our study method provides accurate access to all patient details and, on the other hand, limits the number of small samples because the number of ICP occurrences in pregnancy is very low. Therefore, the small number of samples can be mentioned as the main limitation of this study.

CONCLUSION

This paper supports that there is no difference between frozen-thawed and fresh IVF pregnancies in maternal characteristics and perinatal results. Management of pregnant women with ICP is recommended regardless of fertilization methods. Twin pregnancies are more affected with ICP, and the impact of fertilization methods on twin pregnant women with ICP in future work should be given more attention..

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Doğu Akdeniz University Clinical Researches Ethics Committee (Date: 24.05.2022, Decision No: 2022-0148).

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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Investigation of self-esteem and sexual function levels of patients who diagnosed with polycystic ovary syndrome: a prospective study

Polikistik over sendromu tanısı almış hastaların benlik saygısı ve cinsel işlev düzeylerinin incelenmesi: prospektif bir çalışma

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ABSTRACT

Aim: Polycystic ovary syndrome (PCOS) is seen in 5-10% of women, it affects many systems as a result of hyperandrogenism. In addition to its endocrinological and metabolic results, it has been reported that women with PCOS have a decrease in their self-esteem levels due to body image disorders. Sexual dysfunction such as sexual desire, orgasm, arousal and sexual satisfaction occurs in patients with PCOS due to both physical changes and emotional differences. Our aim in this study is to analyze the self-esteem levels and self-esteem levels of women diagnosed with PCOS and to evaluate the factors affecting them.

Material and Method: Women between the ages of 18-55 who were diagnosed with PCOS were prospectively included in the study. Demographic characteristics, such as age, marital status, and employment status, were recorded. The patients' self-esteem levels were analyzed with the Rosenberg self-esteem scale (RBSS). The sexual dysfunction scale (SDS) was used to evaluate the sexual dysfunctions of the women participating in the study. The $p<0.05$ was considered statistically significant in all analyzes.

Results: Overall 51 patients diagnosed with PCOS were included in the study. The median age was 28 years (IQR 24-32). The most common symptoms and signs were obesity (68.6%), oligomenorrhea (66.7%), polycystic ovaries (66.7%), and hirsutism (52.9%). The mean RBSS score was 1.41±2.1; 49.0% of women had high self-esteem, 43.1% had medium self-esteem and 7.8% had low self-esteem. Women with acne and hirsutism had a higher rate of low self-esteem ($p=0.014$ and $p=0.023$, respectively). While the sexual desire levels were low in 47.1% of the women; the median sexual desire score was 4.2 (IQR 3-4.8). Sexual arousal levels were significantly lower who had hirsutism (72.0%-37.5%) and oligomenorrhea (68.8%-29.4%) ($p=0.015$ and $p=0.022$, respectively). Only 43.1% of women had low orgasm levels during sexual intercourse; and 31.4% had low level of sexual satisfaction. Pain level during sexual intercourse was low in all women. Sexual dysfunction was also observed in 43.2% of women with PCOS.

Conclusion: One of the most important comorbidities of PCOS is sexual dysfunction. Sexual reluctance, especially with the effect of physical changes and hirsutism, is the most important part of sexual dysfunction.

Keywords: Polycystic ovary syndrome, self-esteem, sexual desire, sexual satisfaction, sexual dysfunction

ÖZ

Amaç: Polikistik over sendromu (PKOS), kadınların %5-10'ununda görülürken hiperandrojenizm sonucu birçok sistemi etkilemektedir. Endokrinolojik ve metabolik sonuçlarının yanısıra, PKOS'lu kadınların beden imaj bozuklukları nedeni ile benlik saygı düzeylerinde azalma olduğu da bildirilmektedir. Ayrıca, PKOS'lu hastalarda gerek bedensel değişiklikler gerekse de emosyonel farklılıklar nedeni ile cinsel istek, orgazm, uyarılma ve cinsel doyum gibi cinsel işlev bozukluğu da ortaya çıkmaktadır. Bu çalışmadaki amacımız, PKOS tanısı olan kadınların benlik saygı düzeyleri ve benlik saygı düzeylerinin analiz edilmesi ve bunlara etki eden faktörlerin değerlendirilmesidir.

Gereç ve Yöntem: Çalışmaya 18-55 yaş arasında PKOS tanısı konulan kadınlar prospektif olarak dahil edildi. Kadınların yaş, medeni durum, çalışma durumu gibi demografik özellikleri kaydedildi. Rosenberg benlik saygısı ölçeği (RBSÖ) ile hastaların benlik saygı düzeyleri analiz edildi. Çalışmaya katılan kadınların cinsel işlev bozukluklarını değerlendirmek için cinsel işlev bozukluk ölçeği (CİBÖ) kullanıldı. Tüm analizlerde $p<0,05$ istatistiksel olarak anlamlı kabul edildi.

Bulgular: Çalışmaya PKOS tanısı konulan 51 hasta dahil edildi. Kadınların ortanca yaşı 28 yıl (IQR 24-32) idi. En sık görülen semptom ve bulgular, obezite (%68,6), oligomenore (%66,7), poliklistik overler (%66,7) ve hirsutizm (%52,9) şeklindeydi. Ortalama RBSÖ puanı 1,41±2,1 iken; kadınların %49,0'ının yüksek, %43,1'inin orta ve %7,8'inin de düşük benlik saygısına sahipti. Aknesi ve hirsutizmi olan kadınlardaki düşük benlik saygısı oranı daha fazlaydı (sırasıyla, $p=0,014$ ve $p=0,023$). Kadınların %47,1'inde cinsel istek düzeyleri düşük iken; ortanca cinsel istek puanı 4,2 (IQR 3-4,8) olarak saptandı. Hirsutizm (%72,0-%37,5) ve oligomenore (%68,8-%29,4) olan PKOS'lu kadınlarda cinsel uyarılma düzeyleri anlamlı derecede düşüktü (sırasıyla, $p=0,015$ ve $p=0,022$). Kadınların %43,1'inde cinsel ilişki sırasında orgazm düzeyleri düşük olarak görülürken; sadece %31.4'ünde cinsel doyum düzeyi düşüktü. Cinsel ilişki sırasında ağrı düzeyi tüm kadınlarda düşüktü. PKOS tanılı kadınların %43,2'sinde de cinsel işlev bozukluğu olduğu görüldü.

Sonuç: PKOS'un en önemli komorbiditelerinden birisi de cinsel işlev bozukluklarıdır. Özellikle bedensel değişiklikler ve hirsutizmin de etkisi ile ortaya çıkan cinsel isteksizlik cinsel işlev bozukluğunun en önemli kısmıdır.

Anahtar Kelimeler: Polikistik over sendromu, benlik saygısı, cinsel istek, cinsel doyum, cinsel işlev bozukluğu

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INTRODUCTION

Polycystic ovary syndrome (PCOS), first described by Stein and Leventhal in 1935, is a clinical picture that has a heterogeneous genetic basis and many factors play a role in its etiology (1). PCOS, which is accepted as one of the most common endocrinopathies in women, affects 5-10% of women (2). Oligomenorrhea or amenorrhea, signs of hyperandrogenism (clinical and/or laboratory), and polycystic ovaries in pelvic ultrasonography (USG) constitute the diagnostic criteria used for the diagnosis of PCOS (2,3). Because it affects many systems, it can also cause hyperinsulinemia, glucose intolerance, obesity, hypertension, cervical cancer and psychiatric disorders in women (4).

Self-evaluation of individuals and their expression of the resulting mood is defined as self-esteem (5). Self-esteem is affected by people's physical health and physical appearance. It has been shown that physical appearance disorders cause a decrease in self-esteem (6, 7). However, in a study conducted on patients with PCOS, it was reported that their self-esteem was lower than that of normal women due to their physical appearance and health problems (8). The presence of acne and hirsutism, especially in women with PCOS, further lowers their self-esteem (9).

Sexual dysfunctions in women; desire and arousal disorders, orgasm disorder and sexual pain disorders. The most common sexual dysfunctions are desire, orgasm and arousal disorders (10). Loh et al. (4), who examined sexual dysfunctions in patients with PCOS, reported that the risk of sexual dysfunction in women with PCOS was 30% higher than in women in the normal population. In addition, in the study conducted by Dashti S et al. (11) on patients with PCOS, they reported the rate of sexual dysfunction in women diagnosed with PCOS as 62.5%. On the other hand, there are also studies in the literature reporting that women diagnosed with PCOS do not have significant sexual dysfunction (12,13).

Our aim in this study is to examine the effect of the disease on self-esteem in women diagnosed with PCOS. In addition, the sexual dysfunctions of women with PCOS and the factors affecting their sexual functions will be investigated.

MATERIAL AND METHOD

The study was carried out with the permission of Demiroglu Bilim University Faculty of Medicine Scientific Researches Ethics Committee (Date: 2022, Decision No: 2022-06-02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection

Patients aged 18-55 years diagnosed with PCOS in the tertiary gynecology and obstetrics clinic were prospectively included in the study. After giving written or verbal information about the study, written consent was obtained from the patients who agreed to participate in the study.

Data Collection and Evaluation of Patients

Age, marital status, employment status and educational status of the women participating in the study were recorded. The time elapsed after being diagnosed with PCOS was analyzed. It was recorded which symptoms (acne, hirsutism, obesity, menstrual irregularities, etc.) were diagnosed with PCOS.

Evaluation of Self-Esteem

The Rosenberg Self-Esteem Scale (RBSS) was used to assess women's self-esteem (14). The first 10 questions of the RBSS, which consisted of 12 questions in total, were used. "True", "Very true", "Very false" and "False" options were used in each question. As a result of the analysis of the RBSS used, if the sum of the scores obtained from all items was 0-1, self-esteem was considered high, if it was 2-4, it was considered moderate, and if it was >5, it was considered low self-esteem.

Evaluation of Sexual Dysfunction

The sexual dysfunction scale (SDS) consisting of 19 questions was used to evaluate the sexual dysfunctions of the women participating in the study (15). While the first and second questions show the level of sexual desire, the answer to each question is scored between 1-5 and the total score is multiplied by 0.6. If the resulting total score was ≤3.6, it was thought that there was a decrease in the sexual desire levels of the women. Other parameters were scored in the range of 0-5. While the sexual arousal levels were evaluated with the 3rd, 4th, 5th and 6th questions; lubrication levels were evaluated in the 7th, 8th, 9th and 10th questions. The total scores of these two analyzes were multiplied by a coefficient of 0.3. A sexual arousal total score of ≤3.9 and a lubrication total score of ≤3.6 were accepted as pathology. Women's orgasm levels were evaluated in the 11th, 12th, 13th questions; sexual satisfaction levels were evaluated in the 14th, 15th, and 16th questions and pain levels during sexual intercourse were analyzed in questions 17, 18 and 19. The total scores obtained in orgasm, sexual satisfaction and pain questions were multiplied by a coefficient of 0.4. Sexual satisfaction and orgasm score of ≤3.6 and a pain score of ≤4.4 were accepted as pathology (10, 15). A total score of ≤22.7 on the SDS administered to women was considered to have sexual dysfunction in women (10).

Statistical Analysis

Data were analyzed using the program SPSS 25.0 (IBM, Armonk, NY: IBM Corp.). Mean±standard deviation for parametric tests in presenting continuous variables; For non-parametric tests, the median (interquartile range, IQR) and categorical variables were expressed as numbers and percentages. In the comparison of independent group differences, one-way analysis of variance provided parametric test assumptions; Kruskal Wallis analysis of variance was used when parametric test assumptions were not met. A simple correlation test was applied to evaluate the relationship between the two variables. Chi-square analysis was used to analyze the differences between categorical variables. The $p<0.05$ was considered statistically significant in all analyzes.

RESULTS

Overall 51 patients diagnosed with PCOS were included in the study. The median age was 28 years (IQR 24-32). More than half of the patients (52.9%) had a university degree or higher, 78.4% were married and 54.9% (n=28) were working in any job (**Table 1**). The median time elapsed after the diagnosis of PCOS was 3 years (minimum 1-maximum 4, IQR 2-4 years). The most common symptoms and findings were obesity (68.6%), oligomenorrhea (66.7%), polycystic ovary appearance on USG (66.7%), and hirsutism (52.9%), respectively (**Table 2**).

Table 1. Demographic characteristics of patients in the study

Age [median (IQR)] (year)	28 (24-32)
Education status, [n (%)]	
<University	24 (47.1)
≥University	27 (52.9)
Married status, [n (%)]	
Single	11 (21.6)
Married	40 (78.4)
Working status, [n (%)]	
Working	28 (54.9)
No working	23 (45.1)
The time elapsed after the diagnoses of PCOS [median (IQR)] (year)	3 (2-4)

PCOS: polycystic ovary syndrome

Table 2. Symptoms and signs of women who diagnosed with PCOS

Symptoms and signs	n (%)
Oligomenorrhea	34 (66.7)
Obesity	35 (68.6)
Hirsutism	27 (52.9)
Insulin resistance	24 (47.1)
Acne	21 (41.2)
Infertility	7 (13.7)
Polycystic appearance on USG	34 (66.7)

PCOS: polycystic ovary syndrome, USG: ultrasonography

The self-esteem results of the women with PCOS who participated in the study, as assessed by the RBSS, are shown in **Table 3**. While the mean RBSS score was 1.41±2.1; it was observed that the self-esteem was at a moderate level. It was observed that 49.0% of the women had high self-esteem, 43.1% had medium self-esteem, and 7.8% had low self-esteem (**Table 4**). While no relationship was found between educational status and the number of self-esteem; only the rate of seeing themselves as unsuccessful was significantly higher for those whose education level was below the university degree than those whose education level was university or higher (p=0.039). It was determined that the age, marital status and employment status of women diagnosed with PCOS did not have any effect on their self-esteem. When the effect of women's PCOS findings on self-esteem is examined; women with acne and hirsutism had a higher rate of low self-esteem (p=0.014 and p=0.023, respectively). There was no statistically significant difference between obesity, insulin resistance, and oligomenorrhea and the number of self-esteem.

Table 3. Self-esteem results of women with PCOS as assessed by Rosenberg self-esteem scale.

Rosenberg self-esteem scale	Yanıtlar [n (%)]			
	Very True	True	False	Very False
I find myself as valuable as other people	29 (56.9)	19 (37.3)	2 (3.9)	1 (2.0)
I think I have some positive traits	30 (58.8)	19 (37.3)	2 (3.9)	0 (0)
I generally tend to see myself as an unsuccessful person	7 (13.7)	7 (13.7)	23 (45.1)	14 (27.5)
I can do as much as most other people can	33 (64.7)	17 (33.3)	1 (2.0)	0 (0)
I can't find much to be proud of myself	2 (3.9)	3 (5.9)	22 (43.1)	24 (47.1)
I have a positive attitude towards myself	13 (25.5)	32 (62.7)	5 (9.8)	1 (2.0)
I am generally satisfied with myself	21 (41.2)	24 (47.1)	4 (7.8)	2 (3.9)
I wish I could respect myself more	19 (37.3)	11 (21.6)	15 (29.4)	6 (11.8)
Sometimes I think I'm absolutely useless	6 (11.8)	7 (13.7)	24 (47.1)	14 (27.5)
Sometimes I think I'm not a good enough person at all	6 (11.8)	7 (13.7)	24 (47.1)	14 (27.5)

PCOS: polycystic ovary syndrome

Table 4. Self-esteem levels of women diagnosed with PCOS

Self-esteem levels (points)	n	%
Low (0-1)	4	7.8
Normal (2-4)	22	43.1
High (≥5)	25	49.0

PCOS: polycystic ovary syndrome

The sexual dysfunctions of women with PCOS who participated in the study were evaluated. When the total sexual desire scores were analyzed, 47.1% (n=24) of the women had low sexual desire levels; the median sexual desire score was 4.2 (minimum 1.2-maximum 6.0, IQR 3-4.8) (**Table 5**). The age, marital status and employment status of the women did not affect on the level of sexual desire. In addition, no significant relationship was found between the time elapsed after the diagnosis of PCOS and the PCOS findings and sexual desire levels.

Table 5. Sexual dysfunction scale results of women diagnosed with PCOS

Sexual dysfunction	SDS points [Median (IQR)]	Level [n (%)]		
		Low	Normal	High
Desire	4.2 (3-4.8)	24 (47.1)	21 (41.1)	6 (11.8)
Arousal	3.9 (3.3-5.1)	29 (56.9)	18 (35.3)	3 (5.8)
Lubrication	2.0 (1-2)	14 (27.5)	30 (58.6)	7 (13.7)
Orgasm	4.2 (2.8-5.6)	22 (43.1)	23 (45.1)	6 (11.8)
Pain	3.6 (3.2-4.0)	51 (100)	0 (0)	0 (0)
Satisfaction	4.8 (3.6-6.0)	16 (31.4)	25 (49.0)	10 (28.6)
Total sexual dysfunction	24.0 (21.9-29.9)	22 (43.2)	27 (52.9)	2 (3.9)

SDS: Sexual dysfunction scale, PCOS: polycystic ovary syndrome

The median sexual arousal score was 3.9 (minimum 0-maximum 6.0, IQR 3.3-5.1) (**Table 5**). It was observed that 56.8% (n=29) of the women had a low level of sexual arousal. Age, marital status, educational status and employment status of the women did not affect on their sexual arousal levels. In contrast, women with PCOS with hirsutism (72.0%-37.5%) and menstrual irregularity (68.8%-29.4%) had significantly lower sexual arousal levels (p=0.015 and p=0.022, respectively).

The median lubrication level score of the women during the sexual intercourse was 2.0 (minimum 1-maximum 2, IQR 1-2) (**Table 5**). More than half of the women (58.8%) had normal lubrication levels; only 31.4% (n=14) had low lubrication levels. Age, marital status, educational status and employment status of the women did not affect on their sexual arousal levels. In addition, no significant relationship was found between the time elapsed after the diagnosis of PCOS and PCOS findings and sexual desire levels.

While 43.1% of women had low orgasm levels during sexual intercourse; only 31.4% had low level of sexual satisfaction (**Table 5**). In addition, the level of pain during the sexual intercourse was a low in all women. Orgasm levels were significantly higher in women with high school or below education level than those with the university education and above (81.3% vs 51.6%, p=0.047, respectively). However, the sexual satisfaction level was a low in 46.4% of working women with PCOS; only 13.1% of unemployed women had low level of sexual satisfaction (p=0.015). In addition, 72.7% of single women with PCOS had low sexual satisfaction levels; only 20% of married women with PCOS had low sexual satisfaction (p=0.002). Sexual dysfunction was also observed in 43.2% of women with PCOS who participated in the study (**Table 5**).

DISCUSSION

In this study, the self-esteem levels and sexual dysfunctions of women diagnosed with PCOS were analyzed. An important part of people's health status is their sexual life and sexual health. The body image of women changes depending on their physical appearance and body health; it is stated that this situation has a significant effect on their self-esteem (5). In the study conducted by Nazik et al. (5) in our country, it was observed that the self-esteem levels of women diagnosed with PCOS were low. However, Acmaz et al. (16) also reported that the self-esteem levels of women with PCOS were lower than those of healthy women. In addition, 62.1% of obese patients had low self-esteem, while 75.4% of PCOS patients with hirsutism and acne had moderate self-esteem. In our study, contrary to the literature, only 7.8% of women diagnosed with PCOS had low self-esteem levels; only women with acne and hirsutism had a higher rate of low self-esteem. Compared to other studies, the fact that the women in our study were younger and had a higher education level may explain this result.

The available information about the sexuality of women is less and insufficient compared to men (10). On the other hand, it is known that emotional factors and hormonal levels of women are effective on sexual functions (3,10,17). In epidemiological studies in the literature, 43% of women reported sexual dysfunction in the United States; this rate has been reported as 58% in Latin America and 5.8% in the United Kingdom (18-20). Women's sexual dysfunctions, especially low sexual desire and impaired body image perception are the most blamed conditions in the etiology (21). In a meta-analysis, in which many studies investigating sexual dysfunction in women with PCOS were analyzed, it was stated that the risk of sexual dysfunction is 30% higher in PCOS patients compared to healthy women (4). On the other hand, it has been shown that women with PCOS do not have any sexual dysfunction despite obesity and hirsutism (12). In addition, a meta-analysis evaluating ten studies and 1163 PCOS patients, showed that there was no relationship between sexual dysfunctions of women and PCOS (13). In our study, sexual dysfunction was found in 43.2% of women with PCOS.

Lack of sexual desire constitutes an important part of sexual dysfunction in women. It has been reported that women with PCOS have less sexual desire and their sexual desire is negatively affected due to physical characteristics such as obesity, hirsutism and/or acne (22,23). In our study, similar to the literature, nearly half of the women diagnosed with PCOS had a low sexual desire and lack of arousal. It was found that women's body image disorders affected them, especially hirsutism and oligomenorrhea, which decreased their sexual arousal levels.

It is thought that sexual satisfaction is affected in women with PCOS who have high testosterone levels. In the literature on this subject, it has been reported that although sexual dysfunctions are observed in patients with PCOS, there is a direct correlation between high testosterone levels and sexual satisfaction (24). On the other hand, the study by Nasiri et al. (3), showed that the testosterone levels of women with PCOS did not affect on sexual satisfaction. However, in a study conducted in our country, it was thought that sexual satisfaction was low in women with PCOS with high testosterone levels, and the reason for this was that hirsutism, acne and oligomenorrhea in these women affected sexual satisfaction (25). In addition, studies are reporting that education level and infertility increase sexual dysfunction in PCOS patients (3). In the study conducted by Kolukcu et al. (25), it was stated that the employment status and education level did not affect the sexual life of women, but sexual dysfunction occurred at a higher rate in those with infertility. In our study, it was observed that infertility, employment status and education level of women with PCOS did not affect on sexual dysfunction; the level of education affects the orgasm status of women with PCOS, while working status and being married have an effect on the level of sexual satisfaction of women.

Limitations of the study; (1) the fact that our study was carried out in a single-center and high-level center constitutes an important limitation in the generalization of our results; (2) an insufficient number of women participating in the study; (3) includes only women diagnosed with PCOS.

CONCLUSION

One of the most important comorbidities of PCOS is sexual dysfunction. Sexual reluctance, especially with the effect of physical changes and hirsutism, is the most important part of sexual dysfunction. Sexual dysfunctions should also be evaluated in the follow-up and treatment of PCOS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Demiroglu Bilim University Faculty of Medicine Scientific Researches Ethics Committee (Date: 2022, Decision No: 2022-06-02).

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.

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Outcomes of de novo extended-release tacrolimus use (Advagraf®) in kidney transplantation: 1-year, single-center experience

Böbrek naklinde de novo uzamış salınımlı takrolimus kullanımı sonuçları: tek merkez, 1 yıllık sonuçlar

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ABSTRACT

Aim: Once daily extended-release tacrolimus (tac-ER) was introduced to support medication adherence in kidney transplant (KTx) recipients, with similar efficacy to immediate-release tacrolimus (tac-IR). However, most of the experiences regarding tac-ER efficacy were obtained from the switches from tac-IR to tac-ER in kidney transplant recipients (KTRs). In this study, we aimed to demonstrate 1-year outcomes of de novo use of tac-ER in KTRs.

Material and Method: This single-center retrospective study included 72 de novo KTRs between January 2020 and January 2021. KTRS were divided into two groups who received a tac-ER or tac-IR. 1-year allograft functions, allograft survival, daily doses of tacrolimus in milligram/day and milligram/kg/day, trough levels, and acute rejection episodes were compared between the two groups. The factors that might have an impact on allograft functions and acute rejection episodes also were investigated.

Results: A total of 69 de novo kidney allograft recipients (30 recipients in the tac-ER and 39 recipients in the tac-ER groups); were evaluated. Three KTRs were excluded due to the deaths within the early posttransplant period. Serum creatinine and tacrolimus trough levels were similar for 12 months after transplantation ($p>0.05$). More daily tacrolimus doses (in milligram/day and milligram/kg/day) were required to obtain a targeted trough level up to 3 months in the tac-ER group. Acute rejection rates also were found similar between the two groups ($p=0.281$). Univariate regression analysis demonstrated that higher total daily tacrolimus doses within a posttransplant month 1 may (milligram/kg/day) have an impact on lower acute rejection episode(s) independent of tacrolimus trough levels ($p=0.02$).

Conclusion: De novo use of extended-release tacrolimus Advagraf® is as effective as immediate-release tacrolimus in preventing acute rejection episode(s) and provides satisfactory 1-year allograft function and survival.

Keywords: Extended-release tacrolimus, acute rejection, kidney transplantation

ÖZ

Amaç: Böbrek nakli alıcılarında günde tek doz uzamış salınımlı takrolimus (tac-ER) kullanımı, erken salınımlı takrolimus (tac-IR) kullanımına benzer etkinlik ve daha iyi ilaç uyumu sağlaması amacıyla geliştirilmiştir. Ancak uzamış salınımlı takrolimus ile ilgili deneyimler daha çok nakil sonrası dönemde yapılan "switch" protokollerine dayanmaktadır. Bu çalışmada böbrek alıcılarında de novo tac-ER kullanımı ile ilgili deneyimlerimizi ve 1 yıllık sonuçları sunmayı amaçladık.

Gereç ve Yöntem: Bu tek merkezli retrospektif çalışmaya Ocak 2022-Ocak 2021 arasında yapılan 72 de novo böbrek nakli hastası dahil edilmiştir. Hastalar tac-ER ve tac-IR alan iki gruba ayrıldı. Bir yıllık allogreft fonksiyonları ve sağ kalımları, hastaların günlük ilaç dozları ve bunların akut rejeksiyon atakları ile ilişkileri karşılaştırıldı. Allogreft fonksiyonları ve akut rejeksiyon atakları üzerine etki eden faktörler incelendi.

Bulgular: Toplam 69 hastanın (uzamış salınımlı grupta 30 hasta ve erken salınımlı grupta 39 hasta) verileri incelendi. Üç hasta posttransplant erken dönemde öldüğü için analize dahil edilmedi. Nakil sonrası 12 aylık izlem boyunca her iki grup arasında serum kreatinin ve takrolimus çukur değerler bencer bulundu ($p>0,05$). İlk 3 ay içinde hedef takrolimus değerlere ulaşmak için, tac-ER grubunda daha yüksek günlük dozlar (milligra/gün ve milligram/gün/kg) gerekti ($p<0,05$). Nakil sonrası ilk 12 ay içinde her iki grupta da rejeksiyon oranları benzerdi ($p=0,281$). Tek değişkenli analizde posttransplant 1. aydaki takrolimus dozu (milligram/kg/gün) takrolimus çukur değerinin aksine rejeksiyon gelişimi üzerinde etkili görüldü ($p=0,02$).

Sonuç: Böbrek naklinde uzamış salınımlı takrolimusun (Advagraf®) de novo kullanımı, erken salınımlı takrolimus kullanımına benzer etkinlik, allogreft sağ kalımı ve fonksiyonu sağlar.

Anahtar Kelimeler: Uzamış salınımlı takrolimus, akut rejeksiyon, böbrek nakli

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INTRODUCTION

Kidney transplantation (KTx) is the preferred choice for the treatment of end-stage renal disease (ESRD). A proper immunosuppressive treatment is a key point to the success of KTx, and the success substantially depends on strict adherence to the medications. Many studies have shown that adherence to the single-dose drug is better than to the multiple-dose drug (1,2).

Tacrolimus, a calcineurin inhibitor, has been the pivotal point of immunosuppression in preventing acute rejection episodes after allograft transplantation since its first introduction (3). Tacrolimus is both a powerful anti-rejection drug and also has important side effects such as nephrotoxicity (4). It has been demonstrated that most acute toxic effects of the drug are associated with peak serum levels occurring within 2 hours of drug ingestion (4). The drug is traditionally given in two equal doses every 12 hours and mostly the doses are adjusted according to trough levels. Morning and evening drug doses may be different due to day and night gastrointestinal motility differences.

Once-daily extended-release tacrolimus (tac-ER) (Advagraf®) is an novel formulation of tacrolimus that might facilitate kidney transplant recipients' compliance to medicines lifelong (5). The tac-ER formulation consists of the drug which is layered onto sugar spheres and an ethylcellulose polymer coating to retard the release of the drug (6). Immediate release tacrolimus (tac-IR) reaches its peak activity 2 hours after taking the drug and 100% of the drug is absorbed in the proximal gastrointestinal system (GİS) (7). Contrastly, tac-ER due to its unique formulation is absorbed along the entire GİS without reaching a peak plasma level of tacrolimus as high as tac-IR (7,8). The extended-release formulation of tacrolimus is used in both two ways, which first is switching from tac-IR to tac-ER in allograft recipients with stable kidney function and the second is de novo use. Literature has reported plausible outcomes of the switching protocols, rather than the outcomes of the de novo use. Additionally, the de novo use of tac-ER is still not the preferred first approach compared to tac-IR in many transplant centers regarding tacrolimus use, probably due to scarce evidence related to the posttransplant 1-year outcomes with de novo tac-ER use (9,10).

Here, we present our 1-year experiences on the de novo tac-ER use compared to tac-IR.

MATERIAL AND METHOD

The study was carried out with the permission of Medicana Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 28.01.2022, Decision No: 2022/01). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective single-center study was conducted between January 2020 and January 2021 in a university affiliated-private hospital. All domestic ESRD patients who underwent a KTx in our hospital were included in the study (since the follow-up protocols varied in patients coming from outside of Turkey they were excluded). All recipients have received center-specific induction and immunosuppression protocols in preventing acute allograft rejection (**Table 1**). All de novo KTx recipients received the center-specific standard immunosuppression protocol involving either an (tac-ER) or tac-IR as a calcineurin inhibitor. Clinical and laboratory features of recipients were noted. Recipients' age, gender, primary kidney disease, comorbidities, tacrolimus doses, and tacrolimus serum trough and creatinine levels, urea, and electrolyte levels and drug-related side effects were documented. Acute rejection episodes, mortality, and hospitalization required infection rates were also noted.

Risk Definition

The recipients addressed in protocol 1 were described as with low immunological risk. Other recipients were labeled to receive one option of protocols 2, 3, 4, and 5 and were considered to have moderate to high immunological risk. Re-transplantation recipients were treated similarly to other recipients according to established protocols as mentioned.

Target trough levels for tacrolimus in our center;

- 8-10 ug/L (within posttransplant month 1)
- 7-10 ug/L (between posttransplant months 1-3)
- 5-8 ug/L after posttransplant month 3

In low immunological risk patients, the lower level of the range and in moderate-high patients higher levels of the range were targeted.

Statistical Analysis

Statistical analyses were performed using SPSS (IBM Corp. Released 2012. IBM SPSS [Statistical Package for Social Science] Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.). The Kolmogorov Smirnow test and a histogram evaluation test were used to demonstrate the normality of the continuous variables. Continuous variables were expressed as mean ± standard deviation or median (interquartile range) depending on the distribution of the variable. Categorical variables were reported as numbers and percentages. Parametric and nonparametric continuous variables were compared by using independent samples t-test and Mann-Whitney U test, respectively. Chi-squared test and Fisher's Exact Test were used in comparison of the categorical variables. Univariate and multivariate regression tests were used to investigate the factors that had an impact on rejection

Table 1. Immunosuppression protocols given to recipients in our cohort

	Protocol 1*	Protocol 2	Protocol 3	Protocol 4	Protocol 5
	LCM (-) + PRA (-) + FULL MATCH	LCM (-) + PRA (-) + FULL MISMATCH	LCM (-) + PRA (+) + Variable HLA compliance	LCM (-) + PRA (+) + DSA MFI < 2000	LCM (-) + PRA (+) + DSA MFI > 2000
Induction	-ATG: Single dose; 1,5 mg/kg + -3 consecutive doses of MP (500 mg/day)	-3 ATG doses + -3 consecutive doses of MP (500 mg/day)			Rituximab* + IVIG** Protocol 3
Maintenance	Prednisolon 40 mg/day, tapered to 5 mg/day in 2 months + Tacrolimus 0,10 mg/kg + MMF 2 gr/day	Prednisolon 40 mg/day, tapered to 5 mg/day in 2 months + Tacrolimus 0,10 mg/kg + MMF 2 gr/day	5-7 sessions pretransplant PE therapy + Protocol 2	Protocol 3	*375mg/1.73 m², two doses, -14 and -7 days ** 2 gr/kg (total dose)

Note: LCM positive recipient candidates received a center-specific desensitization protocol as established in protocol 5 including rituximab + IVIG + PE therapy. After LCM becomes negative Protocol 2 is given (but 5-7 ATG doses were given instead of 3 doses) to recipients. Flow-cytometry is interpreted with other clinical data. MFI >2000 individuals were investigated with C1q in a single-beaded antigen test to detect the potency of the antibodies to activate the complement system.
Abbreviations: LCM; lymphocyte cross-match, PRA; panel reactive antibody, HLA; human leukocyte antigen, DSA; donor-specific antigen, MFI; mean flow intensity, ATG; anti-thymocyte globülin, MP; methylprednisolone, MMF; mycophenolate mofetil, PE; plasma exchange, IVIG; intravenous immunoglobulin
* Variable HLA compliance was assessed along with DR allele existence. Recipients without HLA DR compliance also received additional dose(s) of ATG, however, if they are not full mismatch was assigned to Protocol 1. Note: Tac-IR or Tac-ER were administered on the operation day after observing a satisfactory urine output (> 1-2 ml/kg/hour).

episode(s). $p<0.05$ was accepted statistically significant with a 95% confidence interval (CI).

RESULTS

A total of 125 KTx was performed in our center between January 2020 and January 2021. 72 (57.6%) recipients were citizen of the Republic of Turkey and the remaining 63 (42.4%) recipients were from other countries, most of them from Arabic geography. All recipients from Turkey were evaluated. Three recipients (%2,4) died within the early posttransplant interval; one due to COVID-19 posttransplant month 3, one within the first week of the operation, and one due to a cardiac event within posttransplant month 1. Clinical and laboratory features of the study cohort are given in **Table 2**. Cytomegalovirus and polyoma BK virus DNA were detected positive in only two recipients, by using a polymerase chain reaction kit, however, were in low titers, and those recipients did not require the immunosuppressive dose reduction. Hyperglycemia (62.8%), elevated blood pressure (45.2%), diarrhea (28.6%), tremor (20.5%), and orthostatic hypotension (8.2%) were the most common adverse reaction noted in the hospital health software system regarding tacrolimus use. Two formulations of tacrolimus were found similar for adverse reaction rates ($p>0.05$).

The tac-ER and tac-IR groups were compared for allograft functions, rejection episode(s), trough levels, daily total dose (mg/kg), and recipients' demographic features (**Table 3** and **Table 4**). The two groups were found similar for age, body mass index (BMI) serum creatinine and tacrolimus trough levels at discharge, posttransplant months 1, 3, 6, and 12 ($p>0.05$) (**Table 3** and **Table 4**). Tacrolimus daily total doses (milligram/day and milligram/kg/day) at discharge, posttransplant months 1, and 3 were higher in the tac-ER group; p=0.015 and p=0.014, p=0.016 and p=0.013, and p=0.009 and p=0.004, respectively (**Table 4**). Multivariable logistic regression analysis indicated that the higher daily total doses of tacrolimus at discharge, posttransplant months 1, and 3 did not impact individually on serum creatinine levels; p=0.511 (milligram/day) and p=0.622 (milligram/kg/day). Rate of rejection episode(s), allograft loss, and total ATG doses were similar between the two groups, p=0.281, p=0.127, and p=0.253, respectively (**Table 3**).

The clinical and laboratory features of individuals with rejection episodes were compared with rejection-free individuals. (**Table 5**). As expected, serum creatinine levels were higher in the rejection group and serum creatinine levels remained at higher levels at month 12. Since the number of the sample was small, we did not evaluate the outcomes of the rejection episode(s)' according to classification as early or late rejection. However, according to our clinical observations, most of the early rejections did not recover to a satisfactory level of serum creatinine as can be assumed from **Table 4**. Linear regression analysis test demonstrated retransplantation had no impact on rejection episodes, p=0.414. Also, death-censored including all-cause allograft loss rate was similar between the two groups (p=0.508) (**Table 5**).

Tacrolimus dose in milligram/kilogram/day was similar in the rejection and rejection-free groups (**Table 6**) within post-transplant 12 months. Seven acute rejection episodes occurred within the posttransplant month 6. Recipient age, RRT duration, immunological risk status, tacrolimus dosing at 1, 3, and 6 months, and tacrolimus trough levels at 1, 3, and month 6 also were investigated whether they had an impact on acute rejection by univariate analysis (**Table 7**). A univariate regression analysis revealed only month 1 daily dosage significantly may impact acute rejection episode(s) (p=0.02).

Table 2. Clinical and laboratory features of RTX recipients	
Age, years	43.90 ± 12,35
Gender; male/female, N, %	46 / 26 (63,9% / 36.1%)
BMI, kg/m2	23.89 ± 4.49
Weight, kilogram	68.01 ± 14.94
Immunological risk, N, % Low Moderate to severe	 42 (58.3%) 30 (41.7%)
rATG; number of doses (every dose 100 mg/day)	2.68 (Mean dose 260 mg for each RTx case)
Rejection episode(s) (Yes/No); N, % BPAR, n= ABMR, n= TCMR, n=	9 / 60 (13% / 84.1%) 3 exitus not included 8 (8 of 9 cases were BPAR and 1/9 was diagnosed on clinical suspicion and rapid response to the antirejection therapy) 7 of 8 acute rejection developed within posttransplant month 6 7 1
Renal replacement duration, month, median	6.5 (0-132)
Preemptive yes/no, N, %	24 / 48 (33.3 % / 66.7%)
Allograft source	All from living donor
Re-transplantation, n=(%)	9 (12.5%)
Exitus	3 (4.2%) all deaths within posttransplant 3 months (one death due to COVID-19 at posttransplant month 3, one within the first week of the operation, and one due to cardiac event within posttransplant month 1)
Allograft loss, N, % Death-censored graft loss Allograft loss (except death) Primary nonfunction	7 (9.7%) 3 (4.2%) 4 (5.5%) (1/2 primary nonfunction allograft) 2 (%2.7)
Primary disease, N, % HT DM GN PCKD OTHERS Unknown	 9 (12.5%) 19 (26.4%) 12 (16.7%) (41.7% IgA, 25.0% FSGS and 33.3% FMF) 2 (2.8%) 10 (13.9%) 20 (27.7%)
Follow-up, months mean	11.6
Creatinine, mg/dl (preoperative)	6.85±2.12
Creatinine, mg/dl (at discharge, approx. day 5)	1.40±0.94
Creatinine, mg/dl (month 1)	1.27±0.70
Creatinine, mg/dl (month 3)	1.27±0.40
Creatinine, mg/dl (month 6)	1.27±0.36
Creatinine, mg/dl (month 12)	1.28±0.40
Tacrolimus ER & IR, N, %	30 (43.5%) & 39 (56.5%)
Tacrolimus discharge (approximately day 5) Trough, mg/dl At target, % Dose mg/day	 8.47±3.03 61.5% 7.01±2.39
Tacrolimus month 1 Trough, mg/dl At target, % Dose mg/day	 8.40±2.97 86.8% 6.47±3.70
Tacrolimus month 3 Trough, mg/dl At target, % Dose mg/day	 7.41±2.16 80.4% 5.28±2.58
Tacrolimus month 6 Trough, mg/dl At target, % Dose mg/day	 6.61±1.81 80% 4.70±2.54
Tacrolimus month 12 Trough, mg/dl At target, % Dose mg/day	 7.95±1.93 82.4% 3.61±1.52

rATG; rabbit anti-thymocyte globülin, HT; hypertension, DM; diabetes mellitus, GN; glomerulonephritis, PCKD; polycystic kidney disease, FMF; familial Mediterranean fever, ER; extended-release, IR; immediate release

Table 3. Comparison of tac-IR & tac-ER for clinical and laboratory features.

	Tac-ER, N=30	Tac-IR, N=39	P-value
Age, year	44.96±10.75	41.92±13.01	0.309
BMI, kg/m2	24.52±4,35	23.28±4.54	0.271
Weight, kilogram	68.57±13,46	67.65±16.29	0.810
RRT duration, month	6.5 (0-72)	7 (0-132)	0.675
Rejection episode(s)	2/30 (6.7%)	7/39 (17.9%)	0.281
Allograft loss	0/30 (0%)	4/39 (10.3%)	0.127
Immun risk low/moderate-high	18/21	11/19	0.469
Re-transplantation yes/no, N	4/26	5/34	1.000
rATG dose (every dose 100 mg/day)	2.75±1.18	2.62±1.45	0.253
Serum creatinine;			
At discharge*	1.28±1.03	1.59±1.02	0.242
Month 1	1.16±0,43	1.49±1.16	0.141
Month 3	1.21±0.44	1.51±1.06	0.215
Month 6	1.15±0.25	1.59±1.52	0.132
Month 12	1.10±0.29	1.40±0.43	0.107

BMI; body mass index, RRT; renal replacement therapy, rATG; rabbit anti-thymocyte globulin

Table 4. Comparison of tac-ER and tac-IR for tacrolimus trough levels, milligram/day and milligram/kilogram/day within posttransplant 12 months.

	Tac-ER, N=30	Tac-IR, N=39	P value
Tacrolimus trough level;			
At discharge*	8.19±2.32	8.57±3.50	0.614
Month 1	8.85±3.16	7.95±2.72	0.223
Month 3	7.62±1.72	7.28±2.43	0.578
Month 6	6.58±1.52	6.67±2.00	0.879
Month 12	8.37±2.07	7.53±1.82	0.403
Tacrolimus doses; milligram/day			
At discharge*	7.89±2.59	6.31±1.96	**0.015**
Month 1	7.72±4.46	5.29±2.25	**0.016**
Month 3	6.41±2.93	4.30±1.79	**0.009**
Month 6	5.53±3.07	3.92±1.68	0.101
Month 12	3.80±1.78	3.37±1.18	0.571
Tacrolimus doses; milligram/kg/day			
At discharge*	0.12±0.06	0.09±0.02	**0.014**
Month 1	0.12±0.08	0.08±0.03	**0.013**
Month 3	0.10±0.05	0.06±0.02	**0.004**
Month 6	0.91±0.05	0.59±0.02	0.057
Month 12	0.06±0.04	0.50±0.21	0.372

*Approximately at posttransplant day 5.

Table 5. Comparison of individuals with and without rejection episodes.

	Rejection-Yes, N=9	Rejection-No, N=60	P value
Age, year	40.66±8.93	43.61±12.64	0.501
BMI, kg/m2	23.46±3.39	23.88±4.68	0.650
Weight, kilogram	70.27±8.92	67.60±16.02	0.500
Serum creatinine;			
At discharge*	2.36±1.43	1.31±0.88	**0.003**
Month 1	2.17±1.64	1.21±0.68	**0.003**
Month 3	2.22±1.79	1.22±0.40	**0.001**
Month 6	2.45±1.76	1.18±0.27	**<0.001**
Month 12	2.13±0.23	1.18±0.29	**<0.001**
Tacrolimus trough **level**;			
At discharge*	8.45±2.93	8.39±3.07	0.962
Month 1	7.70±1.24	8.46±3.16	0.473
Month 3	7.06±2.33	7.50±2.05	0.591
Month 6	5.98±1.40	6.75±1.84	0.339
Month 12	8.20±2.68	7.91±1.94	0.855
Tacrolimus daily total doses; mg			
At discharge*	7.00±2.64	6.96±2.38	0.948
Month 1	5.81±2.22	6.57±3.88	0.591
Month 3	5.16±2.33	5.30±2.61	0.907
Month 6	3.16±1.25	4.89±2.61	0.275
Month 12	2.25±0.35	3.78±1.52	0.187
Allograft loss, n(%)	1 (11.1%)	1 (1.6%)	0.252
Death-censored including allograft loss	1(11.1%)	4 (6.6%)	0.508
Immun risk low/moderate-high	3/6	37/23	0.152
Re-transplantation, yes	2/9	7/60	0.333
ATG dose (every dose 100 mg/day)	3.22±1.71	2.59±1.26	0.194
RRT duration, month	0 (0-72)	7 (0-132)	0.402

BMI; body mass index, ATG; anti-thymocyte globulin, RRT; renal replacement therapy

Table 6. Daily total dosing (milligram per kilogram) of tacrolimus in rejection and rejection free groups, and in tac-Er and tac-IR groups

	Rejection-Yes	Rejection-No	P-value
Tacrolimus dosage; (daily milligram/kg)			
At discharge*	0.09±0.027	0.11±0.541	0.532
Month 1	0.08±0.025	0.10±0.072	0.351
Month 3	0.07±0.027	0.08±0.049	0.555
Month 6	0.05±0.027	0.07±0.044	0.343
Month 12	0.03±0.002	0.06±0.032	0.176

Table 7. The impact of the factors on the acute rejection rate

	P value	95% CI
Recipient age, year	0.481	-0,860 (-0.09-0.004)
RRT duration	0.315	-0.126 (-0.04-0.315)
Immunological risk	0.102	0.197 (-0.27-0.295)
Tacrolimus dosing month 1	0.022	-0.123 (-2.187-0.857)
Tacrolimus dosing month 3	0.555	-0.099 (-3.479-1.898)
Tacrolimus dosing month 6	0.343	-0.194 (-4.529-1.639)
Tacrolimus trough month 1	0.452	-0.094 (-0.040-0.018)
Tacrolimus trough month 3	0.595	-0.074 (-0.060-0.035)
Tacrolimus trough month 6	0.339	-0.159 (-0.102-0.036)

DISCUSSION

Calcineurin inhibitors are the key point of immunosuppression in kidney transplant recipients. Tacrolimus is commonly used as a two-divided daily dose. Daily single-dose formulation of tacrolimus (tac-Er) may contribute to the recipient's life-long immunosuppressive adherence and thus to have a good functioning allograft. This study adds new contributions to the effectiveness of tac-ER in KTx recipients.

Kidney transplant recipients are forced to have lifelong strict medical adherence, which involves many daily pills. This rationale depends on that nonadherence to immunosuppressive regimens has a negative impact on allograft functions and survival (11-14). Nonadherence also is associated with de novo donor-specific antibody development and acute rejection. Each acute rejection episode needs more intensive immunosuppression and additional approaches which result in more daily pills. This vicious cycle complicates recipients' therapy adherence and consequently allograft survival.

Nonadherence is associated with either reluctance to take medicine due to drug burden or missed or delayed doses of tacrolimus. On the other hand symptom experience (tremor, headache, diarrhea, high blood pressure levels) may impact recipient drug-tacrolimus- adherence (15). It is well known most acute tacrolimus toxicity is related to the peak serum levels of the drug which is achieved within the 2 hours after ingestion (4,7,15). Recipients under minimal immunosuppression are likely more vulnerable to nonadherence. Only one missed a dose of tacrolimus has resulted in a reduction of 49% in trough serum levels of tacrolimus (15).

Extended-release tacrolimus (Advagraf®) promised more medication adherence and comparable outcomes at its commercial introduction. The ensuing pieces of evidence of tac-ER have revealed improved compliance and satisfaction as well as comparable allograft function and similar adverse reaction compared to tac-IR (16,17). Additionally, at least theoretically it could be expected, a relatively less serum peak levels of tacrolimus with Advagraf® may contribute to achieving a less acute toxicity rate.

In this study, we substantially focused on assessing the effectiveness of 1- year de novo tac-ER compared to tac-IR (16-18). Wakasugi et al. (8) reported the 5-year outcomes of 250 de novo kidney transplants who were addressed to receive tac-ER in their study, however, the study was not in a comparative design to compare the effectiveness of tac-ER and tac-IR. They emphasized that 5-year outcomes and adverse reaction rates did not indicate any safety signals. Andres et al. (9) reported the outcomes of 79 kidney allograft recipients with mean 4 months follow-up and demonstrated a similar safety and efficacy rate in the de novo tac-ER group compared to tac-IR. Our study demonstrates similar 1-year allograft functions with tac-ER use compared to tac-IR. In previous studies rejection rates in de novo tac-ER use have been found lower, however, the difference was not at statistically significant levels (9,19). A similar result was obtained in our study. Biopsy proven acute rejection rate was lower in tac-ER (6.7% vs 17.9), however, it was not at a statistically significant level. Given all, it is known that tac-ER is not inferior to prevent acute rejection in solid organ transplantation including KTx (19-21).

Dosing tac-Er is commercially suggested similar to tac-IR; 0.10 mg/kg/day. However, at a rate of 1:1, 1:1.1, and 1:1.2 dosages in the switches protocols, and in the de novo use of Advagraf may be also utilized (1; tac-IR, the reference point). This may be due to recent, but weak, evidence that suggests using up to a 50% higher dose of tac-ER than tac-IR to achieve similar trough levels during the first 6 months. Crespo et al. (22) reported that de novo kidney transplant recipients need higher doses of Advagraf compared with Prograf to get therapeutic levels, and our study demonstrated a similar result. In our cohort, daily tac-ER dosage was higher at 25% at discharge, 46% at month 1, 49% at month 3, 41% at month 6, and 12% than tac-IR at month 12 posttransplant. Surprisingly, a higher dosage of tac-ER at month 1 (despite statistically similar trough levels between the two groups), likely has had an impact on acute rejection episode(s). ATG doses, immunological risk assessment, RRT duration, and age were similar between the two groups and regression analysis revealed no impact of those parameters on rejection development.

Our study has some limitations; some rejections were pre-diagnosis and anti-rejection therapies were established on clinical view rather than biopsy-proven rejection. Also, since we do have not a routine allograft biopsy protocol we are not able to compare the two groups for CNI nephrotoxicity. Additionally, we did not examine the adverse reactions or symptom-based drug usage behaviors of the recipient. However, we think the study will encourage many clinicians to use de novo extended-release tacrolimus formulation.

CONCLUSION

A lifelong strict adherence to immunosuppressive medications to prevent acute rejection episodes is mandatory in KTx recipients. In this regard, a daily dose instead of multiple doses of immunosuppressive drugs may enhance the patients' compliance to therapy and that is one of the crucial points of the success in KTx. One-daily doses of tacrolimus; extended-release tacrolimus (Advagraf®), may provide more adherence to therapy and similar 1-year allograft function and rejection rates with tac-IR.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana Hospital, Noninvasive Clinical Researches Ethics Committee (Date: 28.01.2022, Decision No: 2022/01).

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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Correlation of subclinic atherosclerosis, proinflammatory status, and insulin resistance with anthropometric measurements in polycystic ovary syndrome

Polikistik over sendromu hastalarında subklinik ateroskleroz, proinflamatuvar durum ve insülin direncinin antropometrik ölçümlerle korelasyonu

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ABSTRACT

Introduction: Polycystic ovary syndrome (PCOS) is the most frequently encountered endocrinopathy in women of reproductive age. Visceral obesity, cardiovascular complications, insulin resistance, and proinflammatory status are frequently seen in PCOS patients. Many anthropometric measurements are used to evaluate visceral obesity. The aim of this study was to evaluate the correlations of anthropometric measurements with cardiovascular risk, insulin resistance and proinflammatory status in PCOS patients.

Material and Method: This retrospective study included 68 PCOS patients and 83 healthy females. Anthropometric measurements were evaluated of waist circumference, hip circumference, waist/hip ratio, body mass index (BMI), visceral adiposity index (VAI), lipid accumulation product (LAP), body adiposity index (BAI), abdominal volume index (AVI), body roundness index (BRI), and a body shape index (ABSI) of all the participants. Carotid intima media thickness (CIMT) for subclinical atherosclerosis cardiovascular risk evaluation, HOMA for insulin resistance assessment, and hsCRP levels for proinflammatory status assessment were determined as the main outcome measure. Correlations of anthropometric measurements with each other and with the main outcome measures were evaluated.

Results: HOMA and CIMT were significantly higher in PCOS patients. Abdominal obesity indicators such as waist circumference, hip circumference, waist-to-hip ratio, BMI, LAP, BAI, BRI, AVI, VAI and ABSI were significantly higher in the PCOS group. There was no significant difference between the groups in respect of hsCRP levels (p=0.317). When the correlations of anthropometric measurements with PCOS status were evaluated, it was seen that all measurements were correlated. The highest correlation with CIMT was obtained in BMI measurement, and the highest correlation with HOMA was obtained in BRI measurement. The anthropometric measurements were not found to be correlated with proinflammatory status in PCOS patients.

Conclusion: It was observed that anthropometric measurements may be functional in predicting PCOS-related subclinical atherosclerosis and insulin resistance. Visceral adiposity was found to be predictive for insulin resistance and subclinical atherosclerosis in PCOS patients.

Keywords: Adiposity, insulin resistance, carotid intima media thickness, CIMT

ÖZ

Amaç: Polikistik over sendromu (PKOS) doğurganlık çağındaki kadınlarda sık görülen bir endokrinopatidir. PKOS hastalarında visseral obezite, kardiyovasküler bozukluklar, insülin direnci, proinflamatuvar durum sıklıkla görülebilmektedir. Visseral obezitenin değerlendirilmesi amacıyla bir çok antropometrik ölçüm kullanılmaktadır. Amacımız antropometrik ölçümlerinin kardiyovasküler risk, insülin direnci ve proinflamatuvar durum ile korelasyonlarını değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif çalışmaya 68 PKOS ve 83 kontrol katılımcı alındı. Tüm katılımcıların bel çevresi, kalça çevresi, bel/kalça oranı, vücut kitle indeksi (VKI), visseral yağlanma indeksi (VAI), lipid birikim ürünü (LAP), vücut yağlanma indeksi (BAI), abdominal hacim indeksi (AVI), vücut yuvarlaklık indeksi (BRI) ve vücut şekli indeksi (ABSI) gibi antropometrik ölçümleri yapıldı. Ana sonuç ölçütü olarak kardiyovasküler risk ve subklinik ateroskleroz değerlendirmesi için karotis intima media kalınlığı (KIMK), insülin direnci değerlendirmesi için HOMA-IR, proinflamatuvar durum değerlendirmesi amaçlı hsCRP düzeyleri belirlendi. Antropometrik ölçümlerin birbirleri ve ana sonuç ölçütleri ile korelasyonları değerlendirildi.

Bulgular: HOMA-IR ve KIMK, PCOS hastalarında anlamlı olarak daha yüksekti. PCOS grubunda bel çevresi, kalça çevresi, bel kalça oranı, LAP, BAI, BRI, AVI, VAI ve ABSI gibi abdominal obezite göstergeleri anlamlı olarak daha yüksekti. hsCRP düzeyleri arasında anlamlı farklılık yoktu (p=0,317). Antropometrik ölçümlerin PCOS olma durumu, KIMK, hsCRP ve HOMA ile korelasyonları değerlendirildiğinde tüm ölçümlerin korele olduğu görüldü. KIMK ile en yüksek korelasyon VKI ölçümü, HOMA ile en yüksek korelasyon BRI ölçümünde elde edildi. Antropometrik ölçümlerin PKOS hastalarında CRP ile korelasyon göstermediği tespit edildi.

Sonuç: Antropometrik ölçümlerin PKOS ilişkili subklinik ateroskleroz ve insülin direncini öngörmede işlevsel olabileceği görülmüştür. PCOS hastalarında visseral adipozitenin subklinik ateroskleroz ve insülin direncini için prediktif olduğu görülmüştür.

Anahtar Kelimeler: Adipozite, insülin direnci, karotis intima media kalınlığı, KIMK

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women of childbearing age. PCOS is characterized by hyperandrogenism, oligo-anovulation, menstrual dysfunction and polycystic ovaries (1). It was first described in 1935 by American gynecologists, Irving F. Stein and Michael L. Leventhal (2). A high cardiovascular risk profile has been demonstrated in PCOS with an increased incidence of type 2 diabetes, insulin resistance, dyslipidemia, hypertension, and obesity (1,3,4). In addition, some studies have found that subclinical inflammation is increased in patients with PCOS and insulin resistance (5).

Obesity is present in 30-75% of women with PCOS and is a factor that exacerbates the clinical entitie metabolic syndrome (6). In particular, visceral adiposity aggravates hirsutism and menstrual abnormalities and exacerbates the clinical presentation of PCOS. In addition, the benefit seen in infertility treatments decreases in the case of obesity (7).

PCOS is often accompanied by abnormal fat distribution beyond obesity. This condition is referred to as visceral adiposity, and is associated with abnormal lipid-metabolic profile, proinflammatory activity, insulin resistance, and subclinical atherosclerosis. Visceral adiposity increases the risk of metabolic syndrome, type 2 diabetes, and cardiovascular events in PCOS patients. Visceral adiposity also exacerbates ovulatory dysfunction and hyperandrogenism (8–10).

Different methods such as bioelectrical impedance, ultrasonography, dual x-ray absorptiometry and magnetic resonance imaging can be used to demonstrate visceral adiposity (11). However, further methods are needed to assess visceral adiposity because of the difficulty and cost of accessing these devices. Body mass index (BMI) is insufficient to predict body fat distribution. Therefore, in addition to conventional methods such as waist circumference, hip circumference, and waist / hip ratio, new anthropometric measurements such as visceral adiposity index (VAI), lipid accumulation product (LAP), body adiposity index (BAI), abdominal volume index (AVI), body roundness index (BRI) and a body shape index (ABSI) have been investigated in some studies recently.(12–19).

The aim of this study was to evaluate the relationship of subclinical atherosclerosis, insulin resistance and proinflammatory activity with obesity and abdominal adiposity in PCOS patients through anthropometric measurements.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 18.10.2021, Decision No: 122/4). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Sixty eight PCOS patients and 85 healthy control subjects referred to the endocrinology and metabolism department of our clinic is included in this retrospective study.

Diagnosis of PCOS is established according the 2003 Rotterdam criteria. Patients with any two of the criteria for menstrual disturbances, clinical and/or biochemical androgen excess, and multiple cystic ovarian morphology were accepted as PCOS (20). Patients with diabetes mellitus, acute infection, cardiovascular disease, renal failure, history of immuno-rheumatic disease, or gynecological neoplasms, were excluded from the study. The control group was formed of patients who presented with non-specific complaints and no pathology was found in the examinations. The anthropometric, clinical, and laboratory findings were recorded.

BMI was calculated by dividing body weight (kg) by height squared(m2). Waist circumference was measured at the midpoint of the the iliac crests and the twelfth rib while standing. Afterward hip circumference was measured at the widest part of the hips (21). The waist-hip ratio was obtained by dividing these two values. Abdominal obesity was assessed using the formulas of ABSI, AVI, BAI, BRI, LAP, and VAI (22–24) (**Table 1**).

Table 1. Formulas of anthropometric measurements

ABSI=	Waist circumference / (BMI 2/3 x Height (meter) 1/2)
AVI =	[2 x (Waist circumference (cm))2 + 0.7 x (Waist circumference (cm) – Hip circumference (cm))2] / 1.000
BAI=	[Hip circumference (cm) / Height (m)3/2]-18
BRI=	364.2-365,5x [1 – ((Waist circumference (m)/ (2π)2) / (0,5x Height (m))2]1/2
LAP (Female)=	(Waist circumference (cm)-58) x Triglyceride (mmol/L)
VAI (Female)=	[Waist circumference (cm)/ (36.58+ (1.88 × VKI)] × (Triglyceride (mmol/L) /0.81) × (1.52/HDL-C (mmol/l))

VAI: visceral adiposity index, LAP: lipid accumulation product, BAI: body adiposity index, AVI: abdominal volume index, BRI: body roundness index, ABSI: body shape index, HDL-C: high density lipoprotein cholesterol

Carotid intima media thickness (CIMT) was measured in term of the evaluation of subclinical atherosclerosis during the first examination of all participants. Measurements were made with a 13 MHz high resolution B-mode ultrasound (EUB 7000 HV; Hitachi, Tokyo, Japan) and linear probe. Three measurements were taken near 1 cm proximal of both right and left common carotid artery bifurcations. The distance between posterior wall lumen echogenicity and media-adventitia echogenicity was measured only from the posterior part of the carotis artery. CIMT was computed as the mean of the three measurements in both arteries.

Blood samples were taken from all the subjects between 08:00 and 10:00 in the morning after an overnight fast in the follicular phase of the menstrual cycle. Fasting blood was drawn to measure serum glucose, insulin and lipid profile. Insulin resistance was calculated using the homeostasis model assessment formula (HOMA) [Fasting insulin (μU/mL) × Fasting glucose (mg/dl)/405)]. To assess the proinflammatory state, hsCRP levels were evaluated.

Statistical Analysis

The parametric distribution of numerical data was defined using the Shapiro-Wilk test. Mean±standard deviation values were used for parametric distributed variables, and median and range values for non-parametric distributed variables. The Student's t test was used to compare normally distributed variables between the groups. The Mann-Whitney U test was used to compare variables with non-normal distribution in independent groups. Categorical variables of the groups were compared with the Chi-square ($\chi 2$) test. Spearman correlation analysis was applied to non-normally distributed data. Correlation analyses were evaluated both in the whole sample and in patients with PCOS only. A value of $p < 0.05$ was considered statistically significant.

RESULTS

The median age was 25 years (range, 18-47 years) in the control group and 23 years (range, 18-36 years) in the PCOS group. In terms of age statistically significant difference did not determined between the groups (p=0.179). PCOS patients had higher triglyceride, LDL, and total cholesterol levels when compared to the control group (**Table 2**). No significant difference was determined between the groups in respect of HDL levels (p=0.056). CIMT and HOMA-IR were meaningfully elevated in PCOS patients. In the PCOS group, visceral obesity indicators such as waist circumference, hip circumference, waist-hip ratio, LAP, BAI, BRI, AVI, VAI and ABSI were significantly higher (p<0.05). There was no significant difference between the groups in respect of hsCRP levels (p=0.317). The demographic data, laboratory findings, and anthropometric measurements are given in **Table 2**.

When the anthropometric measurement correlations were evaluated in all participants, with the exception of ABSI, all anthropometric measurements were found to be correlated with each other. The ABSI value was not correlated with BAI and BMI (r:0.102; p:0.278 and r:0.005; p:0.954, respectively). When the anthropometric measurement correlations were evaluated only in the 68 PCOS patients, the ABSI value showed no significant correlation with VAI (r:0.168; p:0.192), BAI (r:0.023; p:0.860), or BMI (r:0.166; p:0.196). When all the patients were evaluated, a significant correlation was determined between BAI and waist-hip ratio (r:0.321; p<0.001). The correlation between BAI and waist-hip ratio was lost when only PCOS patients were evaluated (r:-0.041; p:753). All other anthropometric measurements were found to be correlated with each other in the PCOS group.

Table 2. Demographic data, laboratory findings, and anthropometric measurements of the PCOS and control groups

	Control	PCOS	p
n	83	68	
Age (years)	25 (18-47)	23 (18-36)	0.179
Height (cm)	161.4 ± 5.8	161.5 ± 6.1	0.774
Weight (kg)	55 (43-94)	69 (35-115)	<0.001
Waist circumference (cm)	71 (61-102)	87 (65-121)	<0.001
Hip circumference (cm)	95.5 (85-123)	103 (77-141)	0.001
Waist/hip ratio	0.72 (0.66-0.81)	0.85 (0.72-0.98)	<0.001
Total cholesterol (mg/dl)	159 (127-251)	168 (126-243)	0.027
Triglyceride (mg/dl)	75 (21-273)	98 (32-382)	0.001
HDL (mg/dl)	56.95 ± 14.45	52.82 ± 12.82	0.056
LDL (mg/dl)	82 (38-176)	94 (69-175)	<0.001
Glucose (mg/dl)	82 (65-104)	81 (75-106)	0.039
Insulin (μU/mL)	8.7 (4.2-13.9)	16.2 (3.73-43.07)	<0.001
HOMA-IR	1.63 (0.79 – 3.0)	3.73 (0.78 – 9.25)	<0.001
CRP	1.0 (0.1-7.0)	1.0 (0.1-8.0)	0.317
CIMT (mm)	0.47 (0.25 -0.85)	0.50 (0.30 -0.80)	0.002
ABSI	0.073 (0.07-0.09)	0.0751 (0.07-0.09)	0.044
LAP	9.21 (1.45–74.52)	29.27 (6.95-245.84)	<0.001
BAI	27.88 (22.60-38.40)	31.45 (22.96—55.78)	0.001
BRI	2.26 (1.03-6.49)	4.04 (1.59-10.33)	<0.001
VAI	0.85 (0.30 – 6.67)	1.45 (0.37 – 9.53)	<0.001
AVI	9.80 (7.44 – 15.84)	14.96 (8.45 – 29.28)	<0.001
BMI	20.56 (15.94-34.53)	26.64 (17.36-48.49)	<0.001

HDL: high density lipoprotein, LDL: low density lipoprotein, HOMA-IR: homeostasis model assessment formula, CIMT: carotid intima media thickness, VAI: visceral adiposity index, LAP: lipid accumulation product, BAI: body adiposity index, AVI: abdominal volume index, BRI: body roundness index, ABSI: body shape index, BMI: body mass index

When the anthropometric measurements of all the participants were evaluated with PCOS status, all the measurements were found to be correlated with a positive PCOS status. ABSI was the poorest correlated antropometric measurement (r:0.178; p:0.044). The highest correlation with PCOS was seen with the waist-hip ratio measurement (r:0.818; p<0.001). When the anthropometric measurements were evaluated with CIMT, with the exception of ABSI and BAI, all the other measurements were found to be correlated. When anthropometric measurements were evaluated with hsCRP, with the exception of ABSI, BRI, and waist-hip ratio, all other measurements were found to be correlated. When anthropometric measurements were evaluated with HOMA, with the exception of ABSI, all other measurements were found to be correlated (**Table 3**).

Table 3. Correlations of PCOS status, CIMT, hsCRP and HOMA-IR, with anthropometric measurements (all participants)

		PCOS	CIMT	CRP	HOMA
BRI	r	0.615	0.297	0.206	0.626
	p	<0.001	0.001	0.053	<0.001
VAI	r	0.421	0.264	0.250	0.486
	p	<0.001	0.004	0.018	<0.001
LAP	r	0.572	0.278	0.266	0.582
	p	<0.001	0.002	0.012	<0.001
BAI	r	0.331	0.110	0.194	0.497
	p	<0.001	0.264	0.069	<0.001
AVI	r	0.697	0.304	0.238	0.574
	p	<0.001	-0.076	0.025	<0.001
ABSI	r	0.178	0.411	0.036	0.121
	p	0.044	0.875	0.736	0.211
BMI	r	0.590	0.351	0.253	0.610
	p	<0.001	<0.001	0.016	<0.001
WHR	r	0.816	0.330	0.163	0.530
	p	<0.001	<0.001	0.128	<0.001

VAI: visceral adiposity index, LAP: lipid accumulation product, BAI: body adiposity index, AVI: abdominal volume index, BRI: body roundness index, ABSI: body shape index, BMI: body mass index , WHR: waist/hip ratio

When the anthropometric measurements of only PCOS patients were evaluated, only BMI was correlated with CIMT (r:0.285; p:0.031). There was no correlation of CRP with any anthropometric measurement (**Table 4**). When the PCOS patients anthropometric measurements were evaluated with HOMA, with the exception of waist-hip ratio, all other measurements were found to be correlated. The poorest correlation with HOMA was seen with ABSI and the highest correlation was seen with BMI (**Table 4**).

Table 4. Correlations of CIMT, hsCRP and HOMA-IR with anthropometric measurements (PCOS patiens)

		CIMT	CRP	HOMA
BRI	r	0.182	0.112	0.401
	p	0.184	0.516	0.002
VAI	r	0.001	0.132	0.531
	p	0.993	0.553	<0.001
LAP	r	0.040	0.049	0.450
	p	0.771	0.778	0.001
BAI	r	0.034	0.226	0.415
	p	0.805	0.186	0.002
AVI	r	0.217	0.114	0.346
	p	0.111	0.508	0.010
ABSI	r	0.256	0.175	0.305
	p	0.059	0.307	0.024
BMI	r	0.285	0.244	0.547
	p	0.031	0.140	<0.001
WHR	r	0.174	0.009	0.129
	p	0.204	0.960	0.347

VAI: visceral adiposity index, LAP: lipid accumulation product, BAI: body adiposity index, AVI: abdominal volume index, BRI: body roundness index, ABSI: body shape index, BMI: body mass index, WHR: waist/hip ratio

DISCUSSION

The results of the current study demonstrated that obesity, insulin resistance, and subclinical atherosclerosis increase in PCOS patients. In addition, atherosclerotic deterioration was observed in the lipid profile. It was also determined that waist circumference is increased and visceral obesity is seen at a higher rate in PCOS patients. This situation was shown through many anthropometric measurements. With the exception of ABSI, the anthropometric measurements were found to be generally correlated with each other. All the anthropometric measurements were found to be correlated with PCOS status. Waist-hip ratio showed the highest correlation with PCOS status, while BMI showed the highest correlation with insulin resistance, and subclinical atherosclerosis. However, ABSI showed the poorest correlation. None of the anthropometric measurements were correlated with proinflammatory status in PCOS patients.

Central obesity and dyslipidemia are thought to contribute to the aggravated risk of atherogenesis in women with PCOS (6,7). CIMT has recently been used as a indicator of the progress of subclinical atherosclerosis, and studies have reported that increased CIMT is a strong predictor of the risk of stroke, myocardial infarction, and cardiovascular death (25,26). Altın et al. (27) declared that both early atherosclerotic changes and CIMT were significantly ameliorated following sleeve gastrectomy in obese cases. In the current study, CIMT was meaningfully elevated in cases with PCOS.

Correlations were determined between CIMT and AVI, BRI, LAP, VAI, BMI, and waist-hip ratio. However, no correlation was found between CIMT and ABSI and BAI. In a recent study of 62 PCOS patients, no correlation was found between ABSI measurement and CIMT, similar to the findings of the current study (13). This indicates that new anthropometric measures other than ABSI and BAI can be considered to prognosticate atherosclerotic risk in patients with PCOS.

It has been stated in some studies that subclinical inflammation is the ongoing process in patients with PCOS (5,30). According the current study, the hsCRP levels did not differ between the groups. Although correlations between hsCRP and AVI, BAI, LAP, VAI, BMI, and waist/hip ratio were detected in the whole sample, when only the PCOS group was evaluated this correlation was lost. This indicates that hsCRP elevation is mainly affected by visceral adiposity in the general population. However, other factors that affect the proinflammatory state in PCOS patients need to be considered.

A strict relationship between insulin resistance and splanchnic adiposity has been previously demonstrated (28,29). Similarly, significantly increased HOMA was seen in the current study PCOS patients. Correlations were determined between HOMA and AVI, BAI, BRI, LAP, VAI, and BMI. However, no correlation was found between HOMA and ABSI. The increased visceral adipose tissue in the current study was associated with increased insulin resistance in these patients. These results were compatible with those of other recent studies conducted in Turkey (13,14). Consequently, visceral adiposity can be accepted as an important determinant of insulin resistance in PCOS.

The main limitation of this study was the small number of participants. Besides that, the retrospective design and that there was no long-term patient follow-up reduce the power of the study. Multiple regression analyses could not performed because the main outcome criteria of this study, such as HOMA, CIMT, and hsCRP, were non-parametric linear variables. Therefore, the inability to evaluate the anthropometric predictors of the main outcome measures can be considered a limitation of the study. More information on the development of cardiometabolic events in PCOS will be able to be obtained with further prospective studies with larger numbers of participants.

CONCLUSION

The results of this study demonstrated that anthropometric measurements may be functional in predicting PCOS-related subclinical atherosclerosis and insulin resistance. However, it was observed that ABSI measurements may not be suitable for use in PCOS patients. Visceral adiposity was found to be predictive for insulin resistance and subclinical atherosclerosis in PCOS patients. The highest correlation with CIMT was obtained in the BMI measurement, and the highest correlation with HOMA was obtained in the BRI measurement. Anthropometric measurements were not found to be correlated with proinflammatory status in PCOS patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 18.10.2021, Decision No: 122/4).

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

Referee Evaluation Process: Externally peer-reviewed.

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Nailfold capillaroscopic pattern and modified Rodnan skin score associated with deterioration of right ventricle functions in systemic sclerosis patients without overt pulmonary hypertension

Aşikâr pulmoner hipertansiyonu olmayan sistemik sklerozlu hastalarda tırnak kapilaroskopi bulguları ve modifiye Rodnan skoru sağ ventrikül fonksiyonlarında bozulma ile ilişkilidir

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ABSTRACT

Objective: Although nailfold capillaroscopy (NC) and modified Rodnan skin score (mRSS) have already been studied in a variety of contexts related to Systemic Sclerosis (SSc) progression, there is limited data about the relationships between NC, mRSS, and right ventricle (RV) function in SSc patients without overt pulmonary arterial hypertension (PAH). In this study, we examined the relationship between RV function and clinical SSc parameters such as NC pattern and mRSS.

Material and Method: Thirty two patients with SSc and twenty healthy participants as a control group were enrolled in this study. Patients with SSc were assessed for digital ulcers, Raynaud's phenomenon, and severity of skin involvement by a rheumatology specialist. Also, all participants underwent echocardiographic examinations by cardiology specialists. The echo parameters were measured considering the criteria of the American Society of Echocardiography guidelines.

Results: Systolic pulmonary arterial pressure (sPAP) was statistically higher in the SSc group (26.4±3.2 vs 30.8±3.6 mmHg, p<0.001). Tricuspid annular plane systolic movement (TAPSE), pulmonary accerelation time and mean RV free wall strain were found to be lower in the SSc group (p=0.003, p<0.001, p<0.001 for all). Patients with capillaroscopic active and late pattern and late pattern had significantly lower TAPSE, ventricular isovolumic acceleration (IVA) and RV free wall mean strain (p=0.002, p=0.005, and p<0.001, respectively) compared to patients with capillaroscopic early pattern and active and early pattern In the univariant linear regression analisys, in the SSc group, mRSS was significantly associated with RV free wall mean strain (R2=0.192; p=0.007).

Conclusion: In this study, early deterioration of sPAP and RV functions were shown in SSc patients without overt PAH. Also, high scores of mRSS and abnormal capilloroscopic pattern were associated with worse RV function.

Keywords: Systemic sclerosis, nailfold capillaroscopy, modified Rodnan skin score, right ventricle strain imaging

ÖZ

Amaç: Tırnak kapilloskopisi ve modifiye Rodnan skoru sistemik sklerozda (SS) çeşitli durumlarda klinik progresyon ile ilişkili bulunmuş olmasına rağmen sağ ventrikül fonksiyonları ile ilişkileri yeterince çalışılmamıştır. Bu çalışmada aşikar pulmoner hipertansiyonu olmayan sistemik sklerozlu hastalarda sağ ventrikül fonksiyonları ile modifiye Rodnan skoru, tırnak kapillaroskopisi gibi klinik SS klinik parametreleri ile arasındaki ilişki araştırılmıştır.

Gereç ve Yöntem: Otuz iki SS'li hasta ve yirmi sağlıklı birey kontrol grubu için çalışmaya alınmıştır. Hastalar romatoloji uzmanı tarafından dijital ülserler, tırnak kapillaroskopisi ve deri tutulumu için değerlendirilmiştir. Tüm katılımcılara ekokardiyografik değerlendirme kardiyoloji uzmanı tarafından yapılmıştır. Ekokardiyografik parametreler Amerikan Ekokardiyografi Birliğinin kılavuzlarına göre hesaplanmıştır.

Bulgular: Sistolik pulmoner arteriyel SS grubunda istatiksel olarak anlamlı şekilde yüksekti (26,4±3,2 vs 30,8±3,6 mmHg, p=0,001). Triküspit anüler plan sistolik hareketi (TAPSE), pulmoner akselerasyon zamanı ve ortalama sağ ventrikül strain değeri SS grubunda anlamlı olarak daha düşüktü (p=0,003, p=0,001, p=0,001). Kapillaroskopik olarak aktif ve geç patern ve geç paterne sahip hastalarda erken ve aktif paterne ve erken paterne sahip hastalara göre TAPSE, ventriküler isovolumik akselerasyon ve sağ ventrikül ortalama serbest duvar straini anlamlı olarak daha düşüktü (p=0,002, p=0,005, and p=0,001, sırasıyla) Univariat doğrusal regresyon analizde, SS grubunda modifiye Rodnan cilt skoru ile sağ ventrikül serbest duvar ortalama strain arasında anlamlı ilişki vardı (R2=0,192; p=0,007).

Sonuç: Bu çalışmada SS'li hastalarda sistolik pulmoner arteriyel basınçta ve sağ ventrikül fonksiyonlarında erken dönemde bozulma olduğu gösterilmiştir. Ayrıca yüksek modifiye Rodnan cilt skoru ve geç dönem kapillaroskopik değişikliklerin sağ ventrikül fonksiyonlarındaki bozulmayla ilişkili olduğu bulunmuştur.

Anahtar Kelimeler: Sistemik skleroz, tırnak kapillaroskopi, modifiye Rodnan cilt skoru, sağ ventrikül strain görüntüleme

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INTRODUCTION

Systemic sclerosis (SSc) is an immunologic illness caused by fibroblast and endothelial cell dysfunction that results in excessive collagen production. Skin tightening and thickening is a hallmark of SSc. Two types of SSc are described as limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) SSc according to skin involvement. It was reported that extensive and early skin involvement is linked with poor prognosis (1,2).

Pulmonary arterial hypertension (PAH), myocardial dysfunction, conduction abnormalities, pericardial effusion, and myocardial ischemia are consequences of the cardiovascular (CV) involvement of SSc. PAH is considered as the most important CV involvement observed in SSc. Patients with SSc and PAH have a three-fold increased risk of mortality compared to patients without SSc (3). Patients with SSc should be closely monitored for PAH because it is one of the major cause of death.

Right ventricle (RV) 2-D strain imaging in echocardiography gives detailed information about ventricle function and prognosis of PAH (4,5). Strain imaging shows deterioration of myocardial function more sensitively than conventional echocardiographic parameters. Also, 2-D strain imaging gives quantitative values and helps to overcome observer dependent errors. Decreases in RV free wall strain values in PAH are associated with poor prognosis.

Nailfold capillaroscopy (NC) shows microvascular damage in SSc and is useful for detecting early disease. It is also non-invasive and gives valuable data for diagnosis of SSc (6). Because many studies have shown that NC correlates with visceral involvement in SSC, nowadays, NC has been used as a proxy marker for disease of SSc activity (7,8). The modified Rodnan skin score (mRSS), a standardized method for assessing thicknessof the skin, was used in SSc clinical trials (9,10). Previous studies have shown mRSS to be corelated with some adverse cardiac and pulmonary parameters (9). Although NC and mRSS were studied in many circumstances associated with SSc progression, limited data exists about the relations of RV function with NC and mRSS in patients without overt PAH.

In this study, we examined RV function, which was assessed with strain imaging in echocardiography, in patients with SSc who did not show overt PAH. We compared echocardiographic RV functions of patients with SSc and healthy controls. We aimed to find out the associations between mRSS, NC pattern and RV functions.

MATERIAL AND METHOD

The study was carried out with the permission of Kayseri City Hospital Ethics Committee (Date: 25.06.2020, Decision No: 2020/97). The written consents were obtained from the patients. The study complied with the ethical principles of Helsinki Declaration.

Thirty two patients with SSc, being followed in the rheumatology and cardiology clinics and twenty healthy controls were included in the study. The study's data collection was done in the period from May 1, 2020 to April 1, 2021.

2013 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for SSc) were used to classify as SSc. The entire population's sociodemographic characteristics, such as age, sex, body mass index, and smoking habits, were recorded. A rheumatology specialist examined all patients for digital ulcers, Raynaud's phenomenon, as well as the severity of skin involvement. The standard method defined in Khanna D's study was used to calculate mRss for each patient (11). LeRoy and Medsger's classification criteria were also used to categorize dcSSc and lcSSc (12).

Patients with overlapping syndromes with SSc such as rheumatoid arthritis, and also patients with any other chronic disease were excluded.

NC was carried out using a videocapilleroscopy at magnifications 200x. The NCs were categorized into four groups based on the following criteria:

1. Dimensions, shape, and density greater than 7 mm are considered normal (early pattern).
2. An early pattern with large size, density greater than 7 mm, and the presence or absence of haemorrhages (active and early pattern).
3. Active pattern; lower density (4-6 mm), patchy giant pattern, capillary absence, and some abnormal shapes (active and late pattern).
4. Late pattern; low density (3mm), frequent abnormal shapes, but no giant capillaries (late pattern) (13).

Echocardiography

All participants underwent echocardiographic examinations by a cardiology specialist. All measurements were performed with Philips Epic 7 (Philips, Amsterdam, Netherlands) echocardiography machine and X5-1 TTE probes. Left lateral position and apical 2 and 4 cavity images were obtained from the parasternal short and long axes. M-mode was used to measure the left ventricular (LV) end-sistolic and end-diastolic diameters from the parasternal long axis (at the mitral chordal level perpendicular to the long axis of the ventricle). Posterior and interventricular septal wall diastolic diamater, internal dimension of the LV, left atrial area, peak A and E waves of mitral inflow, and lateral and septal peak E' of the mitral annulus were all assessed.

Right Ventricle Functions

The echo parameters were measured considering the American Society of Echocardiography's guidelines (14). The tricuspid valve annulus level is used to calculate the RV free wall's tissue Doppler imaging value. A', E' and

S' waves were asssessed, and the E/A and E/ E' ratios were computed. Tricuspid annular plane systolic movement (TAPSE) was measured in an apical four-chamber view of the lateral tricuspid annulus using M-mode imaging. The systolic pulmonary arterial pressure (sPAP) was calculated using continuous wave Doppler by adding the estimated right atrial pressure and the pressure value of Bernoulli's equation of tricuspidal regurgitation jet velocity. Also, pulmonary valve stenosis was excluded (14).

Isovolumetric contraction velocity (IVV) divided by acceleration time (AT) yielded right ventricular isovolumic acceleration (IVA). IVV was defined as the peak myocardial speed during isovolumic contraction from the lateral tricuspid annulus. The time it takes to reach top speed is referred to as "AT" (14)

The RV end-diastolic area (RVADA) and RV end-systolic area (RVASA) were assessed from an apical 4-chamber view. The RV-fractional area change (RVFAC) was calculated as follows: RVFAC (percentage)=RVADA-RVASA/RVADA x 100.

Using the Philips QLAB 9.0 program, speckle tracking analysis of the RV was acquired from the apical four-chamber view images. At the end of systole, the endocardial border of the RV free wall was drawn manually and changed automatically to comprise the complete myocardium. To adjust the thickness of the myocardium, the physician manually changed the region of interest. The RV longitudinal strain was estimated as the average of the three segments recorded in the basal, mid-ventricular, and apical segments of the RV free wall. The fraction of myocardial shortening relative to the baseline length is referred to as longitudinal strain. Their values are negative, and lower strain values show more shortening.

Statistical Analysis

The data was analyzed using the IBM SPSS Statistics 21.0. The mean and standard deviation are used to express continuous variables. To determine the normality of a continuous variable's distribution, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used. To compare continuous variables between groups, the Mann-Whitney U test or the Student's t test were used. The Chi-square test was also used to analyze categorical variables. Univariate linear regression analysis was used for demostarating the association between RV free wall mean strain to mRSS, duration to first symptom and duration to first diagnosis As statistically significant, $p<0.05$ values were accepted.

RESULTS

The characteristics of the participants were shown in **Table 1**. There was no difference in terms of age between the SSc and healthy controls (51.6±11.3, 47.9±7.4, p=0.137 respectively). BMI was similar in groups (27.5±4.6, 25.3±4.1, p=0.062). Heart rate, systolic and diastolic blood pressure were statistically similar in the SSc and healthy controls (p=0.564, p=0.649 and p=0.398 respectively). CRP and WBC levels were found to be higher in the SSc group (p=0.020 and P=0.007). AST, ALT, Hgb and Plt levels were similar in two groups (p=0.920, p=0.918, p=0.115 and p=0.733, respectively).

Table 1. Clinical characteristics of the participants

	Systemic sclerosis patients (n=32)	Control group (n=20)	p value
Age	51.6±11.3	47.9±7.4	0.137
Female sex	27 (%84)	11 (%55)	0.318
BMI (kg/m2)	27.5±4.6	25.3±4.1	0.102
Crp (mg/dl)	4.24±4.27	1.79±2.02	**0.020**
AST (mg/dl)	19.9±7.1	20.1±6.1	0.920
ALT (mg/dl)	18.3±11.1	16.3±6.5	0.918
WBC $\times 10^9$/L	7306±1813	5908±1660	**0.007**
HGB (gr/dl)	13.3±1.5	13.9±1.2	0.115
PLT $\times 10^9$/L	285600±75085	277200±102503	0.733
Systolic blood pressure, (mmHg)	122.6±14.7	120.8±12.1	0.649
Diastolic blood pressure, (mmHg)	75.9±6.5	74.9±7.0	0.398
Heart rate (beats/min)	72.75±7.5	74.9 ±9.0	0.564
Limited cutaneous systemic sclerosis, n, %	16, %50		
Modified rodnan score	15.1±11.0		
Capillaroscopic pattern 1	10 (%31.2)		
Capillaroscopic pattern 2	9 (%28.1)		
Capillaroscopic pattern 3	2 (% 6.2)		
Capillaroscopic pattern 4	11 (% 34.3)		
Severity index of raynoud phenome	4.38±2.21		
Duration to first diagnosis, (year)	5.0±4.26		
Duration to first complain, (year)	12.0±10.2		

BMI: Body mass index, Crp: C reactive protein, AST: aspartate aminotransferase, ALT: alanine aminotransferase,WBC: White blood cells, PLT: platelet

Half of the SSc patients were limited cutaneous systemic sclerosis type. The mean mRSS was 15.1±11.0. Numbers of patients according to capilloroscopic pattern 1, 2, 3 and 4 were 10, 9, 2 and 11, respectively. The Raynaud phenomen was first seen at the age of 40.9±14.0 and the severity index of the Raynaud phenomen was 3.96±1.89. The mean duration to diagnosis of SSc was 12.0±10.2 years ago and the mean duration to first symptom was 5.0±4.26 years ago.

Table 2 shows the echocardiographic parameters of the patients with SSc and healthy controls. LV structural and functional parameters were not statistically different in the two groups. sPAP was statistically higher in the SSc group (26.4±3.2 vs 30.8±3.6 mmHg, p=0.001). TAPSE and AT were found to be lower in the SSc group (p=0.003). IVA and IVV were significantly higher in healthy controls (p<0,001 for all). The E/A ratio was higher in the SSc group but not statistically significant (p=0.149). The SSc group had statistically significant lower basal S', RV free wall basal strain, RV free wall apical strain and RV free wall mean strain values (p=0.019, p=0.023, P<0.001and P<0.001, respectively). **Figure 1** shows that strain value of RV free wall segments and RV free wall mean strain in the groups. RVEDA and RVESA were found higher in the SSc group but not statisically significant (p=0.057, p=0.053, respectively). RVFAC was lower in the SSc group but not statistically significant (p=0.279).

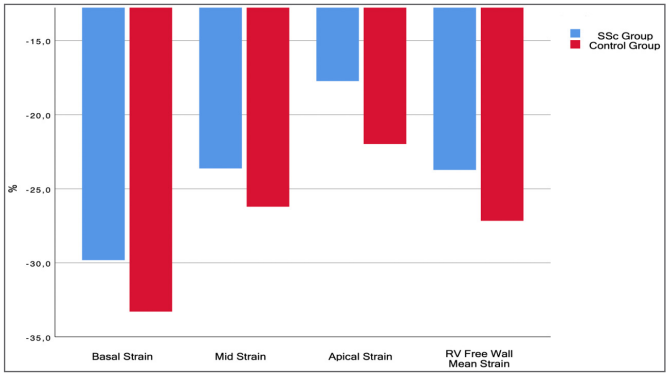

Figure 1. Strain value of right ventricle free wall segments and right ventricle free wall mean strain in the groups. RV: Right ventricle

Table 2. Comparision of echocardiographic parameters between groups

	Systemic sclerosis patients	Control group	p value
LV structure and function function			
End-diastolic diameter (mm)	4.37±0.66	4.41±0.33	0.824
End- systolic diameter (mm)	2.92± 0.59	2.88±0.30	0.768
IVSD (mm)	0.99±0.10	1.0±0.09	0.460
PWD (mm)	0.92±0.09	0.97±0.88	0.069
LVEF, %	66.8±5.1	67.2±6.0	0.534
Mitral E wave, (cm/s)	0.68±0.11	0.66±0.12	0.583
Mitral A wave (cm/s)	0.56±0.10	0.54±0.09	0.622
E/A	1.27±0.34	1.25±0.29	0.827
Deceralation time, (msec)	163.6±20.5	171.3±17.7	0.173
Tissue Doppler velocities			
E' wave (cm/s)	10.9±2.04	11.3±2.32	0.488
A' wave (cm/s)	8.46±2.35	9.00±1.07	0.344
S' wave (cm/s)	13.3±2.61	14.5±2.37	0.131
E/E'	6.36±0.95	6.03±1.32	0.290
RV Structure and Function			
sPAP (mmHg)	30.8±3.67	26.4±3.2	**< 0.001**
TAPSE (mm)	2.52±0.21	2.71±0.20	**0.003**
Pulmonary accerelation time (msec)	106.1±13.4	120.1±10.0	**< 0.001**
IVA (m/sec2)	3.29±0.80	4.34±0.68	**< 0.001**
IVV (m/sec)	12.49±2.40	14.93±2.07	**< 0.001**
AT (msec)	38.75±5.86	34.6±3.71	**0.007**
Tricuspid E wave (cm/s)	0.65±0.14	0.55±0.08	**0.014**
Tricuspid A wave (cm/s)	0.48±0.10	0.46±0.10	0.476
E/A	1.36±0.27	1.24±0.28	0.149
Decerelation time (msec)	157.2 ±43.9	166.6±28.2	0.401
Basal S' (cm/sec)	12.5±3.27	14.9±2.29	**0.019**
Basal strain, %	-29.8±6.00	-33.2±3.47	**0.023**
Mid strain, %	-23.6±5.33	-26.2±2.77	0.051
Apical strain, %	-17.7±4.58	-21.9±2.80	**< 0.001**
RV free wall mean strain, %	-23.7±3.83	-27.1±1.70	**< 0.001**
RVADA mm2	25.3±6.98	22.0±3.56	0.057
RVASA mm2	13.8±5.17	11.3±2.29	0.053
RVFAC, %	46.2±7.99	48.4±4.77	0.279

LV left ventricle, IVSD: intraventricular septum diameter, PWD: posterior wall diameter, LVEF: left ventricular ejection fraction, RV: right ventricle, sPAP: systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic movement, IVA: isovolumic acceleration, IVV: isovolumic velocity, RVADA: right ventricle end-diastolic area, RVASA: Right ventricle end-systolic area, RVFAC: Right ventricle fractional area change.

SSc patients were divided into two groups considering the capillaroscopic pattern 1,2 (SSc-1) and capillaroscopic pattern 3,4 (SSc-2). **Table 3** show comparision of systolic pulmonary artery pressure and right ventricle function between SSc-1 and SSc-2 groups. sPAP is significantly higher in the SSc-1 group than in the SSc-2 group (32.5±3.1 , 29.6±3.6 , p=0.025). The SSc-1 group had significantly higher TAPSE, IVA, and RV free wall mean strain (p=0.002, p=0.005, and p<0.001, respectively) compared to the SSc-2 group. **Figure 2** show RV free wall mean strain values according to capilloroscopic patterns. There was no statisically difference in terms of RVEDA, RVESA and RVFAC between SSc-1 and SSc-2.

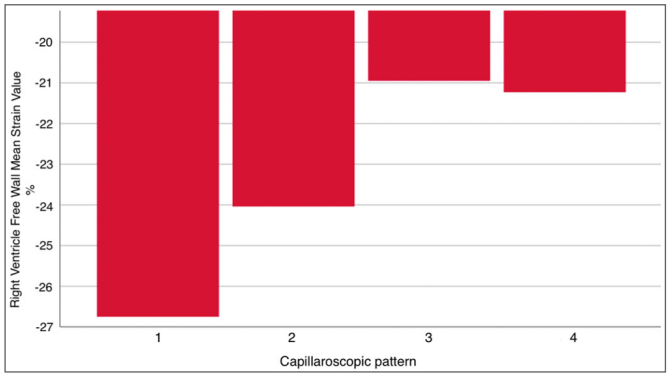

Figure 2. Right ventricle free wall mean strain values according to capilloroscopic patterns

Table 3. Comparision of systolic pulmonary artery pressure and right ventricle function between SSc-1 and SSc-2 groups

	SSc-1 (capillaroscopic pattern:1,2) n: 19	SSc-2 (capillaroscopic pattern:3,4) n:13	p values
sPAP (mmHg)	29.6±3.6	32.5±3.1	**0.025**
TAPSE	2.61±0.19	2.39±0.15	**0.002**
IVA	3.61±0.72	2.83±0.71	**0.005**
RV free wall mean strain, %	-25.4±3.66	-21.1±2.45	**< 0.001**
RVEDA	24.7±6.7	26.1±7.5	0.577
RVESA	13.1±5.2	14.7±5.1	0.426
RVFAC	47.7±8.5	44.1±6.9	0.222

RV: right ventricle, sPAP: systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic movement, IVA: isovolumic acceleration , RVADA: right ventricle end-diastolic area, RVASA: Right ventricle end-systolic area, RVFAC: Right ventricle fractional area change.

In the SSc group, the results of univariant linear regression analysis demostrating the association of mRSS, duration to first diagnosis, duration to first complain and type of SSc with RV free wall mean strain are shown in **Table 4**. In the SSc group, mRSS was significantly associated with RV free wall mean strain (p=0.007, respectively). Duration to first symptom, duration to first diagnosis and type of SSc were not associated with RV free wall strain. (p=0.053, p=0.099 and p=0.703)

Table 4. Univariate linear regression analysis demonstrating the association of RV mean free wall strain

	β	SE	95% CL	Adjusted R2	p
mRSS	0.163	0.056	0.048 to 0.278	0.192	0.007
Duration to first symptom	0.129	0.064	-0.002 to 0.259	0.090	0.053
Duration to first diagnosis	0.267	0.157	-0.053 to 0.587	0.058	0.099
SSc type	0.533	1.385	-2.296 to 3.361	-0.028	0.703

mRSS: modified Rodnan skin score, SSc: systemic sclerosis

DISCUSSION

In this study, three main findings were listed as: firstly, SSc patients have larger RV sizes, poorer RV function, and higher sPAP levels than the control group, 2. These outcomes are associated with mRSS, 3. Patients with capillaroscopic patterns 3 and 4 had higher sPAP and poorer RV function.

In SSc patients, the presence of PAH and RV dysfunction is associated with a poor prognosis. Determining clinical and echocardiographic predictors of PAH and RV dysfunction in SSc patients is critical for early diagnosis and treatment. According to the ESC guidelines, > 25 mmHg mean PAP with right heart catheterization is accepted as PAH (15). But the pathophysiologic changes occurred before the development of the 25 mmHg mean PAP (16). In SSc patients, late diagnosis PAH had a worse prognosis (17). So, early treatment and early diagnosis of vulnerable SSc patients for PAH is important for improving the prognosis of patients with SSc.

Some echocardiographic imaging techniques and calculations are used for early determination of deterioration of RV functions. In this study, we evaluated tissue Doppler imaging, RV free wall strain imaging, IVV, and IVA. They are valuable markers for the assessment of RV systolic function. IVV reflects RV contractility, which is assessed invasively (18). Also, IVV was found to be a marker for predicting poor prognosis in PAH (19). In this study, IVV and IVA were lower in SSc patients. So, it could be considered that RV systolic deterioration begins before the beginning of overt PAH.

In this study, RV sizes were higher in the SSc group. Bratis et al. (20) found lower RV sizes in asymptomatic SSc patients. They considered that lower RV sizes were associated with higher heart rates. In our study, the heart rates of the two groups were not different. Because echocardiographic parameters were not established in Bratis K's study, real sPAP values were not known. In our study, however, sPAP values were in the normal range, but they were higher in the SSc group. Higher sPAP and similar heart rate could be reasons for the higher RV volumes compared to the control group. Also, these factors may explain the different results compared to Bratis K's findings.

Strain values give crucial data about systolic function of the myocardium, prognosis and disease severity in many conditions such as SLE, PAH, sarcoidosis, and SSc (21,22). Deterioration of strain can be used as an early predictor for some diseases' cardiac involvement (21,22). Kusunose et al. (23) showed that decreasing strain in sarcoidosis patients without cardiac involvement is associated with adverse effects of sarcoidosis. In our study, we found a reduction in RV free wall strain in SSc patients. Also, this deterioration was associated with sPAP. Although in our study, we excluded patients with over sPAP 40 mmHg, slightly elevated sPAP could be important for SSc patients.

The mRSS was shown to predict disease severity, activity and mortality (24). Clements et al. (25) mRSS was associated with heart involvement. But they did not define heart involvement in detail. So, the relationship between PAH, RV function echo parameters, and mRSS has not been studied adequately previously. In our study, mRSS was associated with sPAP, TAPSE, IVV, IVA, and the global RV strains RVEDA, RVESA, and RVFAC. These data show that fibrotic process deposition occurs together with the skin and the heart. However, skin thickness begins to increase after the initial disease, and with the progression of SSc skin thickness can vary. Sometimes skin thickness progresses to a peak, then regresses or slowly continues to progress. We can consider that the intermediate age of disease is accompanied by thick skin. Because we excluded patients with over 40 mmHg sPAP, mRSS can be a good parameter for predicting RV function and sPAP for SSc patients without overt PAH.

NC is a noninvasive method which is a useful tool for distinguishing the etiology of raynoud phenomena, whether secondary to SSc or not. Morphologic changes in nailfold associated with organ involvement. Riccieri et al. (26) reported a link between mean PAP and NC score. In our study, even though patients had no overt PAH, severe capillaroscopic pattern could predict higher sPAP and worse RV function.

SSc is classically divided into two groups: diffuse and limited cutaneous SSc. However, the diffuse cutaneous type is accompanied by more organ involvement (interstitial lung disease, gastrointestinal diseases, or renal disease). PAH has the same incidence in diffuse cutaneous and limited cutaneous types. In our study, we did not find differences in sPAP, RV volumes and functions in two groups. Also, the correlation of sPAP and mRSS, capillaroscopic pattern continued. A high mRSS score and capillorscopic pattern 3, 4 may indicate a high risk of PAH development.

This study has several limitations. PAP values and RV functions were measured by using echocardiography. Invasive measurement of PAP can give more reliable data. Cardiac MR gives detailed information about the function and sclerosis of the RV. A relatively small sample size is another limitation. The study designed with a larger sample size may help to understand how PAP and RV function do change in SSC patients without overt PAH.

CONCLUSION

In this study, we demonstrated that early deterioration of sPAP and RV functions in SSc patients without overt PAH. Also, high scores of mRSS and abnormal capilloroscopic pattern were associated with worse RV function.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Kayseri City Hospital Ethics Committee (Date: 25.06.2020, Decision No: 2020/97).

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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Work disability and factors associated with work productivity loss in ankylosing spondylitis

Ankilozan spondilitte iş engelliliği ve iş verimliliği kaybı ile ilişkili faktörler

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ABSTRACT

Objective: To assess the rate of employment and factors associated with work productivity loss in Ankylosing spondylitis (AS).

Material and Method: This study was designed as a cross-sectional study that included 70 patients with AS. Fatigue, morning stiffness, and pain were assessed on a visual analogue scale (VAS). Disease activity, physical function, quality of life, anxiety and depression were assessed using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Quality of Life (ASQoL), and Hospital Anxiety and Depression Scale (HAD), respectively. We used the Work Productivity and Activity Impairment Questionnaire (WPAI) to determine the impact of AS on work productivity. The clinical and demographic characteristics of working and not working patients were compared. Factors associated with absenteeism and presenteeism were assessed using univariable logistic and linear regression analysis, respectively.

Results: Mean age of 70 patients (24 women, 46 men) with AS was 42.96 ± 7.83 years. The percentages of working patients was 65.7%. The percentages of presenteeism and absenteeism were 60.21% and 37%, respectively. The clinical and demographic characteristics of working and not working patients were not different (p>0.05). Absenteeism was associated with low educational level (odds ratio [OR]=7.636; 95% confidence interval [CI]=1.782-32.723; p=0.006), morning stiffness (OR=1.545; 95% CI=1.118-2.134; p=0.008), BASDAI (OR=1.645; 95% CI=1.088-2.489; p=0.018), and ASQoL (OR=1.392; 95% CI=1.094-1.772; p=0.007). In the linear regression model, BASDAI (β=8.394; 95% CI=5.570-11.217; p<0.001), fatigue (β=6.656; 95% CI=3.015-10.298; p=0.001), pain (β=6.011; 95% CI=2.669-9.352; p=0.001), morning stiffness (β=6.108; 95% CI=3.949-8.268; p<0.001), BASFI (β=5.703; 95% CI=2.701-8.705; p< 0.001), ASQoL (β=3.209; 95% CI=1.781-4.637; p<0.001), and HAD-A (β=2.095; 95% CI=0.243-3.947; p=0.027) were significantly associated with presenteeism.

Conclusion: The percentage of absenteeism and presenteeism were high in working AS patients. Absenteeism was associated with low educational level, morning stiffness, and disease activity. Presenteeism was associated with patient-reported outcomes, including fatigue, pain, morning stiffness, function, anxiety, quality of life, and disease activity.

Keywords: Ankylosing spondylitis, absenteeism, presenteeism, patient-reported outcomes

ÖZ

Amaç: Ankilozan spondilitte (AS) çalışma durumunu ve iş verimliliği kaybıyla ilişkili faktörleri değerlendirmek.

Gereç ve Yöntem: Bu kesitsel çalışmaya 70 AS tanılı hasta dahil edildi.Yorgunluk, sabah tutukluğu ve ağrı visual analog skala (VAS) kullanılarak değerlendirildi. Hastalık aktivitesi, fiziksel fonksiyon, yaşam kalitesi, anksiyete ve depresyon sırasıyla Bath Ankilozan Spondilit Hastalık Aktivite İndeksi (BASDAI), Bath Ankilozan Spondilit Fonksiyonel İndeksi (BASFI), Ankilozan Spondilit Yaşam Kalitesi (ASQoL), Hastane Anksiyete ve Depresyonu (HAD) ölçeği kullanılarak değerlendirildi. AS'nin iş verimliliği üzerindeki etkisini belirlemek için İş Verimliliği ve Faaliyet Bozulması Anketini (WPAI) kullanıldı. Çalışan ve çalışmayan hastaların klinik ve demografik özellikleri karşılaştırıldı. Absenteeism ve presenteeism ile ilişkili faktörler, sırasıyla univariable lojistik ve doğrusal regresyon analizi kullanılarak değerlendirildi.

Bulgular: AS'li 70 hastanın (24 kadın, 46 erkek) yaş ortalaması 42,96 ± 7,83 yıl idi. Çalışan hasta oranı %65,7 idi. Presenteeism ve absenteeism oranları sırasıyla %60,21 ve %37'dir. Çalışan ve çalışmayan hastaların klinik ve demografik özellikleri farklı değildi (p>0.05). Absenteeism, düşük eğitim seviyesi (odds ratio [OR]=7,636; 95% confidence interval [CI]=1,782-32,723; p=0,006), sabah tutukluğu (OR=1,545; 95% CI=1,118-2,134; p=0,008), BASDAI (OR=1,645; 95% CI=1,088-2,489; p=0,018), ve ASQoL (OR=1,392; 95% CI=1,094-1,772; p=0,007) ile ilişkiliydi. Univariable linear regression modelinde, presenteeism BASDAI (β=8,394; 95% CI=5,570-11,217; p<0,001), yorgunluk (β=6,656; 95% CI=3,015-10,298; p=0,001), ağrı (β=6,011; 95% CI=2,669-9,352; p=0,001), sabah tutukluğu (β=6,108; 95% CI=3,949-8,268; p<0,001), BASFI (β=5,703; 95% CI=2,701-8,705; p< 0,001), ASQoL (β=3,209; 95% CI=1,781-4,637; p<0,001), ve anksiyete (β=2,095; 95% CI=0,243-3,947; p=0,027) ile ilişkili bulundu.

Sonuç: Çalışan AS hastalarında absenteeism ve presenteeism yüzdesi yüksekti. Absenteeism, düşük eğitim düzeyi, sabah tutukluğu, hastalık aktivitesi ile ilişkiliydi. Presenteeism, yorgunluk, ağrı, sabah tutukluğu, fonksiyon, anksiyete, yaşam kalitesi ve hastalık aktivitesi dahil olmak üzere hasta tarafından bildirilen sonuçlarla ilişkiliydi.

Anahtar Kelimeler: Ankilozan spondilit, absenteeism, presenteeism

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INTRODUCTION

Ankylosing spondylitis (AS) is a chronic disease with axial inflammation (1), which not only impairs physical function and quality of life but also causes a significant economic burden (2-4). Pain, morning stiffness, fatigue, sleep quality, and spinal mobility affect function and quality of life in AS (5).

AS typically affects people of working age, with an impact on work productivity as well (6). It has been reported that the rate of quitting work in AS is three times higher than in the general population, with 20% in ten years and 30% in 20 years (7). Thirty-one per cent of the patients reported being work-disabled, and 15% reported a reduction in working hours or changing jobs due to AS (8).

Work disability is one of the key patient-reported outcomes, which includes reduced working hours, job loss, and early retirement due to disease (8,9). Work productivity loss includes reduced on-the-job effectiveness (presenteeism) as well as work time missed (absenteeism) due to illness (10). Work disability in AS seems to be associated with age, physical function, disease duration, disease activity, depression, physically demanding jobs, and lower educational levels (9,11,12), and the effect of drug treatments on work disability has been demonstrated (13).

Work disability and productivity are important patient-reported outcome measures for assessing the impact of AS, and prevention of work disability is an important goal of treatment. Therefore, it is essential to assess the impairment at work and be aware of its associated factors in AS. The present study aimed to identify the employment status of AS patients, differences among working and not working patients, and factors associated with presenteeism and absenteeism in AS.

MATERIAL AND METHOD

The study was carried out with the permission of Marmara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 11.08.2018, Decision No: 09.2018.650). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Informed consent was obtained from all the participants.

Study Design and Patients

This cross-sectional study included patients with AS who are members of the Ankylosing Spondylitis Patient Society (ASHAD) web page. The questionnaire prepared for the study was sent to the patients via e-mail, and data was collected by this self-administered questionnaire.

Demographic and Clinical Variables

Data on age, sex, educational status, disease duration (years), age at diagnosis, and body mass index (BMI) were collected. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used to assess disease activity.

Patient-Reported Outcome Measures

Fatigue, pain, morning stiffness, and patient global assessment (PtGA) were evaluated separately with a visual analogue scale (VAS). Psychological well-being was evaluated using the Hospital Anxiety and Depression Scale for Anxiety (HAD-A) and Depression (HAD-D) (14). The physical disability and health-related quality of life were assessed using the Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Quality of Life (ASQOL), respectively (15, 16).

Working status and work productivity

We classified the patients according to their working status as employed (working full-time or part-time) or not working. Patients were asked whether they had reduced working hours, changed jobs, quit their job, or retired early due to AS. We used the Work Productivity and Activity Impairment questionnaire (WPAI) to determine work productivity (17,18). WPAI gives four different domains based on six questions. The results are expressed as percentages, with higher percentages indicating greater degradation. We evaluated the percentage of presenteeism and the presence of absenteeism.

Statistical Analysis

Variables were given as frequency, percentages, mean, standard deviation, median, minimum, maximum, 25th and 75th percentiles. Comparisons of groups were performed using the Chi-square and Fisher's exact tests for categorical variables and the Mann-Whitney U test for continuous variables. Univariable logistic and linear regression analyses were used to determine the associations of absenteeism and presenteeism (dependent variables) with demographic and clinical features and patient-reported outcomes, including fatigue, pain, morning stiffness, HAD-A, HAD-D, ASQoL, and BASFI, respectively. Statistical significance was set at $p<0.05$. SPSS Statistics (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) was used for statistical analysis.

RESULTS

The mean age of 70 patients (24 women, 46 men) with AS was 42.96±7.83 years. The mean age at diagnosis was 31.75±9.41, and disease duration was 11.27±9.11 years.

According to working status, 65.7% of the patients were working. Patients stated that 34.3% of them quit jobs, 31.4% changed jobs, 48.6% reduced their working hours, and 10% retired early due to AS. The mean percentage of presenteeism was 60.21±26.11. The percentage of the patient with absenteeism was 37%.

Comparisons of the characteristics of working and not working AS patients are given in **Table 1.** The age, gender, BMI, educational level, age at diagnosis, disease duration, BASDAI, BASFI, ASQoL, fatigue, pain, morning stiffness, PtGA, HAD-A, and HAD-D were similar between working and not working patients (p>0.05).

Table 1. Comparison of working and not working patients with AS

	Not Working N = 24	Working N = 46	P value
Age, median (25-75%)	43 (37-53)	41 (36-47)	0.099
Male, n (%)	13 (54.2)	33 (71.7)	0.142
Body mass index (kg/m2), median (25-75%)	26.1 (22.7-28.3)	26 (24.2-28.2)	0.592
Educational level, n (%)			0.748
Primary school	2 (8.3)	4 (8.7)	
Middle school	2 (8.3)	7 (15.2)	
High school	10 (41.7)	14 (30.4)	
University	10 (41.7)	21 (45.7)	
Disease duration (months), median (25-75%)	12 (5-23)	8 (4-13)	0.130
Age at diagnosis, median (25-75%)	31 (23-42)	31 (26.5-38)	0.729
BASDAI, median (25-75%)	6.9 (5.6-8.7)	7.8 (5.5-8.4)	0.512
BASFI, median (25-75%)	6 (3.6-7.7)	5 (3.9-7.1)	0.729
ASQoL, median (25-75%)	15 (11-16)	14 (10-17)	0.985
VAS PtGA, median (25-75%)	4 (2-5)	5 (3-5.5)	0.073
VAS fatigue, median (25-75%)	8 (7-9)	8 (6.5-8)	0.442
VAS morning stiffness, median (25-75%)	6 (2-8)	7 (5-9)	0.222
VAS pain, median (25-75%)	8 (6-9)	8 (7-9)	0.409
HAD anxiety, median (25-75%)	16 (9-17)	13 (9.5-15)	0.339
HAD Depression, median (25-75%)	12 (8-16)	10 (7.5-13.5)	0.244

BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; PtGA: patient global assessment; VAS: Visual Analogue Scale; HAD: Hospital Anxiety and Depression.

In working patients, absenteeism was associated with educational level (odds ratio [OR]=7.636; 95% confidence interval [CI]=1.782-32.723; p=0.006), morning stiffness (OR=1.545; 95% CI=1.118-2.134; p=0.008), BASDAI (OR=1.645; 95% CI=1.088-2.489; p=0.018), and ASQoL (OR=1.392; 95% CI=1.094-1.772; p=0.007). In the linear regression model, BASDAI (β=8.394; 95% CI=5.570-11.217; p<0.001), fatigue (β=6.656; 95% CI=3.015-10.298; p=0.001), pain (β=6.011; 95% CI=2.669-9.352; p=0.001), morning stiffness (β=6.108; 95% CI=3.949-8.268; p<0.001), BASFI (β=5.703; 95% CI=2.701-8.705; p<0.001), ASQoL (β=3.209; 95% CI=1.781-4.637; p<0.001), and HAD-A (β=2.095; 95% CI= 0.243-3.947; p=0.027) were significantly associated with presenteeism (**Table 2**). There was no difference in the percentage of presenteeism among AS patients according to gender and education level (p>0.05).

Table 2. Univariable logistic and linear regression analysis of factors associated with absenteeism and presenteeism

Variable	Logistic regression analysis Absenteeism		Linear regression analysis Presenteeism	
	OR (95% CI)	P value	Beta coefficient (95% CI)	P value
Age	0.960 (0.868-1.062)	0.427	-0.576 (-1.896-0.743)	0.383
Gender	1.714 (0.463-6.346)	0.420	-	
Body mass index	1.024 (0.836-1.253)	0.819	-0.324 (-2.982-2.335)	0.807
Educational level	7.636 (1.782-32.723)	0.006	-	
Disease duration	1.023 (0.945-1.107)	0.574	0.478 (-0.600-1.555)	0.375
Age at diagnosis	0.978 (0.912-1.050)	0.541	-0.706 (-1.607-0.195)	0.121
BASDAI	1.645 (1.088-2.489)	0.018	8.394 (5.570-11.217)	<0.001
BASFI	1.303 (0.980-1.733)	0.069	5.703 (2.701-8.705)	<0.001
ASQoL	1.392 (1.094-1.772)	0.007	3.209 (1.781-4.637)	<0.001
VAS fatigue	1.468 (0.951-2.267)	0.083	6.656 (3.015-10.298)	0.001
VAS pain	1.516 (0.989-2.324)	0.057	6.011 (2.669-9.352)	0.001
VAS morning stiffness	1.545 (1.118-2.134)	0.008	6.108 (3.949-8.268)	<0.001
HAD anxiety	1.041 (0.894-1.212)	0.606	2.095 (0.243-3.947)	0.027
HAD depression	1.113 (0.965-1.283)	0.142	1.634 (-0.030-3.299)	0.054

OR: odds ratio; CI: confidence interval; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; ASQoL: Ankylosing Spondylitis Quality of Life; VAS: Visual Analogue Scale; HAD: Hospital Anxiety and Depression. Significant P-values were presented in bold.

DISCUSSION

Because of affecting young people of working age, it is important to evaluate adverse work-related outcomes in AS. In the present study, we found high rates of absenteeism and presenteeism in AS patients. We demonstrated that work productivity is associated with patient-reported outcomes such as pain, fatigue, function, and psychological well-being, apart from sociodemographic and clinical characteristics.

In the present study, 65.7% of the patients were employed. Patients stated that 34.3% of them quit jobs, 31.4% changed jobs, 48.6% reduced their working hours, and 10% retired early due to AS. It has been reported that quitting work is three times more common in AS (7). Another study found that 31% of patients were unable to work, and 15% reduced working hours or changed their jobs due to AS (8). In another study from Turkey, 44.6% of the patients changed their job, and 24% retired early due to AS (19). The wide variation in rates of work disability reported among studies is due to methodological differences in these studies and differences in the populations included (13). The

high proportion of young, male patients and the short duration of the disease in our study may have affected these results.

On the other hand, we found that the mean percentages of presenteeism and absenteeism were 60% and 37%, respectively. A recent multicenter study with a large population reported 79% presenteeism and 19% absenteeism in patients with axial spondyloarthritis (20). Data on presenteeism and absenteeism vary widely in the literature, and the level of presenteeism seems to be higher than absenteeism (13,21,22).

In the present study, working and not working AS patients were similar in age, sex, educational level, BMI, disease, disease duration activity, and patient-reported outcomes, including fatigue, pain, morning stiffness, anxiety, depression, function, and quality of life. In previous studies, compared with full-time employment, work disability was found to be related to age, disease duration, low educational level, disease activity, physical disability, pain, fatigue, morning stiffness, anxiety, depression, older age of disease onset, decreased spinal mobility, and hip involvement (8,9,19,23). However, our study could not compare employed patients with work-disabled AS patients due to the low sample size. The not working patient group in our study also included the unemployed, retirees, and housewives.

We found that absenteeism was associated with low educational level, morning stiffness, disease activity, and quality of life. Absenteeism was reported to be correlated with disease activity and physical function in axial spondyloarthritis (21). In another study, several factors, including disease activity and function, as well as a labour-intensive job, quality of life, pain, fatigue, and sleep quality, were associated with absenteeism in axial spondyloarthritis (20). On the other hand, in a recent study, lower education, older age, female gender, and higher disease activity were related to sick leave in axial spondyloarthritis (24). The results of our study are compatible with the literature in some respects, suggesting that patient-related factors other than disease-related factors can also be determinants of absenteeism in AS.

Additionally, we determined that presenteeism was associated with disease activity and patient-reported outcomes, such as fatigue, pain, morning stiffness, anxiety, quality of life, and function in patients with AS. Similarly, presenteeism was found to be associated with patient-reported outcomes, including disease activity, physical function, quality of life, pain, fatigue, sleep disturbance, anxiety, and depression in axial spondyloarthritis (20-22,25). According to our study results, in line with the literature, presenteeism seems to be related to patient-reported outcomes rather than the socioeconomic and clinical characteristics of AS patients.

The main limitation of this study is including a small sample size. Additionally, we could not evaluate sleep quality, spinal mobility, and work type in AS patients, which can affect work productivity. Furthermore, we were unable to perform an adjusted multivariate regression analysis due to the small sample size. Considering that the disease duration may have an impact on work disability, short disease duration was another limitation of this study.

CONCLUSION

The percentage of presenteeism was higher than absenteeism, and it is associated with patient-reported outcomes, including disease activity, physical function, quality of life, pain, fatigue, morning stiffness, and anxiety in patients with AS. This highlights the importance of continuous evaluation of patient-reported outcome measures in determining the burden of AS. Multicenter prospective studies of work disability in AS patients in the Turkish population are needed, as rates and determinants of work disability may differ significantly between countries depending on socioeconomic status.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Marmara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: 09.2018.650).

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

Referee Evaluation Process: Externally peer-reviewed.

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The monocyte/high-density lipoprotein cholesterol ratio in patients with primary hypolipoproteinemia

Primer hipolipoproteinemili hastalarda monosit/yüksek yoğunluklu lipoprotein kolesterol oranı

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ABSTRACT

Aim: Hypolipoproteinemia is low blood lipid levels in adults. Primary hypolipoproteinemia due to genetic mutations is a rare condition. Studies to demonstrate the clinical significance of hypolipoproteinemia are limited. It was aimed to evaluate the clinical and laboratory characteristics of patients with primary hypolipoproteinemia and the monocyte/high-density lipoprotein (HDL) ratio in this study.

Material and Method: Eight patients with primary hypolipoproteinemia and twelve healthy control subjects were compared in terms of lipid profiles, monocyte/HDL ratios, hemogram, acute phase response tests, and liver tests.

Results: Triglycerides (TG), low-density lipoprotein (LDL), and total cholesterol (TC) levels were found to be significantly lower in the patient group than in the control group (p=0.037 and <0.001 for LDL and TC both, respectively). There was no difference between the groups in terms of HDL levels. Lipoprotein (a) (Lp(a)) levels were found to be significantly lower in the patient group compared to the control group (p=0.006). Absolute monocyte count (AMC) was found to be significantly higher in the patient group than in the control group (p=0.002). Monocyte/HDL ratios (MHR) were significantly higher in the patient group than in the control group (p=0.016). There was a negative correlation between MHR and LDL (p=0.001).

Conclusion: AMC and MHR were found higher in patients with primary hypolipoproteinemia than in the healthy control group in this study. Monocytes are involved in all stages of the progression of atherosclerotic disease. HDL is known to have a protective role in atherosclerotic diseases with its anti-inflammatory and antioxidant effects. MHR, which is an index that combines both, has been shown to be a prognostic marker in cardiovascular diseases. This study is the first to investigate MHR in primary hypolipoproteinemia patients. Despite the small sample size and the heterogeneous nature of the patients included high AMC and MHR levels are important findings of the current study. Although patients with hypolipoproteinemia are attributed to a low risk for atherosclerotic diseases, high AMC and MHR are a warning that these patients should be followed carefully due to changes in lipid redistribution in terms of the risk of atherosclerotic disease.

Keywords: Hypolipoproteinemias, hypobetalipoproteinemias, lipoprotein(a), monocytes, non-alcoholic fatty liver disease

ÖZ

Amaç: Hipolipoproteinemi erişkinlerde kan lipid düzeylerindeki düşüklüktür. Genetik mutasyonlara bağlı primer hipolipoproteinemi nadir görülen bir durumdur. Hipolipoproteineminin klinik önemini gösteren çalışmalar sınırlıdır. Bu çalışmada primer hipolipoproteinemili hastaların klinik ve laboratuvar özelliklerinin ve monosit/yüksek yoğunluklu lipoprotein (HDL) oranının değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Primer hipolipoproteinemili sekiz hasta ile on iki sağlıklı kontrol grubunun lipid profilleri, monosit/HDL oranları, hemogram, akut faz yanıt testleri ve karaciğer testleri karşılaştırıldı.

Bulgular: Trigliserid (TG), düşük yoğunluklu lipoprotein (LDL) ve total kolesterol (TK) düzeyleri hasta grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (sırasıyla p=0,037 ve LDL ve TK'nın her ikisi için <0,001). HDL düzeyleri açısından gruplar arasında fark yoktu. Lipoprotein (a) (Lp(a)) düzeyleri hasta grubunda kontrol grubuna göre anlamlı derecede düşük bulundu (p=0,006). Absolü monosit sayısı (AMS) hasta grubunda kontrol grubuna göre anlamlı olarak yüksek bulundu (p=0,002). Monosit/HDL oranları (MHO) hasta grubunda kontrol grubuna göre anlamlı derecede yüksekti (p=0,016). MHO ile LDL arasında negatif korelasyon saptandı (p=0,001).

Sonuç: Bu çalışmada primer hipolipoproteinemili hastalarda AMS ve MHO sağlıklı kontrol grubuna göre daha yüksek bulundu. Monositler, aterosklerotik hastalığın ilerlemesinin tüm aşamalarında yer alır. HDL'nin antiinflamatuar ve antioksidan etkileri ile aterosklerotik hastalıklarda koruyucu rolü olduğu bilinmektedir. Her ikisini birleştiren bir indeks olan MHR'nin kardiyovasküler hastalıklarda prognostik bir belirteç olduğu gösterilmiştir. Bilindiği kadarıyla bu çalışma, primer hipolipoproteinemi hastalarında MHO'yu araştıran ilk çalışmadır. Küçük örneklem büyüklüğüne ve dahil edilen hastaların heterojen doğasına rağmen yüksek AMS ve MHO düzeyleri mevcut çalışmanın en önemli bulgularıdır. Hipolipoproteinemili hastalara aterosklerotik hastalıklar için düşük risk atfedilmesine rağmen, yüksek AMS ve MHO, aterosklerotik hastalık riski açısından lipid redistribüsyonundaki değişiklikler nedeniyle bu hastaların dikkatle izlenmesi gerektiğine dair bir uyarı niteliğindedir.

Anahtar Kelimeler: Hipolipoproteinemiler, hipobetalipoproteinemiler, lipoprotein(a), monositler, non alkolik yağlı karaciğer hastalığı

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INTRODUCTION

Hypolipoproteinemia (hypolipidemia or hypocholesterolemia) is low blood lipid levels in adults, usually detected during routine lipid profile screening. Although it is not very common, it usually occurs due to secondary causes. Causes of secondary hypolipoproteinemia include solid and hematological malignancies, infections, critical diseases like sepsis or other conditions requiring hospitalization in the intensive care unit, malnutrition and malabsorption, liver parenchymal diseases, neuropsychiatric diseases, and thyrotoxicosis (1). Also, there are genetic conditions that cause low cholesterol. The hereditary causes of primary hypolipoproteinemia are genetic mutations in cholesterol absorption, biosynthesis, or metabolism.

The causes of hereditary hypolipoproteinemia include mainly abetalipoproteinemia, familial hypobetalipoproteinemia, familial combined hypolipidemia, chylomicron retention disease, and familial hypoalphalipoproteinemia. In abetalipoproteinemia, low-density lipoprotein cholesterol (LDL-C) and apolipoprotein B (apo B) are at levels that cannot be measured. There is a mutation in the microsomal transfer protein (MTP) gene and it is inherited autosomal recessively (2). Patients are usually diagnosed with failure to thrive, steatorrhea, and conditions related to deficiencies of fat-soluble vitamins in childhood. Chylomicron retention disease is usually diagnosed in childhood with similar clinical findings. There is a mutation in the Sar1b gene, it is inherited autosomal recessively. Besides LDL-C, high-density lipoprotein cholesterol (HDL-C) is also low (3).

There are various mutations in the APOB gene in hypobetalipoproteinemia, and it has an autosomal dominant inheritance pattern. Homozygous hypobetalipoproteinemia clinically is similar to abetalipoproteinemia. Heterozygous familial hypobetalipoproteinemia is usually diagnosed during routine lipid profile screening or while investigating the etiology of non-alcoholic fatty liver disease (NAFLD) (4). LDL-C and apo B plasma concentrations are decreased in these patients. Some patients may experience deficiencies in fat-soluble vitamins (5).

In familial hypoalphalipoproteinemia, apolipoprotein A1 (apo A1) deficiency and low HDL-C are observed. While patients with low HDL due to acquired causes are at risk for early-onset coronary artery disease and cerebrovascular disease, there is not enough literature data on the risk status for atherosclerotic diseases since familial hypoalphalipoproteinemia is not a common condition (6).

Loss-of-function mutations in the angiopoietin-like protein 3 (ANGPTL3) gene are involved in familial combined hypolipidemia. It is inherited autosomal recessively, there is a decrease in lipoproteins such as very-low-density lipoprotein (VLDL) and LDL containing apo B, as well as a low level of HDL containing apo A1 (7).

In contrast to hypercholesterolemia, the causes of hypocholesterolemia and its consequences on morbidity have not been adequately studied in clinical practice. Even if primary hypolipoproteinemia is not a common condition, it is important because it must be differentiated from secondary causes and it requires follow-up in terms of pathologies that may occur in lipid metabolism related to the underlying genetic mutation. In addition, it is another important point to raise the awareness of clinicians in terms of the necessity of referral to genetic counseling in order to avoid the risks of severe fat malabsorption and related developmental, neurological, and ophthalmological complications in the children of the affected individual depending on the inheritance pattern.

Studies to demonstrate the clinical significance of hypolipoproteinemia are limited and are generally associated with fat-soluble vitamin deficiencies, atherosclerotic diseases, and NAFLD (8). Contrary to the hypercholesterolemia associated with hyperinflammation, there are no adequate studies on whether inflammation is suppressed in patients with hypolipoproteinemia. In this study, it was aimed to evaluate the clinical and laboratory characteristics of patients with primary hypolipoproteinemia and the monocyte/HDL ratio, which is one of the indicators of inflammation associated with atherosclerosis.

MATERIAL AND METHOD

The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 26.07.2022, Decision No: 35). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The study is retrospective and observational in nature. Eight patients without consanguinity, whose lipid profile was evaluated and hypolipidemia was detected in their application to the Internal Medicine outpatient clinic of our hospital were included. Secondary causes of hypolipidemia were excluded. A control group consisted of 12 healthy individuals who had applied for routine health check-ups, were age and gender matched, had no family history of hypolipidemia, had no chronic disease, had no history of using lipid-lowering therapy, and had their lipid profile measured.

Blood samples of the patients were obtained in the morning after at least 8 hours of fasting. The measurements of triglycerides (TG), HDL-C, LDL-C, total cholesterol (TC), and gamma glutamyl transferase (GGT) were made by enzymatic colorimetric method; lipoprotein (a) (Lp(a)) by particle enhanced immunoturbidimetric method; Apo A1 and Apo B, and serum C-reactive protein

(CRP) by immunoturbidimetric method; aspartate aminotransferase (AST) and alanine aminotransferase (ALT) by spectrophotometric method; alkaline phosphatase (ALP) by colorimetric method. Roche Cobas 702 device was used for these analyses. Complete blood count parameters were determined on a Sysmex XN 9100 hematology analyzer. Erythrocyte sedimentation rate (ESR) was studied in a fully automated Vacuplus ESR-120 analyzer by the Westergren method.

Statistical Analysis

Continuous data are given as mean±standard deviation. Categorical data are given as a percentage (%). The Shapiro Wilk test was used to investigate the suitability of the data for normal distribution. In the comparison of normally distributed groups, independent sample t-test analysis was used. The Mann-Whitney U test was used for the comparison of groups that did not conform to the normal distribution. Spearman correlation coefficients were calculated to determine the direction and size of the relationship (correlation) between variables, due to the small sample size. Pearson Exact Chi-Square analyzes were used in the analysis of the created cross tables. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) program was used in the analysis. A value of $p<0.05$ was accepted as a criterion for statistical significance.

RESULTS

The mean age of the patient group (n=8) was 51.9±18.6, and the mean age of the control group (n=12) was 52.8±15.5. The patient group consisted of five men and three women, and the control group consisted of five men and seven women. The groups were statistically similar in terms of age and gender.

In the comparison of the lipid profiles between the groups, TG, LDL, and TC levels were found to be significantly lower in the patient group than in the control group (p=0.037 and <0.001 for LDL and TC both, respectively). There was no difference between the groups in terms of HDL levels. Among all participants, only one person from the patient group had a high Lp(a) level, while Lp(a) levels were within the reference ranges in the other participants. Lp(a) levels were found to be significantly lower in the patient group (n=7) compared to the control group (p=0.006) when the groups were compared excluding the patient with elevated Lp(a) levels from the evaluation.

In the evaluation of hemogram parameters, no difference was found between the groups in terms of hemoglobin, red cell distribution width (RDW), white blood cell count (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), and platelet count (Plt) and mean platelet volume (MPV). Absolute monocyte count (AMC) was found to be significantly higher in the patient group than in the control group (p=0.002). When the monocyte/HDL ratios (MHR) were compared, significantly higher rates were found in the patient group than in the control group (p=0.016). There was a negative correlation between MHR and LDL (p=0.001). The acute phase response tests ESR and CRP were similar between the groups.

AST, ALT, GGT, and ALP levels were within reference ranges in both the patient and control groups, and there was no statistical difference between the groups. The median of 25 hydroxy vitamin D levels was consistent with a mild deficiency in both groups, and no significant difference was found between the groups. The comparison of the laboratory tests of the patient and control groups and the p values are given in **Table**.

Table. The demographic characteristics and laboratory parameters of the patient and control groups

	Patients (n: 8)	Healthy controls (n: 12)	p
Age (years)	51.9±18.6	52.8±15.5	0.817*
Gender			0.648
Male	5 (62%)	5 (42%)	
Female	3 (38%)	7 (58%)	
TG (mg/dl)	39.5 (32.3-99.8)	115 (100-137)	**<0.0372****
HDL (mg/dl)	46.9±22	53.8±13.3	0.537*
LDL (mg/dl)	32.9±20.8	119±26.3	**<0.001***
TC (mg/dl)	102±23.6	189±28.6	**<0.001***
Lp(a) (nmol/L)	7.4 (2.3-8.1)	21.4 (12.1-29.4)	**0.0068****
ESR (mm/h)	15±6.12	12.7±8.85	0.333*
CRP (mg/L)	1.6 (1-2)	1.85 (1.2-2.6)	0.509**
Hb (g/dl)	14 (13.8-14.2)	14.2 (13.5-15.1)	0.436**
RDW (%)	12.8 (12.1-13.9)	12.9 (12.6-13.7)	0.67**
WBC (#/uL)	7450 (5050-7880)	5450 (4780-7650)	0.757**
ANC (#/uL)	3930±1400	3910±1760	1*
ALC (#/uL)	1910±645	1910±548	0.786*
AMC (#/uL)	565±113	410±66.9	**0.0025***
MHR	11.9 (8.87-16.2)	6.94 (6.44-9.31)	**0.0168****
Platelet (10^3/uL)	253±24.4	287±83.9	0.247*
MPV (fL)	10.3±0.814	9.83±0.881	0.315*
AST (U/L)	19 (17.8-23.3)	16.5 (14.8-20.3)	0.122**
ALT (U/L)	18.5 (15.3-20.8)	19.5 (16.8-24.3)	0.671**
ALP (U/L)	74.1±19	93.9±30.1	0.063*
GGT (IU/L)	18 (17.8-26.5)	26 (15.8-38.3)	0.699**
25-OH-D (ng/ml)	21 (15.4-28.6)	23 (17.5-25.5)	0.908**

TG: triglycerides (40-205 mg/dl), HDL: high-density lipoprotein (34-82 mg/dl), LDL: low-density lipoprotein (75-172 mg/dl), TC: total cholesterol (139-249 mg/dl), Lp(a): Lipoprotein(a) (0-75 nmol/L) , ESR: erythrocyte sedimentation rate (0-20 mm/h), CRP: C-reactive protein (0-5 mg/L), Hb: hemoglobin (11.9-14.6 g/dl), RDW: red cell distribution width (12.1-14.3%), WBC: white blood cells (4490-1268/uL), ANC: absolute neutrophil count (1900-7900/uL), ALC: absolute lymphocyte count (1300-3600/uL), AMC: absolute monocyte count (200-500/uL), MHR: monocyte/HDL ratio, Plt: platelet count (173-390 10^3/uL), MPV: mean platelet volume (9.1-11.9 fL), AST: aspartate aminotransferase (0-31 U/L), ALT: alanine aminotransferase (0-33 U/L), ALP: alkaline phosphatase (0-104 U/L), GGT: gamma-glutamyl transferase (6-42 IU/L), 25-OH-D: 25-hydroxy vitamin D (25-80 ng/ml). *: Independent Sample t Test, **: Mann-Whitney U test, Statistically significant data is shown in bold

In the patient group, grade 1 hepatosteatosis was found in two patients, grade 2 in one, and grade 3 in one patient, while the liver was of normal size and echogenicity in the ultrasonographic examination of four patients. In the control group, grade 1 hepatosteatosis was detected in one patient, grade 2 in two, and grade 3 in one patient, while normal ultrasonographic findings were observed in eight. Since the number of patients was small, and the number of grades was heterogeneous a statistical comparison could not be made.

While the mean of apo A1 levels evaluated only in the patient group was 99.4±50.8 and the median 116 (25th-75th 71.8-143) (laboratory reference range 104-163 mg/dl), the mean of apo B levels was 45.9±21 and median 38 (32.3-59.9) (laboratory reference range 60-117 mg/dl). While only apo B was low in five patients and only apo A1 was low in one patient, the deficiency of both was found in two patients. Genetic test results were not evaluated in this study.

Prothrombin time (PT) and international normalized ratio (INR) measurements, which were requested to evaluate vitamin K deficiency, were found to be at normal levels in the entire patient group.

DISCUSSION

In this study, laboratory data of eight patients with primary hypolipoproteinemia were compared with those of 12 healthy control participants. Apo A1 deficiency and low HDL consistent with hypoalphalipoproteinemia were found in one of the patients with primary hypolipoproteinemia, low LDL consistent with apo B deficiency, and heterozygous familial hypobetalipoproteinemia in five patients. In the other two patients, both apo A1 and apo B deficiency and both HDL, LDL, and TG were low, so familial combined hypolipidemia was considered. Genetic tests were not included in the study since it has not been performed on all patients yet.

As expected, TG, LDL, and TC levels were found to be low in the patient group. Although apo A1 deficiency and low HDL were detected in a total of three patients and mean HDL values were lower in the patient group, no statistically significant difference was found between the groups.

When Lp(a) levels were evaluated, significant Lp(a) elevation was observed in only one patient in the patient group. When this patient was excluded from the evaluation and the groups were compared, Lp(a) levels in both groups were found to be in the normal range, but statistically significantly lower in the patient group than in the control group. Lp(a) is an LDL-like lipoprotein. It can be said that it will be affected by LDL-C levels due to the component that shares structural and functional properties with LDL in its composition, therefore it may be low in patients with hypobetalipoproteinemia (9). It is also known that anti-sense oligonucleotides used in the treatment of dyslipidemia inhibit apo B synthesis and Lp(a) levels decrease with this treatment (10). When the literature was reviewed, it was stated in the publications that there was no difference in Lp(a) levels in patients with primary hypolipoproteinemia compared to healthy control groups (11-13).

In the current study, the patient excluded in the Lp(a) evaluation was also the patient in whom TG, HDL, and LDL were all low, and both apo A1 and apo B were found to be low and whose diagnosis was considered as possible familial combined hypolipidemia. The patient's Lp(a) level was 113.4 nmol/L. It has been reported that the Lp(a) levels of patients with familial combined hypolipidemia are not affected and they are not different from controls in terms of NAFLD (13). In this patient, contrary to the theoretically expected low levels, Lp(a) was found elevated. It is also interesting that the same patient was the only one in whom grade 3 hepatosteatosis was determined in the patient group. NAFLD can be seen in patients with familial combined hypolipidemia in homozygous individuals (1). Since the genetic analysis of the patient was not performed, further interpretation could not be made.

The present study showed that AMC and MHR were higher in patients with primary hypolipoproteinemia than in the healthy control group. Monocytes are cells that have an important part in the release of pro-inflammatory and pro-oxidant cytokines. They are involved in all stages of the progression of atherosclerotic disease (14). HDL is known to have a protective role in atherosclerotic diseases with its anti-inflammatory and antioxidant effects. MHR, which is an index that combines the hematopoietic system, which represents the inflammatory component, and the metabolic profile, has come to the fore in recent publications as a prognostic marker in cardiovascular diseases (15,16). High MHR has also been shown in conditions such as metabolic syndrome and NAFLD, which are thought to be closely related to atherosclerosis (17,18). To the author's knowledge, this is the first study to investigate MHR in patients with primary hypolipoproteinemia. Despite the small sample size and the heterogeneous nature of the patients included, high AMC and MHR levels are important findings of the current study.

When the patient and control groups were evaluated in terms of NAFLD, fatty liver was detected ultrasonographically in four patients (50% and 33.3%, respectively) in both groups. However, AST, ALT, ALP,

and GGT tests were at normal levels in all participants, and no difference was found between the groups. Intergroup comparisons for NAFLD are difficult because of the small sample size and the heterogeneous grades of hepatosteatosis.

CONCLUSION

In a patient with hypolipoproteinemia, secondary causes should be excluded first. It is important to evaluate patients for diseases, infestations, and malignancies that may cause malabsorption related to the gastrointestinal tract; also in terms of symptoms such as weight loss and night sweats due to occult solid and hematological malignancies, and to perform the necessary screening tests to exclude the malignancies.

Primary hypolipoproteinemias are rare conditions. Heterozygous familial hypobetalipoproteinemia, which is the most common genetic cause of low LDL, has been reported with a frequency of 1 in 10,000 (19). However, despite this rare incidence, it is a situation that clinicians should consider in the evaluation of lipid profile results, which are frequently done in every day routine, due to the potential complications that may occur and the potential to require genetic counseling. It is important to monitor patients with heterozygous familial hypobetalipoproteinemia for NAFLD (20). Since it is known that low LDL has a protective effect against atherosclerotic diseases, it can be assumed that patients with hypobetalipoproteinemia have a low cardiovascular risk. However, since there is insufficient data on the risk of atherosclerotic disease associated with low HDL in patients with hypoalphalipoproteinemia, these patients and their families should be carefully monitored due to the autosomal dominant inheritance pattern. With the prolongation of human life, it may be beneficial to monitor patients with hypolipoproteinemia in terms of cognitive dysfunction that may occur in the future.

Although patients with hypolipoproteinemia are attributed to a low risk for atherosclerotic diseases, high AMC and MHR, which are among the most important findings of the current study, are a warning that these patients should be followed carefully due to changes in lipid redistribution in terms of the risk of atherosclerotic disease, as well as the increased risk of NAFLD. Evaluation of this condition, which has not been examined in terms of MHR, which is accepted as an atherosclerotic risk indicator, with larger patient groups will contribute to a better understanding of hypolipoproteinemia and also the effects of lipid-lowering treatments on atheroinflammation. This work is a preliminary study in this respect.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Eskisehir Osmangazi University Non-interventional Clinical Research Ethics Committee (Date: 26.07.2022, Decision No: 35).

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.

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IL-35 levels and their association with thyroid function tests in Hashimoto's thyroiditis

Hashimoto tiroiditinde IL-35 düzeyleri ve tiroid fonksiyon testleri ile ilişkisi

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ABSTRACT

Aim: In this study, it was aimed to examine interleukin-35 (IL-35) levels and their association with thyroid function tests in Hashimoto's thyroiditis (HT).

Material and Method: Included in the study were 128 individuals, between 18 and 65 years of age, who had been newly diagnosed with HT (euthyroid, subclinical hypothyroidism and overt hypothyroidism) and 38 health controls who had no known diseases or drug use.

Result: No significant difference was determined between the groups in terms of the IL-35 levels (p=0.285), although in the in-group comparisons, the IL-35 levels were found to decrease progressively towards overt hypothyroidism. In the in-group comparisons, however, a statistically significant difference was determined between the control group and the overt hypothyroidism group (550.05±411.50 vs. 369.80±253.33; p=0.046). When the patient groups were grouped according to their thyroid stimulating hormone values, a significant difference was determined between the groups with a threshold value of ≥6 uIU/ mL and those below it, in terms of the IL-35 levels (p=0.043). When two groups were created, comprising those with a threshold value of ≥10 uIU/mL and those below it, it was observed that there was a more significant difference between the groups in terms of the IL-35 levels (p=0.024). As a result of the correlation analysis performed by taking into account the controllable factors (smoking, diabetes mellitus, hypertension, and body mass index), a low-significant correlation was determined between the IL-35 levels and antithyroid peroxidase (p=0.029).

Conclusion: In this study, it was determined that the IL-35 levels, an antiinflammatory cytokine involved in HT, decreased progressively from the euthyroid patient group towards the overt hypothyroidism group.

Keywords: Hashimoto's thyroiditis, antiinflammatory cytokine, autoimmunity, IL-35

ÖZ

Amaç: Bu çalışmada Hashimoto tiroiditinde (HT) interlökin-35 (IL-35) düzeylerinin ve tiroid fonksiyon testleri ile ilişkisinin incelenmesi amaçlandı.

Gereç ve Yöntem: Çalışmaya 18-65 yaş arasında yeni HT tanısı almış (ötiroid, subklinik hipotiroidi ve aşikar hipotiroidi) 128 kişi ile bilinen herhangi bir hastalığı veya ilaç kullanımı olmayan 38 sağlık kontrolü dahil edildi.

Bulgular: IL-35 düzeyleri açısından gruplar arasında anlamlı bir fark saptanmadı (p=0,285), ancak grup içi karşılaştırmalarda IL-35 düzeylerinin aşikar hipotiroidizme doğru giderek azaldığı görüldü. Grup içi karşılaştırmalarda, kontrol grubu ile aşikar hipotiroidizm grubu arasında istatistiksel olarak anlamlı bir fark belirlendi (550,05±411,50 ve 369,80±253,33; p=0,046). Hasta grupları tiroid uyarıcı hormon değerlerine göre gruplandırıldığında, eşik değeri ≥6 uIU/ mL olan gruplar ile bunun altındakiler arasında IL-35 düzeyleri açısından anlamlı fark saptandı (p=0,043). Eşik değeri ≥10 uIU/mL olanlar ve altındakilerden oluşan iki grup oluşturulduğunda, gruplar arasında IL-35 düzeyleri açısından daha anlamlı fark olduğu görüldü (p=0,024). Kontrol edilebilir faktörler (sigara, diabetes mellitus, hipertansiyon ve vücut kitle indeksi) dikkate alınarak yapılan korelasyon analizi sonucunda IL-35 seviyeleri ile antitiroid peroksidaz arasında düşük anlamlı bir korelasyon tespit edildi (p=0,029).

Sonuç: Bu çalışmada HT'de rol oynayan bir antiinflamatuar sitokin olan IL-35 düzeylerinin ötiroid hasta grubundan aşikar hipotiroidi grubuna doğru giderek azaldığı belirlendi.

Anahtar Kelimeler: Hashimoto tiroiditi, antiinflamatuar sitokin, otoimmünite, IL-35

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INTRODUCTION

Hashimoto's thyroiditis (HT) was originally defined by Japanese surgeon Dr. Hakaru in 1912, in 4 patients with chronic thyroid disease and enlarged thyroid glands (1). HT is the most common global cause of hypothyroidism in iodine-sufficient areas (2). Furthermore, it is the most common cause of hypothyroidism in adults, with a recently increasing incidence (3,4). HT is an autoimmune thyroid disease that is characterized by diffuse lymphocytic infiltration of the thyroid gland, which is clearly revealed by the presence of circulating thyroid autoantibodies and clinical or immunological co-existence with other autoimmune diseases (5,6). This disease is also called chronic autoimmune thyroiditis (7).

Cellular and humoral immunity together play a role in the pathogenesis of HT and the activation of CD4 (+) T lymphocytes specific to thyroid antigens is thought to be the first step in its pathogenesis (8). There is a cell-cell interaction and cytokine control, which are mediated by regulatory (or suppressor) cells (CD4+CD25+Foxp3+), or so called Treg cells, in the immune system. Treg cells secrete antiinflammatory interleukin-10 (IL-10) and IL-35. HT patients have reduced or inadequately functional regulatory cells (9). Suppressor T lymphocyte dysfunction has been suggested to be important in the pathogenesis of this event and the pathology has been thought to be caused by an impairment in immune tolerance (10–12). A reduced number of cells with suppressor properties leads to a reduction in the tolerance of the organism to self-tissue antigens. As a result of this defect, suppressor CD8+ T lymphocytes cannot suppress helper CD4+ T lymphocytes. Activated helper CD4+ T lymphocytes interact with B lymphocytes and these activated B lymphocytes then produce antibodies against several thyroid antigens (13,14).

IL-35 is a newly described cytokine with immunosuppressive and antiinflammatory effects (15). In recent studies, the role of IL-35 in autoimmunity has been demonstrated and IL-35-expressing Treg cells and IL-35 were required for an optimal suppressive effect (16). In the literature review conducted herein, a limited number of studies were encountered on the relationship between IL-35 and HT.

It was therefore aimed in this study to examine the IL-35 levels and their relationship with thyroid function tests.

Considering that IL-35 is an antiinflammatory cytokine that is secreted by Treg cells, it was hypothesized that it may be involved in development of HT. Because HT is an autoimmune disease and lymphocytic infiltration of the thyroid gland is crucial in its histopathogenesis, a potential reduction in the secretion of IL-35, due to a reduced number and the function of Treg cells in HT and consequently, reduced antiinflammatory effectiveness, may be associated with lymphocytic infiltration of the thyroid gland. Thus, the role of IL-35 in autoimmunity has been demonstrated in recent studies (16), and it was shown in different experimental model systems that adaptively transferred iTR35 cells have effectively suppressed autoimmune diseases. In addition, in in vivo mice models, it has been demonstrated that, when IL-35 derivatives were obtained from natural Treg cells, these cells induced iTR35-secreting cells while suppressing T cells. It has been proven in different studies that IL-35 regulates T cell activity and the suppression of T cell proliferation following the administration of recombinant IL-35 (18).

MATERIAL AND METHOD

The study was carried out with the permission of Fatih University Clinical Researches Ethics Committee (Date: 13.09.2012, Decision No: B30-2-FTH-0200000/1099). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

This study was planned at the Department of Internal Diseases of the Turgut Ozal University Faculty of Medicine. Included in the study were 128 individuals, between 18 and 65 years of age, who had been newly diagnosed with HT (euthyroid, subclinical hypothyroidism, and overt hypothyroidism) and 38 health controls who had no known diseases or drug use.

Those who were <18 years and >65 years of age, pregnant, had congenital hypothyroidism, hypothyroidism secondary to surgery, hypothyroidism secondary to drug use, evidence of a known acute or chronic infection, malignancy, acute-chronic kidney failure, chronic liver failure or did not sign the informed consent were excluded from the study.

While establishing the diagnosis of HT, clinical findings, physical examination, positive autoantibodies [elevated antithyroglobulin (anti-TG) (>34 IU/mL) and/or antithyroid peroxidase (anti-TPO) (>115 IU/mL)], and ultrasonographic findings (heterogenous appearance of thyroid parenchyma and reduced echogenicity) were taken into consideration, and a biopsy was not considered necessary. The period that was compensated by a mildly elevated thyroid stimulating hormone (TSH) (4.5 mU/L–10 mU/L) and when minor symptoms were observed only in some patients was defined as subclinical hypothyroidism, whereas the period when the TSH were elevated above 10 mU/L and the symptoms became more prominent was defined as overt hypothyroidism.

Sociodemographic characteristics, personal histories, family histories, and smoking-drinking and other habits of the patients and healthy volunteers included in the study, as well as the presence of a systemic disease or history of drug use, were investigated.

Biochemical Analysis

For analysis of the biochemical parameters and studying the IL-35 levels of all of the participants, following a 12-h fasting, one tube of blood sample was collected from the antecubital vein before 10:00 A.M. After the collected blood samples were centrifuged at 5000 rpm, the serum and plasma samples were separated. After that, following the collection of blood samples of all of the participants, the IL-35 levels were studied at the same laboratory. Fasting blood glucose, routine biochemical work-ups, and lipid profile were measured spectrophotometrically using a Roche Cobas C501 device (Roche Group, Basel, Switzerland). Fasting insulin, free triiodothyronine (T3) (sT33), free thyroxine (T4) (sT4) and TSH levels were measured via the Enzyme Chemiluminescence Immunoassay (ECLIA) method in a Roche Cobas 6000 module device. Anti-TG and anti-TPO were studied via the ECLIA method in a Roche Cobas e 601 device.

IL-35 Measurement

Serum IL-35 levels were measured via the sandwich ELISA method using the Cusabıo Biotech commercial kit (Cusabio Technology LLC, Houston, TX, USA; Catalogue no: CSB-E13126h). The sensitivity of this method was 15.6 pg/mL, intra-assay precision was <8%, and inter-assay precision was <10%, respectively.

Ultrasonographic Examination

The HD15 PureWave Ultrasound System (Philips Medical Systems, Bothell, WA, USA) was used for ultrasonographic evaluation of the thyroid gland.

Statistical Analysis

For the statistical analyses, IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) was used. Conformity of the variables to normal distribution was examined using the Shapiro-Wilk test. Descriptive analyses were given as the mean±standard deviation for normally distributed variables and as the median and minimum-maximum values for non-normally distributed variables. Homogeneity of the groups and inter-group difference analyses were performed using one-way ANOVA and the least significant difference post-hoc test. For the inter-variable correlation analysis, the Pearson correlation tests was used. $P < 0.05$ was considered as statistically significant.

RESULT

Sociodemographic and laboratory characteristics of the groups are represented in **Table 1**; the groups were similar with regards to gender, age distribution, smoking status, number of individuals with hypertension, and diabetes mellitus (DM). The body mass index (BMI) was similar between the healthy control group and the subclinical hypothyroidism group; however, the levels in these groups significantly differed from the euthyroid and overt hypothyroidism groups (P=0.006). When the patient groups and the control group were compared, the groups were similar in terms of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride levels.

Although there was no significant difference between the groups in terms of IL-35 levels (P=0.285), it was observed in the in-group comparisons that the IL-35 levels decreased progressively towards overt hypothyroidism. In the in-group comparisons, however, a statistically significant difference was determined between the control group and the overt hypothyroidism group (550.05±411.50 vs. 369.80±253.33; P=0.046) (**Table 2**).

Table 1. Clinical demographic and laboratory findings of the study population

Variables	Control n: 38		Euthyroid n: 59		Subclinical n: 39		Overt hypothyroidism n: 30		P-value
F/M (n)	28/10 (38)		47/12 (59)		30/9 (39)		23/7 (30)		0.927
	mean	**± SD**	**mean**	**± SD**	**mean**	**± SD**	**mean**	**± SD**	
Age	39.29	12.99	39.83	11.47	40.05	11.58	36.30	11.63	0.544
BMI	27.76	3.94	25.45	3.31	27.52	4.92	25.27	4.01	0.006
Smoking (n)	2		2		2		1		0.952
HT (n)	2		9		7		5		0.363
DM (n)	3		7		6		6		0.161
	mean	**± SD**	**mean**	**± SD**	**mean**	**± SD**	**mean**	**± SD**	
TSH (uIU/mL)	1.70	0.67	1.71	0.78	7.59	1.53	27.17	27.73	0.000
ST4 (ng/dL)	1.18	0.16	1.23	0.28	1.00	0.15	0.92	0.17	0.000
ST3 (pg/mL)	2.91	0.45	2.98	0.38	2.84	0.33	2.73	0.32	0.035
TPOAb (IU/mL)	10.8	12.8	479.2	495.1	402.2	379.5	457.6	371.1	0.000
TG Ab (IU/mL)	7.04	4.95	146.7	265.9	101.9	119.0	214.4	246.1	0.002
TC (mg/dL)	204.33	44.3	201.48	45.83	207.76	36.82	195.02	37.48	0.732
TG (mg/dL)	139.67	73.10	106.35	51.90	132.59	76.70	108.36	48.66	0.058
HDL (mg/dL)	50.55	12.97	56.63	15.46	51.13	12.83	53.62	9.14	0.152
LDL (mg/dL)	125.89	36.89	123.51	44.49	130.24	35.14	118.15	34.79	0.701

Table 2. IL-35 levels of the study groups.

	Control n: 38		Euthyroid n: 59		Subclinical n: 39		Overt hypothyroidism n: 30	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
IL-35 level	550.05	411.50	486.84	360.83	475.17	400.53	369.80	253.33
		Full Group	CG EG	CG SCHG	CG OHG	EG SCHG	EG OHG	SCHG OHG
P-value		0.285	0.408	0.372	0.046	0.878	0.156	0.238

When the patient groups were grouped according to their TSH values, a significant difference in the IL-35 levels was determined between the groups, with a threshold value of ≥6 uIU/mL and that below it (P=0.043). When two groups were created, comprising the group with a threshold value of ≥10 uIU/mL and that below it, it was determined that the IL-35 levels more significantly differed between the groups (P=0.024) (**Table 3**) (**Figure 1**).

Table 3. Relationship with IL-35 according to the TSH ≥6 and TSH ≥10 levels.

TSH	N	Mean	± SD	P-value
IL-35 level (ng/dL)				
≥6	61	404.81	327.54	0.043
<6	105	519.60	384.58	
≥10	30	369.80	253.33	0.024
<10	136	501.16	385.31	

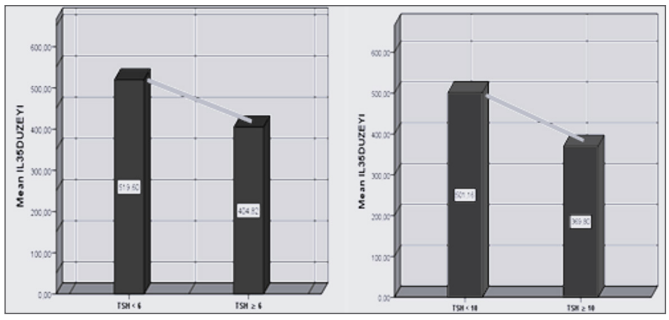

Figure 1. Relationship with IL-35 according to the TSH ≥6 and TSH ≥10 levels.

When the correlation analyses of IL-35 levels with the thyroid function tests were performed, a negative correlation of the IL-35 levels with the TSH, sT4, and anti-TG levels was determined; however, no statistically significant difference was obtained. When the correlation analysis was performed by taking into account the controllable factors (smoking status, DM, hypertension, and BMI), a low-significant correlation was determined between the IL-35 and anti-TPO (P=0.029) (**Table 4**).

Table 4. Correlation relationship between the IL-35 levels and thyroid function tests.

	TSH	sT4	sT3	Anti-TPO	Anti-TG
IL-35 level					
r	−0.050	−0.072	0.025	0.152	−0.099
P-value	0.524	0.355	0.748	0.051	0.202
Controllable variables (smoking status, DM, hypertension, BMI)					
r	−0.063	−0.067	0.052	0.175	−0.096
P-value	0.430	0.404	0.518	0.029	0.232

DISCUSSION

While among the HT groups the IL-35 levels decreased progressively from the euthyroid group towards the overt hypothyroidism group in this study, a statistically significant difference could not be reached between the groups. The IL-35 levels were determined to be higher in the control group when compared to the overt hypothyroidism group. No significant difference was determined between the IL-35 levels and the thyroid function tests and autoantibodies.

In this study, the IL-35 levels in HT we examined. No significant difference was determined between the groups in HT, although a reduction in the IL-35 levels with a progression towards the overt hypothyroidism group was observed in the in-group comparisons. In the in-group comparisons, however, a statistically significant difference was determined between the control group and the overt hypothyroidism group.

Hypothetically, a reduction in the IL-35 levels was expected with progression towards the overt hypothyroidism in HT. Hence, in this study, the reduction of the IL-35 levels with progression towards the overt hypothyroidism group, although not statistically significant, supported this hypothesis. When the patient groups were re-created using a threshold value for TSH, the resulting outcome became another point that supported this hypothesis. Nevertheless, when two groups were created by taking the threshold value for TSH as 6, <6 uIU/mL and ≥ 6 uIU/mL, it was observed that the IL-35 levels were statistically significantly reduced in the group with TSH ≥6 uIU/mL. When the groups were re-created using the TSH value as 10; however, it was found that the statistically significant reduction became more prominent. Based on this result, it can clearly be stated that the IL-35 levels reduced with progression towards manifestations of overt hypothyroidism in HT and that the development of an autoimmune process and the progression of the autoimmune process in HT may be closely associated with the reduction of the IL-35 levels.

In the literature, although there are studies regarding the IL-35 levels in experimental models and animal studies, the number of studies regarding human serum IL-35 levels in autoimmune diseases is insufficient.

The small number of patients and cross-sectional design of this study were the major limitations. Moreover, the

failure to study additional inflammatory parameters to determine the relationship of the IL-35 levels with antibodies in the HT group was another limitation.

CONCLUSION

In this study, it was determined that the IL-35 levels, an antiinflammatory cytokine involved in HT, decreased progressively from the euthyroid patient group towards the overt hypothyroidism group. For a better understanding of whether the IL-35 levels are involved in etiopathogenesis of HT and whether they have a relationship with autoantibodies, studies with a higher number of participants are required.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Fatih University Clinical Researches Ethics Committee (Date: 13.09.2012, Decision No: B30-2-FTH-0200000/1099).

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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Original Article / Özgün Makale

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The effects of the national vaccination program and massive migration on the epidemiology of hepatitis A in children from 2013 to 2018

Ulusal aşı programı ve kitlesel göçün, 2013-2018 arasında çocuklarda hepatit A epidemiyolojisine etkileri

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ABSTRACT

Aim: Acute hepatitis A is a common public health problem in underdeveloped and developing countries. The hepatitis A vaccine was implemented as part of the National Immunization Program in Turkey in November 2012. The present study aimed to investigate the effects of the national vaccination program and massive migration on the epidemiology and clinical burden of hepatitis A infection.

Material and Method: The study was a single center, retrospective chart review study among children diagnosed with viral hepatitis A infection between 0 and 18 years of age from January 2013 to February 2018 in Gaziantep Cengiz Gökçek Maternity and Children Hospital, Turkey. All cases' age, diagnosis time, nationality, and gender information were evaluated. The length of stay, the maximum value of alanine transaminase and aspartate aminotransferase, and the direct medical cost of hospitalization were also evaluated in hospitalized cases.

Results: During the study period total of 1039 cases were diagnosed with hepatitis A infection. Of these cases, 53% were males, 14% were Syrian refugees, and the median age was 7.9-year. The number of cases per year (2013 through 2017) was 321, 360, 157, 119, and 73, respectively. The majority of the cases were detected in November, December, and January. While the total number of cases was declining, we saw that the number of Syrian cases was increasing. The percentage of Syrian children in total cases in 2013 and 2017 was 6.5% and 52.1%, respectively. The hospitalization rate was %49.4, the median length of stay was four days, and the average medical cost of hospitalization was 246.8$/case.

Conclusion: With the national vaccination program, prevalence is declining, but the number of susceptible individuals in society is still adversely affecting the epidemiology of the disease. Continuous monitoring of epidemiological data and efforts to expand vaccine coverage are required for infection control.

Keywords: Hepatitis A, vaccine, pediatric, epidemiology, migration

ÖZ

Amaç: Akut hepatit A, az gelişmiş ve gelişmekte olan ülkelerde yaygın olarak görülen bir halk sağlığı sorunudur. Hepatit A aşısı, Kasım 2012'de Türkiye'de Ulusal Bağışıklama Programının bir parçası olarak uygulanmaya başlanmıştır. Bu çalışma, ulusal aşılama programının ve kitlesel göçün hepatit A enfeksiyonunun epidemiyolojisi ve klinik yükü üzerindeki etkilerini araştırmayı amaçlamıştır.

Gereç ve Yöntem: Çalışma, Cengiz Gökçek Kadın Doğum ve Çocuk Hastanesi, Türkiye'de Ocak 2013 ile Şubat 2018 arasında 0-18 yaş arasında viral hepatit A enfeksiyonu tanısı alan çocuklar arasında tek merkezli, geriye dönük yapılmıştır. Tüm olguların yaş, tanı zamanı, uyruk ve cinsiyet bilgileri değerlendirildi. Hastanede yatan vakalarda kalış süresi, alanin transaminaz ve aspartat aminotransferazın maksimum değerleri ve hastaneye yatışın doğrudan tıbbi maliyeti de değerlendirildi.

Bulgular: Çalışma süresince toplam 1039 vakaya hepatit A enfeksiyonu tanısı konuldu. Bu vakaların %53'ü erkek, %14'ü Suriyeli mülteci ve ortanca yaş 7,9 yıldı. Yılda (2013-2017) vaka sayısı sırasıyla 321, 360, 157, 119 ve 73 idi. Vakaların çoğu Kasım, Aralık ve Ocak aylarında tespit edildi. Yıllar içerisinde toplam vaka sayısı azalırken, Suriyeli vaka sayısının arttığını gördük. 2013 ve 2017 yıllarında toplam vakalarda Suriyeli çocukların oranı sırasıyla %6,5 ve %52,1'dir. Hastanede yatış oranı %49.4, medyan kalış süresi dört gün ve ortalama hastanede yatış maliyeti 246,8$/vaka idi.

Sonuç: Ulusal aşılama programı ile prevalans azalmaktadır ancak toplumdaki duyarlı birey sayısı halen hastalığın epidemiyolojisini olumsuz etkilemektedir. Enfeksiyon kontrolü için epidemiyolojik verilerin sürekli izlenmesi ve aşı kapsamını genişletme çabaları gereklidir.

Anahtar Kelimeler: Hepatit A, aşı, pediatrik, epidemiyoloji, göç

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INTRODUCTION

Hepatitis A virus (HAV) is an important and common cause of viral hepatitis worldwide, with significant differences in geographical endemicity and clinical characteristics (1-3). The severity and clinical course of the infection vary according to the patient's age. When acquired in the early years of life, HAV infection is often asymptomatic. With advancing age, jaundice and other symptoms usually occur; liver failure and death are possible complications, though they rarely occur. Turkey added the HAV vaccine to its routine immunization schedule at the end of 2012. Studies conducted in different parts of Turkey revealed that the hepatitis A seroprevalence varied by region and time (4).

On the one hand, the introduction of the HAV vaccine into the routine national vaccination plan, on the other hand, the mass migration to Turkey due to the war in Syria were the factors that directly affected the epidemiology of HAV infection. Many factors such as the lack of routine HAV vaccination in Syria, the disruptions in the follow-up of childhood vaccinations during mass migration, the lifestyle in crowded conditions, and the lack of attention to adequate sanitation increased the number of individuals susceptible to HAV infection among the immigrants and indirectly in the whole population (5). The present study aimed to investigate the effects of the national vaccination program and massive migration on the epidemiology and clinical burden of HAV infection.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of Fırat University, Non-Interventional Research Ethics Committee (Date: 19.04.2018, Decision No: 08/16). With the ethics committee approval, the data were reviewed retrospectively using the Hospital Information Management System.

The study was conducted as a single center, retrospective chart review study. Children between 0 and 18 years of age diagnosed with HAV infection from January 2013 to February 2018 in Gaziantep Cengiz Gökçek Maternity and Children Hospital were evaluated. The diagnosis of acute viral hepatitis A was made with HAV immunoglobulin M (IgM) positivity. Demographic features (age, gender, nationality, and diagnosis time) were recorded in all patients. In the second part of the study, hospitalizations due to HAV infection were evaluated in detail. The length of stay (LOS), the maximum value of alanine transaminase (ALT) and aspartate aminotransferase (AST) during the hospitalization, and the direct medical costs (including only hospital expenses) were analyzed in hospitalized patients.

Statistical Analysis

The statistical data analysis was performed using IBM SPSS for Windows (IBM statistics for Windows version 25, IBM Corporation, Armonk, New York, United States). In descriptive statistics of the data, mean±standart deviation for normally distributed variables and median (min-max) values for non-normally distributed variables were used. The qualitative data were analyzed by chi-square test, while the quantitative data by Student's t-test or Mann-Whitney test, as appropriate. $P<0.05$ was accepted as a cutoff value for statistical significance.

RESULTS

The total number of HAV IgM tests performed during the study period was 17469. The number of positive results was 1137 (6.5%). When repeated tests of the same person are excluded, 1039 cases were diagnosed with acute HAV infection from January 2013 to February 2018. Of these 1039 cases, 13.8% (144/1039) were Syrian refugees. In the whole group, 53% (546/1039) were males. The median age was 7.9 years, and Turkish cases were older than Syrian cases ($p<0.001$). When we analyzed the group according to years, Turkish patients were still older than Syrians. Hospitalization and admission to the intensive care rates were 49.4% (514/1039) and 0.3% (3/1039), respectively. There was no statistically significant difference between Turkish and Syrian cases regarding gender, hospitalization rate, and need for intensive care. The demographic features of the patients are shown in **Table 1**.

After 2013 and 2014, the number of cases tended to decrease. The months with the highest number of cases in the years were November, December, and January. The distribution of the cases by years and months are shown in **Figure 1**. While the total number of cases declined through the years, we saw the number of Syrian cases increase (**Figure 2**). The percentage of Syrian children in total cases in 2013 and 2017 was 6.5% and 52.1%, respectively (**Figure 3**). As a result, it is seen that the total number of cases has decreased over the years, but both the absolute number and the percentage of Syrian cases have increased over time. When we look at the change in age distribution according to years, while the average age of Turkish patients increased over the years, there was no significant change in the average age of Syrian cases (**Figure 4**).

In the hospitalized cases, the LOS was between 1 and 21 days with a median value of 4 days. ALT and AST median values were 1209 IU/L and 920 IU/L, respectively (**Table 1**). In the hospitalized population, Syrian cases had lower values of ALT and AST than the Turkish cases ($p<0.001$ and $p=0.02$, respectively). The average medical costs of hospitalization for HAV infection were $246.8 per case.

Table 1. Demographic, clinical, and laboratory features of the HAV-infected cases

Variables	Total (n=1039)	Turkish cases (n=895)	Syrian cases (n=144)	p
Age, year median (min.-max.)	7.9 (0.7-17.1)	7.9 (1.4-17)	6.0 (0.7-16.2)	<0.001
2013 (n=321)	6.9 (0.7-17.1)	7 (1.6-17.1)	4.7 (0.7-14.1)	
2014 (n=360)	7.9 (1-16.7)	7.9 (1.4-16.7)	5.8 (1-11.8)	
2015 (n=157)	8.5 (1.5-15.9)	9.0 (1.6-15.9)	6.4 (1.5-15.6)	
2016 (n=119)	8.4 (1.1-16.2)	8.8 (1.5-16.2)	5.9 (1.1-15.4)	
2017 (n=73)	9.1 (1.2-16.2)	10.0 (1.6-15.9)	7.0 (1.2-16.2)	
Gender, male n (%)	546 (53)	463 (52)	83 (57)	0.40
Admission, n (%)				0.08
Inpatient	514 (49)	433 (48)	81 (56)	
Outpatient	525 (51)	462 (52)	63 (44)	
Need for intensive care, n (%)	3 (0.3)	2 (0.5)	1 (0.2)	0.40
In hospitalized patients (n=514)				
LOS, day median (min.-max.)	4 (1-21)	4 (1-21)	4 (1-16)	0.09
ALT IU/ml, median (min.-max.)	1209 (87-4113)	1305 (87-4113)	907 (98-2830)	<0.001
AST IU/ml, median (min.-max.)	920 (96-5111)	936 (96-5111)	535 (120-3302)	0.02

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; LOS, length of stay

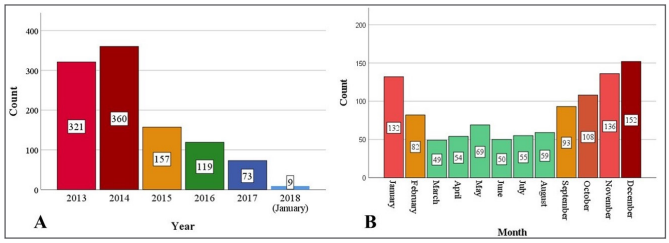

Figure 1. Distribution of the cases by years (A) and months (B)

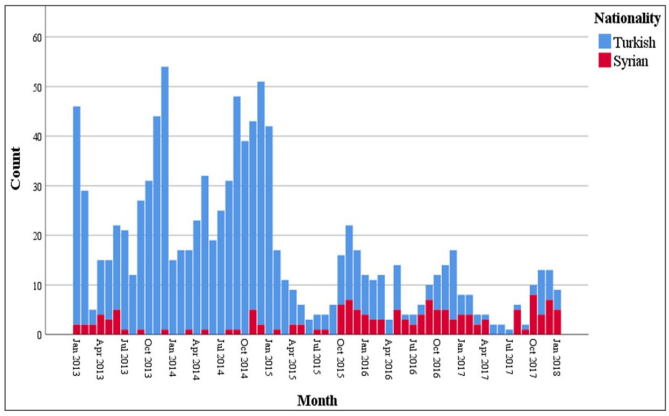

Figure 2. Distribution of the cases by time and nationality

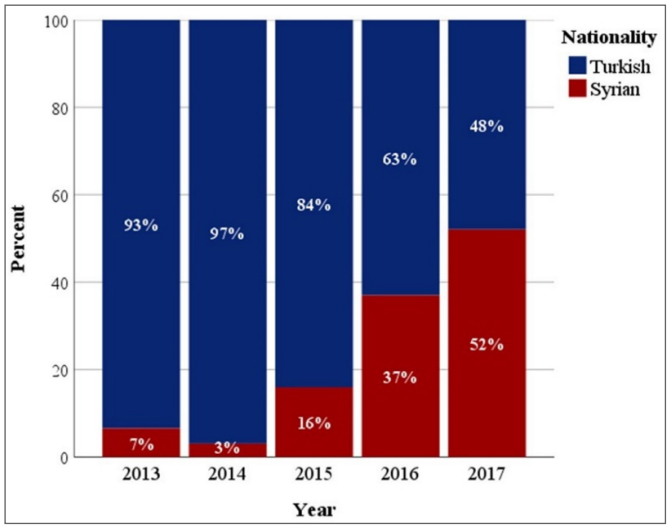

Figure 3. Percentage of the cases by nationality

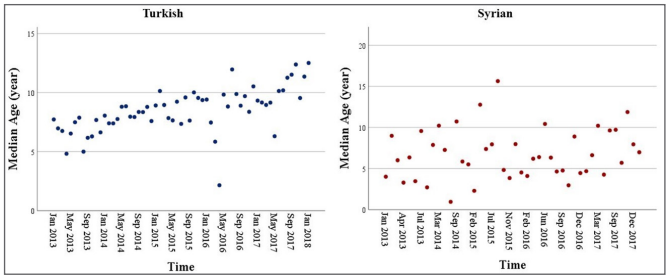

Figure 4. Age distribution of the cases by time and nationality

DISCUSSION

Turkey has an intermediate level of anti-HAV seroprevalence, and HAV infection rates in Turkey have declined over the past 15 years (4,6,7). It should be noted that most children contract HAV infection asymptomatically, so the actual number of infections can be predicted to be much higher than reported. There are many studies conducted at different times in Turkey on HAV seropositivity. Although it varies from region to region, the seroprevalence varies between 29.5% and 80% (8-10). Kurugol et al. (11) revealed that between 1998 and 2008, there was a shift in HAV seroprevalence from younger to older age groups and indicated that HAV infection in childhood was decreasing, and the pool of susceptible adolescents and young adults was increasing. In this study, it was observed that the age of disease acquisition in Turkish cases increased over time. On the other hand, there was no change in age during the study period among Syrian immigrants with a low vaccination rate.

Outbreaks have occurred in several refugee camps in Europe that are hosting refugees from Syria. A sharp rise in reported HAV cases was observed in Lebanon as early as 2013, concurrent with the Syrian crisis and influx of refugees (12). Köse et al. (13) found anti-HAV IgG seroprevalence at 47% in refugee children

in 2014. Between September 2015 and March 2016, parallel to peaking numbers of asylum seekers arriving in Germany, notified cases of hepatitis A in Germany increased substantially (14). In Greece, between April and December 2016, 177 laboratory-confirmed symptomatic cases were reported; 149 (84%) occurred in hosting camps, mostly among Syrian children under 15 years (15). In Turkey, the influx of refugees since 2011 has affected the outcomes of the current vaccination program due to the unvaccinated refugee population, possibly causing a suitable environment for epidemics such as viral hepatitis (16-18). Reporting rates of HAV infection by age group in the Syrian refugee population indicate that the seroprevalence of Syrian children may be lower than that reported in the literature. As we see in our study, the gradual increase in the percentage of immigrants over the years supports this argument. Seroprevalence data are needed for these age groups.

In this study, it was observed that approximately half of the cases with acute HAV infection were hospitalized. Although the LOS is short, it should not be forgotten that unnecessary hospitalization of the cases will also bring medical and economic problems. While making a decision for hospitalization, non-compliance with guidelines or not trusting home care can increase the hospitalization rates improperly. Additionally, the short time allotted to a patient in outpatient clinic conditions may cause insufficient evaluation of the case. Physicians may be inclined to hospitalize cases that they do not think are adequately evaluated in the outpatient clinic in order to be in the safe range. Among the admitted cases, a possible reason for the relatively lower AST and ALT values in Syrian cases may be that physicians tend to hospitalize these cases more for observation purposes.

After the implementation of the HAV vaccine in the national program, case numbers are declining. However, there are still susceptible individuals, especially Syrian refugees. In different studies, seropositivity for HAV is between 45-84% in immigrants, and in children, these ratios are decreasing (13,15,19). In Turkey, nearly 1,6 million Syrian children, and 10% of them are in Gaziantep (20). Prioritizing vaccination of this susceptible group started in the middle of 2017 in this region. We expect these infection rates to decrease in the future.

In this study, the average costs of a HAV infection-related hospitalization were $246, while in the United States, in 2017, the average costs were $16,232 (21). Cost-effective analyses performed in Ireland also showed that where HAV immunity is 45% or less, vaccination is the strategy of choice without a prior screening (22). When the average hospitalization costs are considered, the positive effect of national vaccination is much better understood. The time of being infected with HAV in Turkey is shifting towards advanced ages, so vaccination should be supported in the pediatric population born before 2012 who were not routinely vaccinated against HAV.

There are several limitations in the study. Since the laboratory values of the outpatients were not evaluated, the disease severity of the outpatients and inpatients could not be compared. Indications for hospitalization of the cases are given by the physicians who see them. Although it was a single-center study, evaluating the criteria for the hospitalization decision was impossible. Comparisons of hospitalization rates among physicians could show the differences between physicians' patient management. Since there was no information about the vaccination status of the cases, no comment could be made on breakthrough infections or vaccination rates. Although it has limitations, this study demonstrated the epidemiological change of HAV infection over a long-term period of 5 years in a heavily populated city in Turkey.

CONCLUSION

Population changes due to mass migration movements have markedly affected the epidemiology of HAV infection. Implementing the HAV vaccine in the national vaccination program markedly reduced the possible negative effect of mass migration. However, due to the presence of susceptible individuals in the community, the provision of high vaccination rates remains essential. Continuous monitoring of epidemiological data and efforts to expand vaccine coverage are required for infection control. In order to prevent unnecessary hospitalizations in managing the cases, it is necessary to review the patient management of the physicians in the field.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Fırat University Non-Interventional Clinical Research Ethics Committee (Date: 19.04.2018, Decision No: 08/16).

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: No conflict of interest was declared by the author

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Author Contributions: The author declares that he has responsible for the design, execution, and analysis of the paper and that he has approved the final version.

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Original Article / Özgün Makale

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Diagnostic value of delta neutrophil index in determining axillary metastases in breast cancer

Delta nötrofil indeksinin aksiller metastazları belirlemede tanısal değeri

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ABSTRACT

Aim: The delta neutrophil index (DNI), which shows the percentage of immature granulocytes (IG) in peripheral blood in inflammatory conditions, is an indicator of increased bone marrow activation. Its ability to predict prognosis has been demonstrated in many cancer studies. This study aims to investigate the value of DNI in predicting axillary metastases in breast cancer.

Material and Method: Patients diagnosed with breast cancer and operated on axillary lymph node dissection were screened and 127 patients were included in the study. The patient's age, gender, operation time, length of hospital stay, immature granulocyte (IG) percentages (IG#), and axillary lymph node pathology results were retrospectively scanned from the archive system.

Results: DNI and IG were statistically higher in the group with lymph node metastasis. When examined for IG#, the mean of the group with reactive lymph nodes was 0.02±0.02, while the mean of the metastatic group was 0.04±0.05. This statistically significant difference was high ($p<0.001$). Cut-off values of 0.035 (OR 4.133, CI 95% 0.589-0.777, $p<0.001$) were found with 40% sensitivity and 86.1% specificity for the differentiation IG# of metastasis among patients.

Conclusion: DNI and IG count may be new predictive markers with high sensitivity and specificity in detecting axillary metastasis of breast cancer.

Keywords: Breast cancer, axillary lymph node metastasis, delta neutrophil index, immature granulocyte

ÖZ

Amaç: İnflamatuar koşullarda periferik kandaki olgunlaşmamış granülositlerin (IG) yüzdesini gösteren delta nötrofil indeksi (DNI) artan kemik iliği aktivasyonunun bir göstergesi olarak kullanılabilir.Bu çalışmanın amacı meme kanseri prognozunda önemli rol oynayan aksiller lenf nodu metastazını klinik ve radyolojik tespitinden önce IG sayısı ve DNI ile belirlemektir.

Gereç ve Yöntem: Meme kanseri tanısı alıp opere edilen ve aksiller lenf nodu diseksiyonu yapılmış hastalar tarandı ve 127 hasta çalışmaya dahil edildi. Hastaların yaşı, cinsiyeti, operasyon süresi, hastanede yatış süreleri, immatür granülosit (IG) yüzdeleri (IG#) ve aksiller lenf nodu patoloji sonuçları retrospektif olarak arşiv sisteminden tarandı.

Bulgular: DNI VE IG lenf nodu metastazı olan grupta istatiksel olarak daha yüksekti. IG# açısından inceleme yapıldığında lenf nodu reaktif olan grubun ortalaması 0,02±0,02 iken metastatik grubun ortalaması 0,04±0,05 bulundu, istatistiki anlamlı farklılık gösterecek şekilde yüksekti ($p<0,001$). Hastalar arasında metastazın ayrımı IG#'sı için %40 sensitivite ve %86,1 spesifiteyle 0,035 (OR 4,133, CI%95 0,589-0,777, $p<0,001$) değerleri cut-off olarak bulunmuştur.

Sonuç: DNI ve IG sayısı, meme kanserinin aksiller metastazını saptamada yüksek duyarlılık ve özgüllüğe sahip yeni öngörücü belirteçler olabilir.

Anahtar Kelimeler: Meme kanseri, aksiller lenf nodu metastazı, delta nötrofil indeks, immatur granülosit

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INTRODUCTION

Breast cancer (BC) is the most common type of cancer among women and is an important global health problem (1). Although its incidence has increased recently, mortality rates have decreased due to advances in early diagnosis and neo-adjuvant therapy (2,3). Patient prognosis depends on many variables, including age, ethnicity, tumor biology (tumor size, nodal status, histological grade), and response to systemic therapy (polymerase chain reaction) (4).

In cancer, the clinical outcome may be influenced not only by the histopathological features of the tumor but also by the host response, including the inflammatory response. Therefore, biomarkers showing the inflammatory response in cancer patients may help guide treatment.

Recent studies have confirmed the role of host inflammatory responses in tumor development and the progression of cancers, including breast cancer (5). These studies demonstrated that the secretion of cytokines and chemokines produced by both tumor and associated cells such as leukocytes may contribute to the development of metastasis (6). Inflammatory cell stimulation occurs in lymph node metastases and distant organ metastases such as primary tumors. A neutrophilic response is associated with poor prognosis, as it can inhibit the immune system, for example by suppressing the cytotoxic activity of T cells (7). The presence of tumor-infiltrating lymphocytes (TILs) has been associated with a better response and prognosis to cytotoxic therapy in BC patients (8). Similarly, hematological indices such as neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), lymphocyte-monocyte ratio (LMR), and C-reactive protein (CRP) ratios between different cell types (7,9-11). Its relationship with malignant tumors has been studied in many studies.

Also, recent studies have defined the delta neutrophil index (DNI), which represents the percentage of immature granulocytes (IG) in peripheral blood due to increased bone marrow activation in inflammatory conditions (12). IG fractions are based on the count of granulocyte precursor cells such as promyelocytes, myelocytes, and metamyelocytes. With technological advances, IG count and DNI can be evaluated automatically from complete blood count parameters in automated systems (12,13).

IG count and DNI have been identified as prognostic factors in many inflammatory processes such as sepsis, cardiovascular events, and acute appendicitis (14-16). However, studies related to breast cancer with these parameters are limited. In this study, the utility of IG and DNI in the prediction of axillary lymph node metastasis, which plays an important role in breast cancer prognosis, was investigated.

MATERIAL AND METHOD

The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (Date: 11/08/2022, Decision No: 2022/74). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Population

Our research was carried out retrospectively and cross-sectionally. Data were collected by examining patient files and computer records.

127 patients who were operated on with the diagnosis of breast cancer and underwent axillary lymph node dissection by the General Surgery clinic between 2019-2022 were included in the study.

Inclusion Criteria

Patients over the age of 18 were defined as those who were diagnosed with clinicopathologically breast cancer, did not receive neoadjuvant therapy, whose data could be accessed, and who did not have recurrence or distant metastasis. Exclusion criteria are; Patients with missing clinicopathological features, hematological and oncological diseases, under 18 years of age, whose data could not be reached, who were diagnosed with advanced breast cancer, and whose final pathology result was not reported as breast cancer were determined.

Statistical Analysis

IBM SPSS Statistics for Windows program was used for all statistical analysis (version 26; IBM Corp., Armonk, N.Y., USA). For categorical variables, descriptive statistics were provided using numbers and percentages, and numerical variables were reported with mean, standard deviation, and median in parentheses. The normal distribution of the data was evaluated with the Shapiro-Wilks test. Relationships between variables were investigated with Pearson or Spearman correlation coefficient by the data distribution. Comparison of numerical measurements for two independent groups according to research groups was evaluated with a two-sample t-test for age only, operation times, hospitalization times, IG percentages, and IG numbers were evaluated with Mann Whitney U test by data distribution. The ROC curve was used to show the discrimination of the statistically significant variables, and the cut-off values were found for the markers using the area under it and the Youden index. Sensitivity, specificity, PPV, NPV, and precision were calculated for these cut-off values. Odds ratio values were calculated according to these cut-offs. For the statistical significance level, $p<0.05$ was accepted.

RESULTS

A total of 127 patients were included in the study. All of the patients were women. The mean age of all patients was 58.31±13.11 years. The operation time was 119.37±65.05 minutes. The patients were hospitalized for an average of 9.59±8.48 days. The mean of IG% was calculated as 0.4±0.33, and the mean of IG# was calculated as 0.03±0.04.

Pathology results of 72 patients (56.7%) were reported as reactive lymph nodes. Metastatic lymph nodes were found in 55 patients (43.3%). The patients were divided into two groups according to axillary lymph node pathologies, reactive lymph node, and metastatic lymph node.

While the mean age of the lymph node reactive group was 57.96±12.42 years, the mean age of the metastatic group was 58.76±14.07 years. No statistically significant difference was observed between the two groups (p=0.733).

While the operations of non-metastatic patients lasted 106.94±64.11 minutes on average, this time increased to 135.64±63.19 minutes in metastatic patients. A statistically significant difference was observed (p<0.001). While patients without metastasis in the axilla were hospitalized for an average of 6.6±6.92 days, the duration of hospitalization in the metastatic group was found to be 13.51±8.78 days, which was statistically significantly higher (p<0.001).

The mean IG% of the lymph node reactive group was calculated as 0.28±0.15, and the mean of the metastatic group was calculated as 0.54±0.44, with a statistically significant increase in the metastatic group (p<0.001). In terms of IG#, the mean of the group with reactive lymph nodes was 0.02±0.02, while the mean of the metastatic group was 0.04±0.05, with a statistically significant difference (p<0.001).

To distinguish between patients with axillary lymph node reactive and metastatic patients with breast cancer, IG% and IG# markers with significant differences were evaluated in the area under the ROC curve and the Youden index. For differentiation of metastasis between patients, 0.55 (OR 7.072, CI 95% 2,438-20.518, p<0.001) for IG% with 34.5% sensitivity and 93.1% specificity, 40% sensitivity for IG# and specificity were found with 86.1%. Cut-off values of 0.035 (OR 4.133, CI 95% 0.589-0.777, p<0.001).

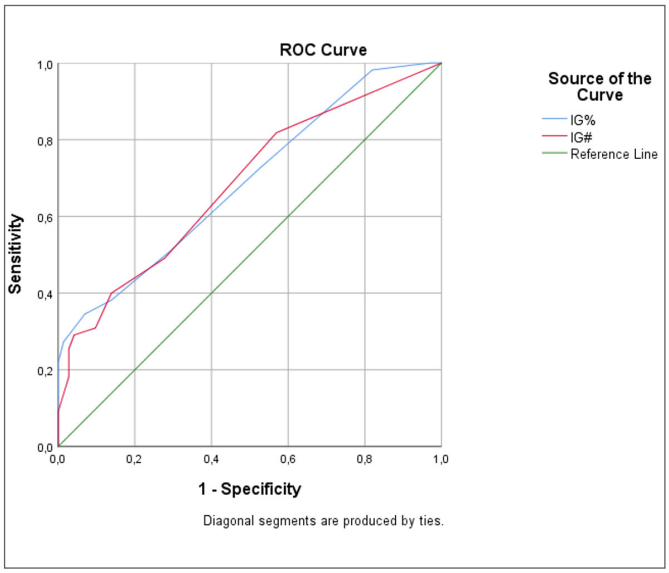

Figure 1.

DISCUSSION

DNI value showing the percentage of IG in peripheral blood in inflammatory conditions can be used as an indicator of increased bone marrow activation. In this study, it was found that DNI and IG values in patients diagnosed with breast cancer were increased in patients with axillary metastases and were a predictive marker in showing axillary metastases.

Table 1. All patients variables and comparison of variables between groups

Variables	All Patients (n=127)	Axilla Reactive (n=72)	Axilla Metastatic (n=55)	Statistical significance
Age	58.1±13.11	57.96±12.42	58.76±14.07	0.733
Operation duration	119.37±65.05	106.94±64.11	135.64±63.19	<0.001
Hospitalization	9.59±8.48	6.6±6.92	13.51±8.78	<0.001
IG%	0.4±0.33	0.28±0.15	0.54±0.44	<0.001
IG#	0.03±0.04 (0.02)	0.02±0.02	0.04±0.05	<0.001
Axilla LN				
Reactive	72 (%56.70)			
Metastasis	55 (%43.30)			

Table 2. Cut-off points and diagnostic values of variables for distinction between normal and appendicitis patients

Variables	Cut-Off	Diagnostic Values					ROC Curve			OddsRatio		
		Sensitivity	Specifity	PPV	NPV	Accuracy	Area (SE)	95% CI	p	Odds Ratio	95% CI	p
IG%	0.55	34.5%	93.1%	79.2%	65.0%	67.7%	0.688 (0.047)	0.596-0.781	<0.001	7.072	2.438-20.518	<0.001
IG#	0.035	40.0%	86.1%	68.8%	65.3%	66.1%	0.683 (0.048)	0.589-0.777	<0.001	4.133	1.752-9.754	<0.001

Predicting recurrence and survival after curative surgical resection for operable breast cancer patients has traditionally been based on standard clinicopathological criteria such as age, tumor size and grade, nodal status, and hormonal receptor status. However, it is known that inflammatory response can increase neoangiogenesis, cause tumor progression and metastatic spread, and further increase genomic instability by causing local immunosuppression. Other host-related factors, such as the systemic inflammatory response, have been previously shown to be associated with poor survival following potentially curative resection for a variety of cancers, including gastroesophageal and urinary tract cancers (17,18). Kim et al. (19) found that inflammatory markers were associated with low survival in patients who underwent cytoreductive surgery+hypec. Similarly, inflammatory response in pancreatic head cancers is associated with poor survival (20).

DNI is a new inflammatory marker that measures the percentage of circulating immature granulocytes as measured by next-generation automated devices. It indicates earlier bone marrow activation than neutrophil response and is a helpful indicator in the diagnosis and prognosis of different diseases (21–23). In a study by Yoonmi et al. (24), it was found to be an easy and useful marker for early diagnosis and prognostic evaluation of patients with sepsis. Bozan et al. (12) reported that preoperative DNI levels in patients with nodular goiter and thyroid malignancy were higher in the malignant patient group. They found the cut-off value for DNI to be 0.35%, with a sensitivity of 79.2% and a specificity of 78.9% in the diagnosis of malignant thyroid diseases. Also, in another study by Barut et al. (25), DNI was found to be a predictive factor in renal cell carcinoma. Another study reported that DNI is an early predictor of severe acute cholecystitis and is an inflammatory marker with a significantly higher predictive value than WBC count or CRP level to detect severe acute cholecystitis (26). Similarly, Shin et al. (27) reported that the preoperative DNI value helps the diagnosis of histologically normal appendicitis and is a useful parameter to distinguish between simple and complicated appendicitis.

As a result of our literature search, although many studies are showing that systemic inflammatory markers are associated with breast cancer prediction and prognosis, there is no comprehensive study revealing the relationship between DNI and axillary metastasis. With this study, we showed that an increase in serum DNI level, which can be processed by automated systems and included in CBC parameters, can be a useful marker for predicting axillary lymph node metastasis in patients with breast cancer.

Our study also has some limitations. First, our study had a retrospective design, and no subgroup analysis was performed according to breast cancer subtypes and receptor positivity or negativity. Also, the sample size was not large enough and outcome analysis with more patients may be required to further validate our model. We hope that in the future these parameters can be used as simple and inexpensive parameters for clinical decision-making and better prediction of axillary lymph node metastasis in breast cancer patients.

Finding a parameter that can predict axillary lymph node metastasis with simple blood values measurement, the absence of a similar breast cancer study in the literature, and the follow-up of patients with the same team and surgical discipline were the strengths of our study.

CONCLUSION

We showed that preoperative DNI and IG can predict axillary lymph node metastasis in patients with breast cancer. The conclusion we have reached as a result of our study is; The high sensitivity and specificity of these parameters can be used to predict preoperative axillary lymph node metastasis in patients with breast cancer.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Hitit University Erol Olçok Training and Research Hospital Non-Invasive Clinical Research Ethics Committee (Date: 11/08/2022, Decision No: 2022/74).

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.

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Original Article / Özgün Makale

MEDICINE PALLIATIVE CARE

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Should we have any predictive marker for estimating the severity of community-acquired pneumonia at admission?

Başvuru sırasında toplum kökenli pnömoninin ciddiyetini tahmin etmek için herhangi bir prediktif belirtecimiz olmalı mı?

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ABSTRACT

Aim: Community-acquired pneumonia (CAP) is a disease that affects children. One hundred fifty-five million children under five years are diagnosed with pneumonia yearly, 20 million are hospitalized, and 2 million die. Early diagnosis and severity assessment reduce mortality and morbidity. This study aimed to determine the effect of basic hemogram parameters, neutrophil-lymphocyte ratio (NLR), immature (IG) granulocyte, immature granulocyte percentage (IG%), C-reactive protein (CRP), and oxygen saturation.

Material and Method: This case-control study was conducted between November 2018 and May 2019 at Erciyes University School of Medicine in the Department of Paediatric Pulmonology. Sixty-nine patients diagnosed with CAP had enrolled in the study by clinical and radiological findings. The patients were classified into two subgroups: mild-to-moderate pneumonia and severe pneumonia. The CAP severity of the disease was determined using the criteria indicated for children by the British Thoracic Society. Univariate analysis was used to identify independent factors that affect the severity of pneumonia.

Results: Pneumonia was mild-moderate in 46.3% (n=32/69) patients. Pneumonia was severe in 63% (n=37/69) of patients. Leukocytes, neutrophils, IGn, IG%, and saturations of these two groups were compared. There was a statistically significant difference between the two groups (p 0.05). However, there was no statistically significant difference in lymphocyte count, NLR, or CRP (p>0.05). Leukocytes, neutrophils, IGn, IG%, and saturation significantly predicted pneumonia severity (p<0.05).

Conclusion: Our studies show that increased IGn, IG%, and decreased oxygen saturation are related to severe outcomes in children with pneumonia. They may be effective parameters in determining the severity of pneumonia.

Keywords: Community-acquired pneumonia, children, immature granulocyte, oxygen saturation, disease severity

ÖZ

Amaç: Toplum kökenli pnömoni (TKP), çocukları etkileyen önemli bir hastalıktır. Her yıl beş yaş altı yüz elli beş milyon çocuğa zatürre teşhisi konmakta, 20 milyonu hastaneye kaldırılmakta ve 2 milyonu ölmektedir. Erken tanı ve şiddet değerlendirmesi mortalite ve morbiditeyi azaltır. Bu çalışmada temel hemogram parametreleri, nötrofil-lenfosit oranı, immatür granülosit, immatür granülosit yüzdesi, CRP ve oksijen satürasyonunun hastalık şiddetine etkisinin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Bu vaka-kontrol çalışması, Kasım 2018-Mayıs 2019 tarihleri arasında Erciyes Üniversitesi Tıp Fakültesi Çocuk Göğüs Hastalıkları Anabilim Dalı'nda yürütülmüştür. Klinik ve radyolojik bulgulara göre TKP tanısı konan altmış dokuz hasta çalışmaya dahil edildi. Hastalar hafif-orta pnömoni ve şiddetli pnömoni olmak üzere iki alt gruba ayrıldı.

Bulgular: Hafif-orta pnömonisi (%32/46,3) ve şiddetli pnömonisi (%37/53,6) olan hastaların lökosit, nötrofil, IGn, IG% ve satürasyonu karşılaştırıldı. İki grup arasında istatistiksel olarak anlamlı fark vardı (p 0,05). Ancak lenfosit sayısı, nötrofil lenfosit oranı (NLO) veya CRP'de istatistiksel olarak anlamlı bir fark yoktu (p>0,05). Pnömoninin şiddetini etkileyen bağımsız faktörleri belirlemek için tek değişkenli analiz kullanıldı. Lökositler, nötrofiller, immatür granülosit, immatür granülosit yüzdesi ve saturasyon, pnömoninin şiddetini öngörmede önemli bir etkiye sahipti (p<0,05).

Sonuç: Çalışmamız, artan immatür granülosit, immatür granülosit yüzdesi % ve azalmış oksijen satürasyonunun pnömonili çocuklarda ciddi sonuçlarla ilişkili olduğunu göstermektedir. Pnömoninin şiddetini belirlemede hastaneye başvuruda bu parametreler etkili olabilirler.

Anahtar Kelimeler: Toplum kökenli pnömoni, çocuklar, immatür granülosit, oksijen satürasyonu, hastalık şiddeti

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INTRODUCTION

A clinical diagnosis of community-acquired pneumonia (CAP) in a previously healthy child is described as pneumonia caused by an infection obtained outside the hospital (1). CAP is a disease that affects children all over the world and has a high mortality and morbidity rate (2). World Health Organization estimates that 155 million children under the age of five are diagnosed with pneumonia each year. Over 20 million are hospitalised, and more than 2 million children die from pneumonia (3). As a result, it is critical to detect the disease early and identify the severity of the condition so that mortality and morbidity can be decreased.

Many research has been conducted to investigate the predictive usefulness of serum inflammatory biomarkers such as white blood cells (WBC) and their subtypes, C-reactive protein (CRP), procalcitonin (PCT), interleukin-8, interferon-alpha, tumor necrosis factor, and kallsitatin, endocan, Mid-regional proadrenomedullin (MR-proADM), and kopeptin in CAP patients. Additionally, since some of these indicators are very costly and difficult to get, there is still a need for simple, specific, generally accessible, and affordable biomarkers in pneumonia patients (4-9).

Nowadays, in blood samples taken from peripheral blood, next-generation analyzers can automatically and extremely correctly count and assess the genuine immature granulocyte number (IGn) and percentage (IG%) (10-12). The immature granulocyte comprises promyelocytic, intermediate, and late granulocytes, all precursor cells for mature white blood cells. They have been used to diagnose several different infections (13). Immature granulocytes are not usually found in the peripheral blood of healthy people. However, severe clinical infections can deplete many neutrophils, and the body compensates by releasing immature granulocytes from the bone marrow into the peripheral bloodstream (13) The neutrophil-to-lymphocyte ratio (NLR) is calculated by dividing the total neutrophil count by the absolute lymphocyte count. Several studies have used the neutrophil-to-lymphocyte ratio to indicate the body's systemic inflammatory response and immune status. NLR measurement is a useful marker for determining the severity of pneumonia patients and predicting their prognosis (14). These markers can be determined with a simple hemogram result, easy to calculate without extra payment. However, no research evaluating the percentage of immature granulocytes and the number of immature granulocytes in childhood community-acquired pneumonia was reported in the literature. To the best of our knowledge, this is the first study to investigate the relationship between the severity of pediatric community-acquired pneumonia and the number of immature granulocytes in the peripheral blood.

This study aimed to determine the effect of basic hemogram parameters such as leukocyte, neutrophil, lymphocyte, neutrophil-lymphocyte ratio, immature granulocyte, and immature granulocyte percentage on the severity of community-acquired pneumonia in children. Additionally, we evaluated the effects of another inflammatory marker, CRP, and a clinical finding, oxygen saturation.

MATERIAL AND METHOD

The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 09.05.2018, Decision No: 2018/237). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This prospective case-control study was conducted between November 2018 and May 2019 at Erciyes University School of Medicine in the Department of Pediatric Pulmonology.

Sixty-nine patients diagnosed with CAP by clinical and radiological findings were included in the study who had not been treated previously and were aged between 3 months and 18 years. The association of clinical symptoms is defined as CAP (i.e., fever>38.0C, coughing, dyspnea, tachypnea, and pleuritic chest pain), physical examination findings (i.e., crackles, retractions, and rhonchus), and chest X-ray findings (i.e., air bronchogram, consolidation, opacities, and pleural effusion) and diagnosed by a pediatrician. If there were suspicious radiological findings, patients underwent a consultation with a pediatric radiologist. If the patients had the above mentioned features, they were enrolled in the study (15).

The following conditions were excluded from the study:<3 months, >18 years, cystic fibrosis, bronchiectasis, tuberculosis, immotile cilia syndrome, sickle cell anemia, Down syndrome, cerebral palsy, acute/chronic renal insufficiency, acute/chronic liver failure, congenital heart disease, chemical pneumonia, hospital-acquired pneumonia, or ventilator-associated pneumonia, patients who had previously been treated at other centers, patients receiving multiple antiepileptic and immunosuppressive treatments.

The patients were classified into two subgroups: mild-to-moderate pneumonia and severe pneumonia. The CAP severity of the disease was determined using the criteria indicated for children by the British Thoracic Society (BTS) (1). The following features in an infant were evaluated as a sign of severe illness: cyanosis;

respiratory rate >70 breaths/min; significant tachycardia for the fever level; prolonged central capillary refill time >2 s; difficulty breathing; intermittent apnea; grunting; and inability to feed. Severe disease in an older child manifested in the following ways: cyanosis; respiratory rate >50 breaths/min; substantial tachycardia at any level; prolonged central capillary refill time >2 s; difficulty breathing; apnea, grunting; and signs of dehydration. A blood sample was obtained from all the patients included in the research during the first 24 hours of admission.

Recent generations of automated cell analysers provide many parameters, including cellular hemoglobin levels, large platelet counts, nucleated red blood cells, and basic hemograms. Detection of specimens was accomplished using the USES in-1000 automatic hematological analyzer (Japan Sysmex Company), and reagents were obtained from the original package of supporting reagents. Sheath flow technology, electrical impedance technology, and nucleic acid fluorescence staining were used to detect IG. This new-generation device can measure the number and percentage of immature granulocytes (16).

Statistical Analysis

Statistical analysis was performed using SPSS (Statistical Package for Science Studies) version 22.0 for Windows. Firstly, descriptive statistics were performed with the data obtained. Then, the Shapiro-Wilk test was used to test whether the variables were normally distributed. Characteristic data are presented as n (%) for categorical variables and as mean±SD or median (interquartile range [IQR1-IQR3] for continuous variables, where appropriate.

Two-group comparisons were performed using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve assessed the leukocyte, neutrophil, lymphocyte, NLR, IGn, IG%, CRP, and oxygen saturation for pneumonia severity. The area under the curve (AUC) was used to calculate the predictive value of the markers. Logistic regression was used to efficiently determine the ability of laboratory values and oxygen saturation to predict the severity of pneumonia. Logistic regression identified associated factors and calculated odds ratios and 95% confidence intervals. Additionally, we generated predicted probability graphs to show how altering immature granulocyte number and oxygen saturation levels affect pneumonia severity's estimated probabilities. All tests were two-tailed, and p-values less than 0.05 were considered statistically significant in all cases.

RESULTS

Demographic characteristics of the study groups are given in **Table 1**. The median age of patients with mild to moderate pneumonia was 7 (IQR1:5-IQR3: 10), and the median age of patients with severe pneumonia was 5 (IQR1:1.5-IQR3:5). When the two groups' ages were compared, a statistically significant difference in their ages was discovered (p=0.03) (**Table 1**).

Table 1. Demographic and hematological markers, CRP and oxygen saturation findings of patients.

	Mild-moderate pneumonia (n:32/46.3%.)	Severe pneumonia (n:37/53.6%)	P value
Age	7 (5-10)	2 (1.5-7)	p:0.03
Sex M(44)/F(25)	22(50%)/10(40%)	22(50%)/ 15(60%)	
Leukocyte	9225 (6500-11790)	12020 (8520-18340	p:0.006
Neutrophil	4600 (3242-8137)	7330 (4879-12220)	p:0.009
Lymphocyte	2465 (1557-3682)	2930 (1880-3860)	p:0.370
NLR	2.27 (1.2-3.3)	2.8 (1.1-6.1)	p:0.208
IGn	30 (20-47.5)	60 (40-125)	p:0.001
IG%	0.3(0.2-0.4)	0.5 (0.4-1)	p:0.001
CRP	26 (11-71)	36(19.5-143)	p:0.112
Oxygen saturation	95 (94-87)	88 (82-92)	p:0.001

Median:(IQR1- IQR3); NLR: Neutrophil/ Lymphocyte ratio; IGn: immature granulocyte number; IG%: immature granulocyte percentage; CRP: C-reactive protein M: male; Female: F

Patients with mild-moderate pneumonia (32/46.3%) and those with severe pneumonia (37/53.6%) had their leukocyte, neutrophil, IGn, IG%, and oxygen saturation compared. There was a statistically significant difference between the two groups (p<0.05). However, there was no statistically significant difference in lymphocyte count, NLR, or CRP (p>0.05) (**Table 1**).

Univariate analysis was used to identify independent factors that affect the severity of pneumonia. Leukocytes, neutrophils, IGn, IG%, and oxygen saturation significantly predicted pneumonia severity (p<0.05). They were positively correlated with the severity of the disease (OR>1), but oxygen saturation was negatively correlated (OR<1) (**Table 2**). The positive predictive value (PPV) of these parameters, respectively, was 56%, 61%, 59%, 51%, and 83%. Negative predictive value (NPV): 65%, 62%, 90%, 81%, and 83%, respectively (**Table 2**). Lymphocyte, NLR, and CRP had no significant effect in predicting the severity of pneumonia (p>0.05) (**Table 2**). As a result of the univariate analysis, multivariate logistic regression analysis (forward LR) was performed for the statistically significant parameters. Step 1: Oxygen saturation (odds ratio [OR] 0.535, 95% confidence interval [CI] 0.384-0.744, p 0.0001; PPV: 81, NPV: 83) and step 2: Oxygen saturation and IGn together (OR 1.008, 95% CI: 1.000-1016 p< 0.045, PPV: 86, NPV: 93) showed sufficient statistical power to discriminate between the two patient groups (**Table 2**). Oxygen saturation and IGn had a significant predictive value for disease severity. For these values, a probability curve was formed (**Figure 1,2**).

Table 2. Logistic regression analysis of hematological markers, CRP, and oxygen saturation

	Univariate logistic regression analysis						βMultivariate logistic regression analysis					
	OR	95% CI	P-value	PPV%	NPV%	OAP%	OR	95%CI	P-value	PPV%	NPV%	OAP%
Leukocyte	1.00	1.000-1.000	0.016	56	65	60						
Neutrophil	1.00	1.000-1.000	0.029	62	62	62						
Lymphocyte	1.00	1.000-1.000	0.216	40	62	52						
NLR	1.138	0.975-1.326	0.102	54	50	52						
IGn	1.008	1.000-1.016	0.05	59	90	74	+1.008	1.000-1016	0.045	86	93	90
IG%	10.792	1.614-72.137	0.014	51	81	65						
CRP	1.006	0.998-1.1013	0.149	52	56	53						
Saturation	0.570	0.428-0.759	0.0001	83	81	82	*0.53	0.384-0.744	0.0001	83	81	82

β: Forward LR; *Step1; +: Strep 2, OR: odds ratio, CI:confidence interval , PPV:positive predictive value, NPV: Negative predictive value; OAP:overall percentage; CRP: C-reactive protein; IGn: Immature granulocyte number IG%:Immature granulocyte percent; NLR: neutrophil/lymphocyte ratio

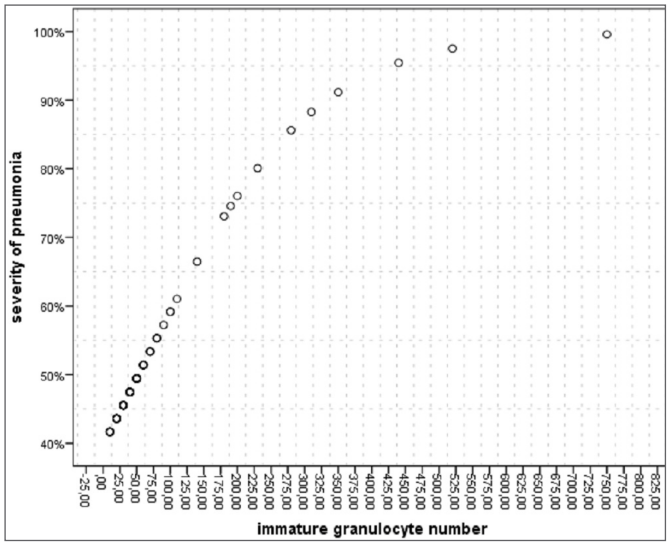

Figure 1. Predicted probability of mild-moderate or severe severe pneumonia by immature granulocyte numbers. IGn was modeled by scatter/dot. For example, if the IGn value is 325, around 90% of patients may be suffering from severe pneumonia.

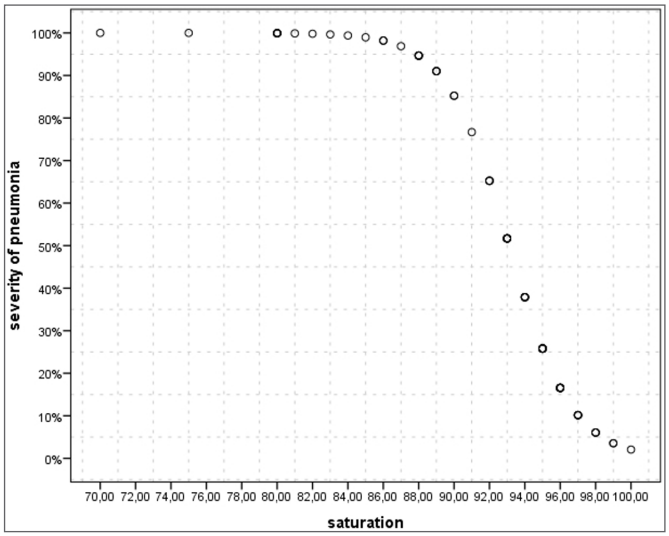

Figure 2. Predicted probability of mild-moderate or severe severe pneumonia by oxygen saturation. IGn was modeled by scatter/dot. For example, if the oxygen saturation value is 90%, around 89% of patients may be suffering from severe pneumonia

The receiver operating characteristic (ROC) curve analysis was performed to assess the ability of leukocytes, neutrophils, lymphocytes, NLR, IGn, IG%, CRP, and oxygen saturation. ROC analysis of pneumonia severity AUC (95% CI) was, leukocytes: 0.694 (0.569-0.818), p=0.006; neutrophils: 0.685 (0.559-0.810), p=0.009; lymphocytes: 0.563 (0.426-0.700), p=0.370; NLR: 0.588 (0.453-0.724), p=0.209; IGn: 0.746 (0.627-0.864), p=0.0001; IG%: 0.775 (0.664-0.887), p=0.0001; CRP: 0.611 (0.478-0.745), p=0.112, oxygen saturation: 0.89 (0.824-0.978), p=0.001 (**Table 3**, **Figure 3**).

Table 3. ROC curve analysis of blood parameters, CRP and, oxygen saturation in the prediction of CAP

Pneumonia severity			
	AUC	CI 95%	P
Leukocyte	0.694	0.569-0.818	0.006
Neutrophil	0.685	0.559-0.810	0.009
Lymphocyte	0.563	0.426-0.700	0.370
NLR	0.588	0.453-0.724	0.209
IG%	0.746	0.627-0.864	0.0001
IGn	0.775	0.664-0.887	0.0001
CRP	0.611	0.478-0.745	0.112
Oxygen saturation	0.891	0,824-0.978	0.001

AUC:Area under the curve; CI: confidence interval; CRP: C-reactive protein; IGn: Immature granulocyte number; IG%:Immaturegranulocyte percent; NLR: neutrophil/ lymphocyte ratio

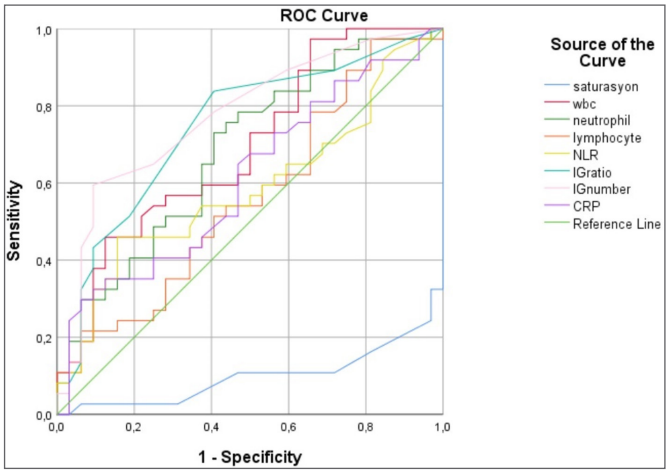

Figure 3. Receiver operating curves for immature granulocyte number (IGn), immature granulocyte number (IG%) percentage, white blood count (WBC), Neutrophil, lymphocyte, Neutrophil/ lymphocyte ratio (NLR), C-reactive protein (CRP), oxygen saturation.

DISCUSSION

Pneumonia is a disease with high mortality and morbidity in children. Many markers have been investigated to determine the severity of pneumonia. However, as a result of the research, a marker with high reliability has not been determined yet. BTS and

many classifications determine disease severity based on clinical findings rather than biological markers (1,17). However, clinical findings can be misleading, as examining children can sometimes be challenging. As a result, objective data on the severity of pneumonia are required. To establish the severity of the disease, we investigated hemogram results and oxygen saturation, both of which are objective data that are easily accessible and cost-effective.

The complete blood count is the most frequent and simple laboratory test, providing a wealth of data on an individual's health state. Due to technological advancements in automated hematological analyzers, the percentage and number of IG and IG% are now detectable. IG and IG% are immature cells that have just been released into the bloodstream. They are seen as signs of bone marrow activity and regeneration. CBC parameters and neutrophil/lymphocyte (NLR), IG, and IG%, which are considered biomarkers of systemic infections and inflammations, have been reported many times in sepsis, bronchiolitis, rheumatological diseases, cardiovascular disease, and various cancers (18-20).

Our study found that IGn, IG%, and oxygen saturation are useful markers to predict community-acquired pneumonia severity. It adds information to the conventional markers WBC, absolute neutrophil count (ANC), NLR, and CRP for the early identification of pediatric patients with CAP. Specifically, when IG number and oxygen saturation (OAP 90%) are used together, it is possible to evaluate the severity of pneumonia more accurately. The NPVa value of IGn (90a%/59b%) and IG (81a%/51b%) percent is greater than the PPVb value when estimating the severity of pneumonia. As a result, lower IGn and IG% levels are more likely to indicate mild-moderate pneumonia than severe pneumonia.

CRP is a blood test widely used to assess inflammation and bacterial infections. It has been related to the severity of the disease in children with bacterial infections (21). However, studies have shown no significant relationship between CRP and the severity of CAP. Elevated CRP was not linked with hypoxemia, dyspnea, or tachycardia in single-center cross-sectional research (22,23). CRP was not as significant in predicting pneumonia severity in our investigation as in previous studies. In determining the severity of pneumonia, IGn and IG% were more effective than CRP.

Florin et al. (7) evaluated proadrenomedulin (ProADM) levels to determine pneumonia severity in children admitted to the emergency room. In their study, ProADM had an AUC of 64% in those with suspected CAP and an AUC of 77% in those with radiographic CAP. Similarly, the prediction value of IGn was 77% in our study. Esposito et al. (8) assessed the relationships between the Soluble Triggering Receptor Expressed on Myeloid Cells (AUC 57%), the Mid regional Proatrial Natriuretic Peptide (AUC 65%), and the Mid regional pro adrenomedullin (AUC 55%) and the severity of pneumonia in children. In our study, IGn (AUC 77%) and IG% (AUC 74%) were more highly predictive of pneumonia severity than the markers used in this study. Esposito et al. (8) also evaluated the levels of WBC (AUC 59%), neutrophils (AUC 59%), and CRP (AUC 58%) to determine the severity of pneumonia. The values of these parameters were relatively similar to the results of our study. IGn and IG% are better options for determining pneumonia's severity than ProADM; Triggering Receptor Expressed on Myeloid Cells, Mid-regional Proatrial Natriuretic Peptide, and Mid-regional ProADM since it is more easily available and less costly.

Gungor et al. (24) evaluated the accuracy of the IG% in predicting severe bacterial infections (SBI). In this study, patients with SBI had a higher IG%, and the IG% had a better sensitivity and specificity for predicting SBI when compared to other biomarkers (WBC, neutrophil, CRP). Pimental et al. (25) assessed the role of immature neutrophils in peripheral blood smears to predict bacteremia in children. There was a significant difference between the number of immature neutrophils in this study when people with community-acquired infections were compared with or without bacterial blood infections. Furthermore, when this study evaluated only children with lower respiratory tract infections, the absolute number of immature granulocytes differed between patients with and without bacteremia. They demonstrated that a high IGn level predicted bacteremia in 82 (AUC) percent of severity pneumonia. In our study, patients with high IGn values have a risk of severe pneumonia. Bacteremia may accompany severe pneumonia in children. It may have the potential to increase the severity of pneumonia. From these study results, it is possible to attribute a role in the severity of pneumonia among these patients to the increased absolute number of immature neutrophils.

Dogan et al. (19) examined the relation between IG% and acute bronchiolitis severity. They found that IG values gradually increased from the mild to the severe group, but their study had no statistically significant difference. The IG value was valuable in determining the pneumonia severity in our study, in contrast to this study. The reason is that viruses are the most prevalent cause of acute bronchitis, but bacteria are the most common cause of pneumonia.

Huang et al. (26) examined the relation between IG% and acute respiratory distress syndrome (ARDS) in patients with acute pancreatitis. This study mentioned an increasing trend in ARDS in patients with acute pancreatitis with increasing IG%, and IG% could discriminate between acute pancreatitis patients with

and without risk for ARDS. Our study determined that IG% is one of the most effective markers for distinguishing mild-moderate from severe pneumonia.

When IGn and oxygen saturation values are evaluated together, they predict pneumonia severity by 90%. Together, these two indicators have more significant prediction power than the severity of pneumonia alone. IGn and oxygen saturation were our investigation's most valuable indicators for determining pneumonia severity. Probability curves that were not available in other studies were generated to show the severity of pneumonia associated with these values. These probability curves demonstrate the ability to estimate disease severity for each value of IGn and oxygen saturation (**Figures 1,2**). For example, if the IGn value is 325, around 90% of patients may suffer from severe pneumonia (figure 1). If the saturation level is 90%, about 89% of patients may suffer from severe pneumonia (**Figure 2**).

In the BTS guidelines, cyanosis is used to determine disease severity. This is not objective data. The cyanotic appearance may not be noticed in some cases because of the lighting, temperature, and other factors (1). Dean et al. (27) report in their study that, even though CAP is a common disease in children, there is no standardised risk classification to guide management. This study aimed to develop expert consensus regarding the parameters associated with varying degrees of disease severity in pediatric CAP. They recommended using oxygen saturation and objective data to determine the severity of pneumonia (24). The study by Awasthi et al. (28) emphasised that hypoxia and pneumonia in children under five years of age increase the mortality rate and may cause severe pneumonia. In their research, Modi et al. (29) emphasised that the sensitivity of the oxygen saturation measurement in evaluating pneumonia is more predictive than other clinical findings in resource-constrained conditions. In our research, oxygen saturation was an efficient parameter in distinguishing between mild-moderate and severe pneumonia, consistent with previous studies. Unlike other studies, we demonstrated the probability of pneumonia severity based on the saturation value on the probability curve. We think using saturation, an objective value, instead of cyanosis, in risk classifications will provide a more accurate assessment.

CONCLUSION

Our studies show that increased IGn, IG%, and decreased oxygen saturation are related to severe outcomes in children with pneumonia. They may be effective parameters in determining the severity of pneumonia. Complete blood count and oxygen saturation measurement are cheap and worldwide available methods. Given pediatric CAP's high incidence and mortality rate in low-income countries, IGn and oxygen saturation measurement give valuable information and may be the most useful method at admission. In addition, our results may contribute to developing more effective management recommendations for pediatric CAP. Additional studies should focus on developing sensitive predictors and a validated scoring system for pediatric pneumonia severity. More research is needed to create clinical-prediction criteria for identifying severe pneumonia in children, including oxygen saturation, IGn, and IG% as predictors of severity.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erciyes University Clinical Researches Ethics Committee (Date: 09.05.2018, Decision No: 2018/237).

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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A comparison of obstetric and perinatal outcomes of spontaneous and in vitro fertilization (IVF) twin pregnancies

Spontan ve invitro fetilizasyon (IVF) ikiz gebeliklerin obstetrik ve perinatal sonuçlarının karşılaştırılması

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ABSTRACT

Aim: We aimed to compare and analyze the perinatal and obstetric outcomes of in vitro fertilization (IVF) method and spontaneous twin pregnancies.

Material and Method: Pregnant women who had had IVF and those with spontaneous fertilization in a tertiary perinatology center between January 2016 and January 2021 were retrospectively included in this study. The demographic data of the women (gender, age, gestational week) and fertilization types (spontaneous or IVF) were analyzed. Premature rupture of membranes (PROM), preterm delivery (PD), and intrauterine growth restriction (IUGR) was recorded. Additionally, Apgar scores, the presence of fetal anomalies, the need for neonatal intensive care (NICU) and mortality were analyzed.

Results: Overall, 261 women who were pregnant with twins were included in this study. The median age of the mothers was 29 years (min 15-max 40 years), and 23.8% were ≥35 years. Spontaneous and IVF pregnancies occurred in 75.9% and 24.1%, respectively. The most common problems in the twin pregnancies were PROM (14.6%), PD (13.4%), GHT (11.5%), oligohydramnios (6.1%), GDM (4.6%), and polyhydramnios (2.3%). Also, 13.8% had IUGR. The median age of the women with IVF pregnancies was higher than the spontaneous pregnancies (33.0 vs 28.0 years) ($p<0.001$). The maternal age was found to be significantly higher in those women with PD compared to those without PD (33.0 vs 28.0 years) ($p=0.009$). The incidence of PROM and the rate of PD were significantly higher in the IVF pregnancies group compared to the spontaneous pregnancies group ($p<0.001$ and $p<0.001$, respectively). The postnatal 1st and 5th minute Apgar scores of the twin babies were significantly lower in the IVF group ($p<0.001$). Over the half of babies needed NICU and this rate was significantly higher in the IVF group compared to the spontaneous pregnancy group (71.4% vs 50.5%) ($p=0.004$).

Conclusion: IVF twin pregnancies are risky pregnancies in terms of PROM and PD. Additionally, the need for NICU is higher for IVF twin birth pregnancies than for spontaneous twin pregnancies.

Keywords: Twin pregnancy, in vitro fertilization, IVF, PROM, twins

ÖZ

Amaç: Spontan ikiz gebelikler ile invitro fertilizasyon (İVF) yöntemi ile gerçekleşen ikiz gebeliklerin perinatal ve obstetrik sonuçlarını karşılaştırmayı ve analiz etmeyi amaçladık.

Gereç ve Yöntem: Ocak 2016-Ocak 2021 tarihleri arasında üçüncü basamak perinatoloji merkezinde İVF yöntemiyle veya spontan şekilde gerçekleşen ikiz gebeler retrospektif olarak çalışmaya dahil edildi. Gebelerin demografik verileri (cinsiyet, yaş, gebelik haftası) ve doğum şekilleri (spontan ve İVF) analiz edildi. Gebelerde görülen erken membran yırtılması (EMR), preterm doğum (PD) ve intrauterin büyüme geriliği (IUBG) sıklıkları kaydedildi. Ayrıca apgar skorları, fetal anomalilerin varlığı, yenidoğan yoğun bakım (YYB) ihtiyacı ve mortalite oranları analiz edildi.

Bulgular: Toplam 261 ikiz gebe çalışmaya dahil edildi. Ortanca yaş 29 (en az 15-en fazla 40 yıl) ve %23,8 'i ≥35 yaşındaydı. Spontan ve IVF gebelik oranları, sırasıyla, %75,9 ve %24,1 idi. İkiz gebeliklerde en sık görülen sorunlar sırasıyla EMR (%14,6), PD (%13,4), GHT (%11,5), oligohidramnios (%6,1), GDM (%4,6) ve polihidramnios (%2,3) idi. Ayrıca %13,8'inde IUBG vardı. IVF gebelerin ortanca yaşı, spontan gebelere göre anlamlı derecede daha yüksekti (33,0-28,0) ($p<0,001$). Preterm doğum olan gebelerde gebelik yaşı, PD olmayanlara göre anlamlı olarak daha yüksek bulundu ($p=0,009$). IVF yönetiyle gerçekleşen ikiz gebeliklerde EMR ve PD insidansı spontan gebeliklere göre daha yüksekti (sırasıyla $p<0.001$ ve $p<0.001$). İkiz bebeklerin postnatal 1-5. dakika Apgar skorları IVF grubunda daha düşüktü ($p<0,001$).Bebeklerin yarısından fazlasında YYB ihtiyacı mevcuttu ve bu oran IVF grubunda spontan gruba göre anlamlı olarak daha yüksekti (%71,4-%50,5) ($p=0,004$).

Sonuç: IVF ikiz gebelikleri EMR ve PD açısından riskli gebeliklerdir. Ayrıca, IVF ikizlerinde YYB ihtiyacı spontan ikiz bebeklere göre daha yüksektir.

Anahtar Kelimeler: İkiz gebelik, invitro fertilizasyon, IVF, EMR, ikiz

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INTRODUCTION

Twin births constitute 3.1% of all live births and 97.5% of all multiple births (1). While the incidence of spontaneous twins varies by country, with the advent of assisted reproductive techniques [In vitro fertilization (IVF), Gamete intrafallopian tube transfer (GIFT), and Intracytoplasmic sperm injection (ICSI)], the incidence of multiple pregnancies has increased significantly (2). In the study of Kulkarni et al. (3), it was reported that assisted reproductive techniques were used with a frequency of 36% in twin pregnancies and 77% in triplet or more pregnancies.

Due to the development of spontaneous and in vitro fertilization (IVF) methods, the increasing number of multiple pregnancies has led to an increase in obstetric and perinatal risks. Preterm and low birth weight deliveries are reported as the main reasons for this in multiple pregnancies (4). In addition, the higher incidence of gestational diabetes mellitus and hypertensive diseases in multiple pregnancies also causes an increase in perinatal and obstetric complications (5,6). Although it has been reported that IVF in singleton pregnancies causes an increased perinatal and obstetric risk compared to spontaneous ones, this issue is highly controversial in twin pregnancies (7,8). In the literature, studies reporting that the frequency of preterm IVF method births in twin pregnancies is similar to spontaneous twins (9,10). On the other hand, in the study conducted by Tandulwadkar et al. (11), it was shown that the rates of late preterm births in IVF twin pregnancies were slightly increased compared to spontaneous twin pregnancies. However, this result was affected by the fact that the IVF group mothers were older than the spontaneous fertilization mothers', or that there are other factors that increase the risk of preterm birth (pregestational diabetes mellitus, chronic hypertension, etc.) (11).

We aimed to compare and analyze the perinatal and obstetric outcomes of IVF and spontaneous twin pregnancies.

MATERIAL AND METHOD

The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 183). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients Selection

All spontaneous and IVF pregnancies during the January 2016 and January 2021 period with mothers aged between 20-42 years were retrospectively included in this study. Singleton pregnancies were excluded from this study.

Data Collection and Assessment of Patients

The demographic data of the pregnant women (gender, age, gestational week) and fertilization types (spontaneous or IVF) were analyzed. Premature rupture of membranes (PROM), preterm delivery (PD), and intrauterine growth restriction (IUGR) was recorded. It was recorded whether the twins were discordant between the twins in terms of their birth weight. Discordance between the birth weights of the newborns was defined as a difference between the birth weights of infants above 25% (12). Gestational hypertension (GHT), gestational diabetes mellitus (GDM), anemia, polyhydramnios, and oligohydramnios during pregnancy were investigated. Apgar scores, the presence of fetal anomalies, the need for neonatal intensive care (NICU) and mortality were analyzed.

Statistical Analysis

Data were analyzed using the SPSS 25.0 (IBM, Armonk, NY: IBM Corp.) program. Continuous variables were expressed as mean ± standard deviation, median (interquartile range, IQR), and categorical variables as numbers (n) and percentages (%). When the parametric test assumptions were met, Student's t-test was used to compare differences between independent groups. When parametric test assumptions were not met, the Mann-Whitney U test was used to compare differences between independent groups. The Chi-square or Fisher's exact probability tests were used to compare demographics. In all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Overall 274 pregnant twins were analyzed. Thirteen twin pregnancies were excluded from the study due to missing data. Therefore, two hundred sixty-one women who were pregnant with twins were included in this study. Their median age was 29 years (min 15-max 40 years), and 23.8% (n=62) were 35 years or older. Spontaneous and IVF pregnancies occurred at rates of 75.9% and 24.1%, respectively (**Table 1**). Nearly half of the IVF pregnancies (42.9%) and only 17.7% of the spontaneous pregnancies were 35 years or older ($p<0.001$). While the median week of delivery was 34+6 (min 17+1-max 40+3 weeks) in all pregnancies, it was 31+6 weeks (min 17+1-max 36+3) in the IVF group and 35+4 weeks (min 24+3-max 40+3) in spontaneous pregnancies group (Table 1). Normal spontaneous vaginal delivery (NSVD) occurred in the majority of the births (92.7%) and cesarean section (C/S) was performed in only 7.3% of cases (**Table 1**).

Table 1. Demographic characteristics of women pregnant with twin

Age (year) [median (min-max)]	29.0 (15-40, 26-34)
Pregnancy [n (%)]	
Spontaneous	198 (75.9)
IVF	63 (24.1)
Pregnancy week [median (min-max)]	34^{+6} (17^{+1}-40^{+3})
Spontaneous	35^{+4} (24^{+3}-40^{+3})
IVF	31^{+6} (17^{+1}-36^{+3})
Birth type [n (%)]	
NSVD	242 (92.7)
C/S	19 (7.3)

C/S: caesarean section, IVF: in vitro fertilization, min: minimum, max: maximum, NSVD: normal spontaneous vaginal delivery

The most common problems in the twin pregnancies were PROM (14.6%), PD (13.4%), GHT (11.5%), oligohydramnios (6.1%), GDM (4.6%), and polyhydramnios (2.3%) (**Table 2**). Additionally, 13.8% of the twin pregnancies had IUGR.

Table 2. Obstetric and prenatal outcomes of twin pregnancies and neonates

Obstetric / Prenatal Outcomes	**n (%)**
PROM	38 (14.6)
IUGR	36 (13.8)
Preterm delivery	35 (13.4)
Pregnancy HT	30 (11.5)
Oligohydramnios	16 (6.1)
Diabetes Mellitus	12 (4.6)
Polyhydramnios	6 (2.3)
Anemia	2 (0.8)
IUFE	8 (3.1)
Fetal anomaly	5 (1.9)
Need for NICU	145 (55.6)

PROM: premature rupture of membranes, HT: hypertension, IUGR: intrauterine growth restriction, IUFE: intrauterine fetal exitus, NICU: neonatal intensive care unit

The median age of the women in the IVF group was statistically significantly higher than the spontaneous pregnancy group (33.0 vs 28.0 years) (p<0.001) (**Table 3**). Also, it was observed that the delivery week of the IVF pregnancy group was significantly lower than the spontaneous pregnancy group (p<0.001) (**Table 3**). The gestational age and IVF or spontaneous pregnancy did not affect the type of delivery (p=0.320 and p=0.785, respectively) (**Table 3**). In addition, the gestational age was found to be significantly higher in those pregnancies with PD compared to those without PD (33.0 vs 28.0, respectively) (p=0.009).

There was no significant difference between the development of GHT and spontaneous or IVF pregnancies (p=0.256) (**Table 3**). In addition, the incidence of PROM and the rate of PD were statistically significantly higher in the IVF group compared to the spontaneous group (p<0.001 and p<0.001, respectively) (**Table 2**).

Table 3. The comparison of pregnancy demographics, features and birth types with spontaneous and IVF pregnancies.

	Pregnancy type		p
	Spontaneous	**IVF**	
Pregnancy age [median (min-max)]	28 (18-40)	33 (21-40)	<0.001
Pregnancy week [median (min-max)]	35^{+4} (24^{+3}-40^{+3})	31^{+6} (17^{+1}-36^{+3})	<0.001
Birth type [n (%)]			0.785
NSVD	184 (92.9)	58 (92.1)	
C/S	14 (7.1)	5 (7.9)	
Pregnancy HT [n (%)]			0.256
+	20 (10.1)	10 (15.8)	
-	178 (89.9)	53 (84.2)	
PROM [n (%)]			<0.001
+	17 (8.6)	21 (33.3)	
-	181 (91.4)	42 (66.7)	
Preterm delivery			<0.001
+	13 (6.6)	22 (34.9)	
-	185 (93.4)	41 (65.1)	

C/S: caesarean section, HT: hypertension, IVF: in vitro fertilization, min: minimum, max: maximum, NSVD: normal spontaneous vaginal delivery, PROM: premature rupture of membranes

The incidence of fetal anomalies in the twin babies was found to be 1.9% (n=5) (**Table 2**). There was no relationship between the presence of IUGR in babies and spontaneous pregnancy or IVF pregnancy (p=0.207) (**Table 4**). In addition, the postnatal 1st and 5th minute Apgar scores of the twin babies were statistically significantly lower in the IVF group (p<0.001) (**Table 4**). While the frequency of discordance between birth weights of the twin babies was 21.1%, it was 26.9% in the IVF group and 19.2% in the spontaneous twin group. There was no significant difference between the two groups in terms of discordance (p=0.215) (**Table 4**). After birth, 55.6% of babies needed NICU and this rate was statistically significantly higher in the IVF group compared to the spontaneous fertilization group (71.4% vs 50.5%, respectively) (p=0.004) (**Table 4**). In addition, while intrauterine fetal exitus (IUFE) occurred in 3.1% (n=5), there were 2 IUFE in the IVF group and 3 in the spontaneous group.

Table 4. The comparison of IUGR, apgar scores, discordance and need for NICU with spontaneous and IVF pregnancies.

	Pregnancy type		p
	Spontaneous	**IVF**	
IUGR			0.207
+	24 (12.1)	12 (19.0)	
-	174 (87.9)	51 (81.0)	
Apgar score [median (IQR)]			<0.001
1st baby (1-5. min)	7 (6-7)-9 (8-10)	6 (3-7)-8 (7-9)	
2nd baby (1-5. min)	7 (6-8)-9 (8-10)	6 (3-7)-8 (6-9)	
Need for NICU			0.004
+	100 (50.5)	45 (71.4)	
-	98 (49.5)	18 (28.6)	
Discordance			0.215
+	38 (19.2)	17 (26.9)	
-	160 (80.8)	46 (73.1)	

IQR: interquantile range, IUGR: intrauterine growth restriction, IVF: in vitro fertilization, min: minute, NICU: neonatal intensive care unit

DISCUSSION

In this study, it has been shown that IVF and spontaneous twin pregnancies have an affect on both obstetric and prenatal outcomes. Accordingly, different problems occur in twins after birth.

The ages of women using assisted reproductive techniques have been reported to be higher than in those with spontaneous pregnancies (13,14). It was reported that 25.8% of twins in Australia were using assisted reproductive techniques and 45.2% of them were 35 years or older (15). In a study conducted by Ozcil MD (16) in our country, it was shown that 9.5% of spontaneous twins and 35% of twins who were conceived by assisted reproductive technique were aged 35 or over. In our study, 42.9% of IVF pregnancies and only 17.7% of spontaneous pregnancies were 35 years or older. While this rate is similar to the literature, it can be observed that the percentage of pregnancies that were ≥35 years was higher in both our IVF group and our spontaneous pregnancy group. Today, the higher gestational age and the more frequent use of assisted reproductive techniques can explain this result.

It was reported that 18% of twin pregnancies in the USA, 18% in the UK, 23.3% in Australia and 41% in Italy are not spontaneous and that assisted reproductive techniques had been used (15-18). In our country, 67-78% of twin births are spontaneous pregnancies (14,16). In this study, similar to the literature, the spontaneous twin pregnancy rate was 75.9%, while the IVF pregnancy rate was 24.1%. In the literature, the C/S ratios in IVF twin pregnancies are significantly higher than in spontaneous twin pregnancies (19,20). Contrary to the literature, in our study, normal birth rates were found to be significantly higher in both groups. The high normal birth rates in both groups were thought to be due to the encouragement of normal birth in our country, and the preference for normal birth except in cases where preterm birth or cephalic presentation are absent.

In the literature, the rates of PROM development in twin pregnancies after IVF are similar to spontaneous twin pregnancies and the use of IVF does not increase this risk (21,22). In a study conducted in our country, the rate of PROM was found to be 22% in IVF twin pregnancies and 19.8% in spontaneous twin pregnancies (16). In our study, contrary to the literature, the risk of PROM was found to be higher in the IVF group than in the spontaneous pregnancy group (33.3% vs 8.6%). The fact that our center is a tertiary referral center and that the majority of pregnancies with PROM are admitted to our center may explain this result.

PD rates are higher in twin pregnancies compared to singleton pregnancies, with a frequency of 36-79% (15,18,23-26). It has been reported that PD rates are similar between spontaneous twin pregnancies and IVF twin pregnancies (15,26,27). In our study, the rate of PD was found to be quite low (13.8%) compared to the literature. The low prevalence of chronic diseases which may increase the rate of PD in pregnancies and the fact that the gestational age is not advanced may explain this low rate of PD. In addition, PD rates were found to be similar between our spontaneous twin pregnancies and IVF twin pregnancies. This finding is in line with the literature.

In the studies conducted by Gluck et al. (10) and Barda et al. (28), GHT increased in IVF twin pregnancies. Additionally, the age of the pregnant women was found to be higher, but advanced age was ignored while reaching this conclusion in these studies. On the other hand, in the meta-analysis published by Pinzauti et al. (29) in 2016, it was stated that GHT rates were similar in IVF and spontaneous twin pregnancies. In our study, while GHT was observed at a rate of 11.5%, which is similar to the literature, there was no difference in the frequency of GHT between IVF and spontaneous twin pregnancies.

In some studies, it was reported that the risk of fetal anomaly increases in IVF twin pregnancies (19). On the other hand, after considering maternal age and accompanying diseases, IVF does not increase the risk of fetal anomaly (20). As only 5 fetal anomalies were observed in our study, no comparison could be made between the two groups.

Many studies are reporting that the discordance seen in twin babies is higher in twin pregnancies using assisted reproductive techniques compared to spontaneous pregnancies (13,30). However, it has been shown recently that there is no discordance difference between IVF and spontaneous twins (14,15,18,31). In our study, the frequency of discordance between the birth weights of the twin babies was found to be similar in both groups. This result is in line with the literature. The incidence of IUGR development in twins has been reported to be between 4.9% and 8.1% in our country (32,33). Some studies have shown that there is no difference between spontaneous twins and IVF twins in terms of IUGR (2,33). In our study, the frequency of IUGR was found to be 13.8%, which is similar to the literature, and there was no significant difference between the two groups.

Intrauterine fetal exitus (IUFE) is a rare complication of multiple pregnancies, and its prevalence was reported to be 3.3% in a study conducted in our country (34). In addition, Sumer et al. (33) reported the frequency of IUFE in spontaneous and IVF pregnancies to be 8.9% and 10.3%, respectively. In our study, similar to the literature, IUFE was found only in 3.1% of the pregnancies, but a

comparison between the two groups could not be made due to the lack of sufficient numbers. Although McDonald et al. (35) showed that the need for NICU is higher in IVF pregnancies, many studies in the literature have reported that there was no difference between these two groups in terms of NICU admissions (34,36). In our study, while more than half of the postnatal babies needed NICU, this rate was significantly higher in the IVF twins group than in the spontaneous twins group.

Limitations of this study; (1) being a single-center study and the low number of cases constitute important limitations in the generalization of our results; (2) Since it is retrospective, follow-ups and the postpartum life expectancy and the development of the fetuses are unknown.

CONCLUSION

IVF twin pregnancies are risky pregnancies in terms of PROM and PD. In addition, while there was no difference in IVF and spontaneous twin babies in terms of IUGR, the need for NICU is higher in IVF twin births than for spontaneous twin births.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Istanbul Kanuni Sultan Süleyman Training and Research Hospital Clinical Researches Ethics Committee (Date: 26.05.2021, Decision No: 183).

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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The role of hyperuricemia in acute renal failure

Akut böbrek yetmezliğinde hiperüriseminin rolü

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ABSTRACT

Objective: Acute renal failure is one of the most important factors affecting mortality in intensive care patients. The aim of this study was to elucidate whether there was a relationship between uric acid levels and/or acute kidney imjury/failıre (AKI).

Material and Method: A total of 1000 individuals who were admitted to intensive care unit (ICU) of our institution without any prior renal disease and glomerular filtration rate (GFR) of 80-120 ml/minutes, have been enrolled in this retrospective analysis. The development of AKI in the ICU were evaluated via RIFLE criteria. In patients who developed AKI, it was checked whether there was an indication for renal replacement therapy (RRT). All patients in the ICU including the unconscious indivuduals and COVID-19 patients have been included in the analysis.

Results: Acute renal failure (ARF) was observed in 27.1% (n=271) of the individuals. Hemodialysis had been administered in 44.3% (n=120) of patients with ARF. The reasons for hemodialysis were ischemia in 36%, sepsis and multifactorial reasons in 32% of the subjects. A statistically significant difference was found compared to the initial measurements in urea, creatinine, uric acid and sodium (Na) increased compared to baseline ($p<0.001$) as all parameters except potassium (K). All values from baseline increased at the time of diagnosis, while a decrease was observed in the GFR value ($p<0.001$). There was a statistically significant difference between the uric acid measurements of the patients undergoing hemodialysis ($p<0.05$) and uric acid measurements were increased compared to baseline.

Conclusion: Regarding the results of this study one can conclude that serum uric acid level has been shown to be an independent risk factor for decreased renal function. Additionally, elevated uric acid levels lead to increased hemodialysis, morbidity and mortality in the ICU.

Keywords: Acute renal failure, hemodialysis, hyperuricemia, uric acid, intensive care unit

ÖZ

Amaç: Akut böbrek yetmezliği (ABY) yoğun bakım hastalarında mortaliteyi etkileyen en önemli faktörlerden biridir. Bu çalışmanın amacı, ürik asit düzeyleri ile akut böbrek hasarı (AKI) / ABY arasında bir ilişki olup olmadığını aydınlatmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmamıza, önceden böbrek hastalığı olmayan ve glomerüler filtrasyon hızı (GFR) 80-120 ml/dakika olan hastanemiz yoğun bakım ünitesine kabul edilen toplam 1000 hasta dahil edildi. Yoğun bakım ünitesinde AKI gelişimi RIFLE kriterleri ile değerlendirildi. AKI gelişen hastalarda renal replasman tedavisi endikasyonu olup olmadığına bakıldı. Bilinci kapalı kişiler ve COVID-19 hastaları dahil yoğun bakım ünitesindeki tüm hastalar analize dahil edilmiştir.

Bulgular: Bireylerin %27,1'inde (n=271) AKI görüldü. AKI'lı hastaların %44.3'üne (n=120) hemodiyaliz uygulanmıştı. Hemodiyaliz nedenleri olguların %36'sında iskemi, %32'sinde sepsis ve multifaktöriyel nedenler idi. Potasyum dışındaki tüm parametrelerde (üre, kreatinin, ürik asit ve sodyumda) başlangıca göre artmıştı ($p<0,001$) ve başlangıç ölçümlerine göre istatistiksel olarak anlamlı bir fark bulundu. Tanı anında başlangıca göre tüm değerler artarken, GFR değerinde azalma gözlendi ($p<0,001$). Hemodiyalize giren hastaların ürik asit ölçümleri arasında istatistiksel olarak anlamlı fark vardı ($p<0,05$) ve ürik asit ölçümleri başlangıca göre arttı.

Sonuç: Bu çalışmanın sonuçlarına göre serum ürik asit düzeyinin azalmış böbrek fonksiyonu için bağımsız bir risk faktörü olduğu gösterilebilir. Ek olarak, yüksek ürik asit seviyeleri yoğun bakım ünitesinde hemodiyaliz, morbidite ve mortalitenin artmasına neden olur.

Anahtar Kelimeler: Hemodiyaliz, akut böbrek yetmezliği, hiperürisemi, ürik asit, yoğun bakım ünitesi

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INTRODUCTION

The mortality rate of patients with end-stage renal disease ARF requiring RRT exceeds 50% in intensive care unit patients (1). In study of 1800 intensive care unit patients, ARF has been detected in 57% of the individuals and 39% of these subjects developed stage 2-3 ARF according to Kidney Disease Improving Global Outcomes (KDIGO) criteria and 13.5% of them required RRT (1). Regarding the severity of the situation several studies on treatment alternatives and predictive bio-markers are still ongoing due to high morbidity and mortality rates in the ICU. Molecules such as calprotectin, cystatin-C, netrin-1, kidney injury molecule-1 have been studied for this purpose, but it has been stated that more studies are needed (2). In addition, the fact that, cost of these molecules are very high and they cannot be investigated in every center is another obstacle.

Uric acid is the end product of the catabolism of the purine nucleotides, guanylic acid, inosinic acid, adenylic acid and adenosine triphosphate in the human body. Endogenous source is from liver, muscle, small intestine, kidney and vascular endothelium tissues (3, 4). Exogenous source, on the other hand, is mostly animal foods, but it is also formed from fruit fructose (3). It consists of a heterocyclic structure with a molecular weight of 168 daltons and is a weak acid with a pKa of 5.8 at physiological pH. Hyperuricemia is identified as plasma uric acid concentrations are higher than 7.0 mg/dL (4). When uric acid level it is higher than 6.8 mg/dL it crystallizes and collapses. Although high uric acid has become more commonly associated with gout, its importance in some other diseases is undeniable. Hyperuricemia is associated with hypertension, vascular diseases, renal disease and cardiovascular events. In addition, there is an antioxidant and pro-inflammatory mechanism of action for uric acid (3). While it is reported that it clears toxic reactants and protects the tissue against oxidative stress at normal levels (4), serum uric acid levels are also decreased when oxidative stress is present.

The uric acid in the serum is saturated at environmental conditions in 6.4-6.8 mg/dL, and 7.0 mg/dL is the upper limit of solubility. When it exceeds this value, uric acid crystallizes and begins to precipitate. Uric acid suppresses the production of nitric oxide, which plays an active role in glucose transport (5). It causes renal vaso-constriction, systemic hypertension, tubulointerstitial damage, decrease in nitric oxide synthase production and deterioration in afferent arteries (6-8). It suppresses nitric oxide bio-activity and insulin resistance via inflammatory factors and adipokines (9). It has been shown to be associated with blood glucose level (7). Şengül et al. (8) reported that HbA1C, which reflects the long-term metabolism and elevation of glucose, is also positively associated with glucose and uric acid elevation.

Increased uric acid levels cause systemic cytokine production, tumor necrosis factor α, local increase in chemokines, monocyte chemotactic protein 1 and cyclooxygenase 2 in blood vessels (3). The majority of the daily excretion (2/3) of uric acid occurs through the kidneys and 1/3 is via the gastrointestinal system (1). In normal and non-diabetic individuals, uric acid is completely filtered from the glomerulus and almost completely reabsorbed from the proximal tubules (7). In the presence of hyperuricemia, uric acid crystals accumulate in the joints and kidneys (10).

Study Hypothesis

Hyperuricemia is a condition seen in chronic renal failure (CRF). While there are studies stating that the level of uric acid increases mainly due to the decrease in GFR in CRF (3), there are also studies stating that hyperuricemia causes chronic kidney failure (7) and causes progression of the disease (5,6). Chonchol et al. (11) stated that the increase in serum uric acid level in CRF was mainly due to the decrease in GFR and that hyperuricemia played a minor role in the progression of the disease. On the contrary, there are studies stating that GFR decrease is observed more rapidly in hyperuricemia patients (5) and that end-stage renal failure develops more frequently in those with hyperuricemia (6). There is also a study stating that CRF develops more in healthy populations with high serum uric acid levels (7).

ARF is one of the most important factors affecting mortality in intensive care patients. Some of these studies are also in the direction of whether uric acid levels are related to AKI. In this study, we aimed to evaluate whether there was a relationship between uric acid levels and AKI and RRT requirement, hence it is a cost-effective and easy to obtain parameter.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: E1-22-2565). The study complied with the Declaration of Helsinki and informed consent has been obtained from all participants.

A total of 1000 individuals who were admitted to ICU of our institution between 01.03.2020-01.01.2022, without any prior renal disease and GFR of 80-120 ml/minutes, have been enrolled in this retrospective analysis.

Patients with an estimated glumerular filtration rate (e-GFR) between 80-120 ml/minutes, calculated with the MDRD formula (Modification of diet in renal disease) were included in this retrospective analysis. Demographic data, age, gender and comorbidity, length of stay in the ICU, duration of mechanical ventilation, mortality rate were obtained from patient files. Since the study was retrospective in nature, all patients in the ICU including the unconscious indivuduals and Coronavirus disease 2019 (COVID-19) patients have been included in the analysis.

Hospitalization urea, creatinine, GFR, uric acid, Na, K data were recorded from the laboratory data of electronic hospital database. The development of AKI in the ICU were evaluated via RIFLE criteria. In patients who developed AKI, it was checked whether there was an indication for RRT. The uric acid level of the patients who needed RRT at that time was also recorded.

Inclusion Criteria

Individuals between 18-90 yars old, that are followed up in the ICU. Additionally, these patients did not have any chronic renal disease at the time of admission.

Exclusion Criteria

Patients <18 and >90 years old, who have diabetes mellitus and chronic renal disease at the time of admission. Pregnant women were also excluded from the study.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences, version 22 (SPSS Inc., Chicago, IL, USA). Data were presented as mean ± standard deviation and/or (Median-IQR) values and as numbers or percentages where appropriate. The homogeneity of variances between the groups was evaluated with the Levene test, and the distribution of continuous variables was evaluated by using Shapiro Wilk and Kolmogorov-Smirnov tests. According to the results of normality tests, differences between independent groups were analyzed by using the Mann-Whitney U test or Student's t-test. The chi-square and/or Fisher's exact test were used to compare groups among the categories of variables. Before ran regression, correlations between variables were obtained by using Spearman or Pearson correlation coefficient and evaluated with rho and relevant p values.

In order to define risk factors of outcome variable ARF (-) or (+), multiple logistic regression analysis and adjusted odds ratios with their confidence intervals were calculated. All covariates with missing data in less than 20% of observations and a p-value <0.05 in univariate testing were considered for inclusion in the final multiple regression model and retained if the p-value was <0.05 or if they demonstrated evidence of significant confounding (>10% change in effect size). Highly collinear covariates (defined as correlation coefficient >0.6) were not included together in the final multiple model and these variables are shown in the regression table). The model fit was assessed by Hosmer-Lemeshow Test. A p-value of less than 0.05 was considered statistically significant for all statistical processes.

RESULTS

A total of 1000 individuals were enrolled within the scope of this study. Patients were segmented into 2 groups as subjects who did and did not develope ARF. In terms of gender difference 63.4% (n=634) of them patients were male, 36.6% (n=366) were female, and there was a correlation between the diagnostic groups in terms of gender distribution (p<0.05). ARF was more common in male patients.

The distribution of demographic and clinical findings by diagnosis groups were given in **Table 1**. When the statistically significant variables among the diagnostic groups were examined, it was seen that the mean laboratory values of patients who developed ARF were higher in all parameters except the neurological disease and the initial GFR value. In terms of their final status of the study group, 79.3% (n=215) of patients with ARF and 18% (n=131) of patients without acute failure had deceased. Additionally, diabetes, hypertension, coronary artery disease (CAD), cancer and neurological diseases were higher in patients with ARF.

ARF was observed in 27.1% (n=271) of the individuals. The laboratory and hemodialysis evaluation results of the patients with ARF at the time of diagnosis were given in **Table 2**. Hemodialysis had been administered in 44.3% (n=120) of patients with ARF. The reasons for hemodialysis were ischemia in 36%, sepsis and multifactorial reasons in 32% of the subjects.

The distribution of laboratory parameters at the onset and at the time of diagnosis of patients with ARF was given in **Table 3.** When the table was examined, it was observed that there was a statistically significant difference compared to the initial measurements in urea, creatinine, uric acid and Na increased compared to baseline (p<0.001) as all parameters except K. All values from baseline increased at the time of diagnosis, while a decrease was observed in the GFR value (p<0.001).

Table 1. Distribution of clinical findings of patients with acute renal failure

Characteristics (n=1000)	Total	ARF (-) (n=729)	ARF (+) (n=271)	P-value
	n (%) or Median±SD	n (%) or Median±SD	n (%) or Median±SD	
Age, years	63±16	62±17	67±14	<0.001
Gender				0.007
Female	366 (36.6)	285 (39.1)	81 (29.9)	
Male	634 (63.4)	444 (60.9)	190 (70.1)	
Day of admission	14±9.1	13±8.2	16.7±10.8	<0.001
Day of intubation	5±9	3±7	10±10	<0.001
HFNO	644 (64.4)	451 (61.9)	193 (71.2)	0.006
NIMV	158 (15.8)	113 (15.5)	45 (16.6)	0.67
IMV	432 (43.2)	202 (27.7)	230 (84.9)	<0.001
Comorbidity				
Diabetes mellitus	251 (25.1)	163 (22.4)	88 (32.5)	0.001
Hypertension	412 (41.2)	280 (38.4)	132 (48.7)	0.003
CAD	238 (23.8)	161 (22.1)	77 (28.4)	0.037
COPD	142 (14.2)	103 (14.1)	39 (14.4)	0.916
Renal	2 (0.2)	1 (0.1)	1 (0.4)	0.469
Cancer	166 (16.6)	108 (14.8)	58 (21.4)	0.013
Neurologic	212 (21.2)	170 (23.3)	42 (15.5)	0.007
APACHE score	8.1±4.7	7.4±4.3	9.9±5	<0.001
SOFA score	3.7±2.2	3.3±1.9	4.7±2.7	<0.001
Baseline urea	45.2±19.5	42.5±18.1	52.5±21.2	<0.001
Baseline creatinine	0.8±2.7	0.8±3.2	0.7±0.2	0.596
Baseline GFR	99.3±18.2	101.3±19.7	93.9±11.5	<0.001
Baseline Na+	138.3±9	138.3±8.5	138.3±10.3	0.961
Baseline K+3	4.1±1.3	4.1±1.4	4±0.6	0.51
Baseline uric acidt	4.4±1.8	4.3±1.7	4.6±1.8	0.021
Procalcitonin	1.2±6.3	1.2±6.5	1.1±5.7	0.938
Inotrope				<0.001
None	631 (63.1)	580 (79.6)	51 (18.8)	
Nor-adrenaline	359 (35.9)	144 (19.8)	215 (79.3)	
Nor-adrenaline+Dopamine	10 (1)	5 (0.7)	5 (1.8)	
Steroid				<0.001
No	394 (39.4)	315 (43.2)	79 (29.2)	
250 Mg Methylprednisolone	202 (20.2)	129 (17.7)	73 (26.9)	
>250 Mg Methylprednisolone	123 (12.3)	90 (12.3)	33 (12.2)	
80 Mg Methylprednisolone	145 (14.5)	99 (13.6)	46 (17)	
6 Mg Dexamethasone	84 (8.4)	60 (8.2)	24 (8.9)	
Hydrocortisone	1 (0.1)	0 (0)	1 (0.4)	
40 Mg Metilprednizolon	51 (5.1)	36 (4.9)	15 (5.5)	
Final Status				<0.001
Discharged	346 (34.6)	131 (18)	215 (79.3)	
Exitus	654 (65.4)	598 (82)	56 (20.7)	

HFNO: High flow nasal oxygen, NIMV: Non invasive mechanical ventilation, IMV: İnvasive mechanical ventilation, CAD: Coronary artery disease, COPD: Chronic obstructive pulmonary disease

Table 2. Acute renal failure related features

Characteristics (n=271)	n (%) or Median±SD
What day did ARF develop?	10±7
Urea when ARF developed	106.9±47.9
Creatinine when ARF developed	1.5±0.5
GFR when ARF developed	45.7±14.9
Sodium when ARF developed	143.1±8
Potassium when ARF developed	6.5±30.3
Uric acid when ARF develops	6.1±3.2
Hemodialysis	120 (44.3)
Reason for hemodialysis	
Ischemic	97 (36)
Sepsis	86 (32)
Multifactorial	86 (32)
Uric acid at the entrance to hemodialysis	8.7±2.7

ARF: Acute renal failure, GFR: Glomerular filtration rate

Table 3. Evaluation of laboratory findings of patients with acute renal failure

Variables (n=271)	Median±SD	P-Value
Baseline urea	52.6±21.2	<0.001
Urea when ARF developed	106.9±47.9	
Baseline creatinine	0.7±0.2	<0.001
Creatinine when ARF developed	1.5±0.5	
Baseline GFR	93.8±11.4	<0.001
GFR when ARF developed	45.7±14.9	
Baseline sodium	138.3±10.3	<0.001
Sodiumwhen ARF developed	143.1±8	
Baseline potassium	4±0.6	0.187
Potassium when ARF developed	6.5±30.3	
Baseline uric acid	4.6±1.8	<0.001
Uric acid when ARF developed	6.1±3.2	

ARF: Acute renal failure, GFR: Glomerular filtration rate

The distribution of uric acid measurements at the beginning, time of diagnosis and during hemodialysis among patients who developed AFR were given in **Table 4.** When the table was examined, it was observed that there was a statistically significant difference between the uric acid measurements of the patients undergoing hemodialysis ($p<0.05$) and uric acid measurements were increased compared to baseline.

Table 4. Uric acid distribution of patients undergoing hemodialysis

Variables (n=120)	Mean±SD	P value
Baseline Uric acid	4.5±2.0	
Uric acid when ARF developed	6.3±3.9	<0.001
Uric acid at the entrance to hemodialysis	8.7±2.7	

ARF: Acute renal failure

DISCUSSION

The most common causes of ARF in the hospital conditions can be stated as prerenal events and acute tubuler necrosis (ATN) (13). In a multicenter study, ATN was reported in 45% of cases, prerenal events in 21%, acute attack due to prerenal causes on the basis of CRF in 12.7%, and postrenal causes in only 10% of cases (14). In an early research by Brivet et al. (15), prerenal causes were found in 17% of the cases, intrinsic renal causes (mostly ATN) in 78%, and postrenal causes in 5% of the individuals. In another single-center study of 81 patients, sepsis was the primary cause of ARF (44%) followed by drug toxicity in 14%, and obstructive uropathy in 11% of cases (16).

Major surgical procedures are an important risk factor for the development of AFR in hospitalized patients, thus it increases the length of hospital stay, cost, morbidity and mortality. Cardiac, vascular and major abdominal surgeries are the ones with the highest risk among surgical procedures. Prerenal azotemia and ATN are usually responsible for perioperative ARF(17). In a study examining 2672 patients who underwent coronary artery by-pass surgery (CABG), it was reported that 8% of the patients developed ARF in the post-operative period, 14% of them resulted in death, and on the contrary, the mortality rate was 1.8% in patients who did not develop ARF (18). Abelha et al. (19), examined 1597 patients in the post-anaesthetic ICU and the incidence of ARF was found to be 7.5%. In the same study, it was observed that the mortality rate in patients with ARF was approximately four times higher than in patients without ARF.

Factors that increase the risk of perioperative ARF can be listed as age, history of CRF, heart disease, use of nephrotoxic agents (radiocontrast, NSAID, ACEI, ARB and diuretics), hypertension, diabetes mellitus, peripheral vascular disease, emergency surgery, type and procedures of surgery (20).

In previous research it was shown that serum creatinine value is not a good predictor for the diagnosis of renal failure in the elderly. Since body muscle mass decreases with increasing age, the creatinine value is low as long as the actual GFR is measured. In addition, when there is a sudden decrease in GFR in the elderly, a rapid and parallel increase in serum creatinine does not occur, since muscle mass is reduced. For this reason, the search for new predictive markers that are not affected by age, muscle mass, diet and physical activities that can be used in the diagnosis of ARF continues. Herget et al. (21) reported that the serum cystatin-C level in elderly patients increased by 50% before clinical ARF has observed. In another study conducted in intensive care patients, serum cystatin C level was found to have a good positive predictive value for ARF (22). Apart from the serum cystatin-C level, there are also studies on some new markers (such as KIM-1, urinary interleukin-18 level, NGAL) in urine and serum (2). In this study, a statistically significant difference was found compared to the initial measurements in urea, creatinine, uric acid and Na increased compared to baseline ($p<0.001$) as all parameters except K. All values from baseline increased at the time of diagnosis, while a decrease was observed in the GFR value ($p<0.001$).

The most important cause of death in patients with ARF are infection (especially sepsis), cardiovascular and pulmonary dysfunction. Although it usually depends on the underlying cause, ARF has a mortality rate of 20-70% despite advances in medical care (23).

In the study of Nash et al. (24), the rate of ARF was found to be 7% in patients admitted to the hospital, while this rate was 23% in ICU. In the study conducted by Medve et al. (25) in 7 ICU between October and November 2009 in Hungary, ARF was detected in 24.4% of patients. The mean age of these patients was 64.9 years. Liano et al. (26) evaluated 740 ARF patients who applied to 13 tertiary health institutions and found ATN in 45% of the patients, prerenal causes in 21% and postrenal causes in 10%.

In the study conducted in Northern Italy, ARF has been found in 25.6% of diabetes patients, 58.5% of hypertension patients, 12.8% of NSAID users, 19.2% of ACEI and ARB users, 5.1% of contrast material administered 5.1% individuals and 25.6% of subjects with sepsis. In the study of Liangos et al. (13), diabetes was 10.6%, hypertension was 13.6%, cancer was 2.9%, and sepsis was 1.7% in ARF patients. The rate of those who needed dialysis was 5.7% (13,15). In the study of Uchino et al. (19) based on multicenter intensive care data, the etiology of 1738 ARF patients was 10% sepsis, 25.6% hypovolemia, 19% drug use, and 2.6% obstructive uropathy. Continuous hemodialysis was required in 80%

of the patients, intermittent hemodialysis was required in 16.9% and peritoneal dialysis was required in 3.2%. In the study conducted by Barrantes et al. (23) of 735 ARF patients, 72.3% of patients had drug use (ARB, ACEI, NSAID, contrast, etc.), 18.1% had infection, 35.8% had hypovolemia (nausea, vomiting, diarrhea, etc.) 12.9% of the patients required RRT (23). In the etiology of ARF patients followed in ICU in Hungary, 44% had septic shock, 39% had hypovolemia, 2% were drug users (25). In our country, 541 ARF patients (mean age 64.9±15.6) were evaluated between 2008 and 2012 in Central Anatolia. The underlying etiology was several diseases in 78%, acute gastroenteritis in 35.1%, drug use in 14.8%, heart failure in 9.6%, use of contrast material in 7% and sepsis in 5.4% (26). In the current study it was seen that the mean laboratory values of patients who developed ARF were higher in all parameters except the neurological disease and the initial GFR value. Additionally, diabetes, hypertension, coronary artery disease, cancer and neurological diseases were higher in patients with ARF.

Uchino et al. (27), reported that mortality was 52% in ARF patients with a mean age of 67 years in ICU. The mortality rate in the hospital excluding intensive care patients was 8%. Among the risk factors, the use of vasopressor agents, mechanical ventilation, and septic shock were more common. In the study of Barrantes, the mortality rate was found to be higher (15.2%) especially in ARF patients over the age of 60 (27). Medve et al. (25), published that mortality was 49% in intensive care ARF patients, and risk factors wereage, sepsis, and mechanical ventilation. In a study conducted from Turkey, the mortality rate was found to be 7.4%, and among the causes of death, cardiopulmonary failure was 70%, and sepsis and myocardial infarction were 10% (28). In this study 79.3% of patients with ARF and 18% of patients without acute failure had deceased.

Elevated uric acid level is a common finding in renal failure. In the past, it was stated that uric acid elevation developed only due to decreased excretion from the kidneys, but today it has been shown that uric acid also plays an active role in the formation and progression of kidney damage. It has been shown that hyperuricemia causes renal vasoconstriction, systemic hypertension, tubulointerstitial damage, decreased nitric oxide synthase production, and afferent arteriolopathy. In this study the presence of diabetes mellitus, hypertension, coronary artery disease was higher in patients with ARF.

Uric acid suppresses nitric oxide bioactivity, affects insulin resistance via inflammatory factors and adipocytokines (22). In this study, uric acid levels were higher in patients with ARF and even higher in individuals who underwent hemodialysis.

CONCLUSION

Regarding the results of this study one can conclude that serum uric acid level has been shown to be an independent risk factor for decreased renal function. Additionally, elevated uric acid levels lead to increased hemodialysis, morbidity and mortality in the ICU. This outcome has been confirmed with published studies.

Abbreviations

ACEI: Angiotensin converting enzyme inhibitors, **AKI:** Acute kidney injury, **ARB:** Angiotensin renin blockers, **ARF:** Acute renal failure, **ATN:** Acute tubuler necrosis, **CABG:** Coronary artery by-pass surgery, **CAD:** Coronary artery disease, **COPD:** Chronic obstructive pulmonary disease, **CRF:** Chronic renal failure, **e-GFR:** Estimated glumerular filtration rate, **GFR:** Glomerular Filtration Rate, **HFNO:** High frequency nasal oxygen, **ICU**: Intensive care unit, **IMV:** Invasive mechanical ventilation, **KDIGO:** Kidney disease improving global outcomes , **MDRD:** Modification of diet in renal disease, **NIMV:** Non-invasive mechanical ventilation, **RRT:** renal replacement therapy, **SD:** Standard deviation, **SPSS:** Statistical package for the social sciences,

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:1 Clinical Researches Ethics Committee (Date: 20.04.2022, Decision No: E1-22-2565).

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.

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Treatment results of intensive care patients with cancer undergoing radiotherapy

Yoğun bakım yatışı sırasında radyoterapi endikasyonu konulan hastalarda tedavi sonuçlarımız

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ABSTRACT

Aim: This paper aims to evaluate the treatment completion status and survival outcomes of patients who were prescribed radiotherapy during intensive care unit (ICU) hospitalization in the radiation oncology clinic.

Material and Method: Data on patients who underwent RT between January 1, 2020, and June 30, 2022, in the Radiation Oncology Clinic of Ankara City Hospital were retrospectively evaluated. The primary endpoint of this study is the patient status at the completion of the planned radiotherapy and the secondary endpoint is the overall survival (OS). The data were recorded and analyzed using SPSS version 26 (IBM Corporation, Armonk, NY, USA).

Results: The data of 11 patients who were indicated for radiotherapy while hospitalized for intensive care between May 20, 2020, and June 30, 2022, in the Ankara City Hospital Radiation Oncology Clinic were retrospectively analyzed. The median follow-up period from the onset of RT was 4.1 months (range 1–9.8). During this period, nine (81.8%) patients had deceased, and two (18.2%) patients were surviving. The median age of the patients was 55 years (range 3–70); four (36.4%) were female and seven (63.6%) were male. Seven (63.6%) of the patients completed the planned radiotherapy scheme and four (36.4%) did not complete the treatment. There was no significant relationship between the inability to complete the treatment and gender (p=0.194) or primary diagnosis (p=0.545). The median OS value of the patients was 4.1 months (range 1–9.8). In addition, the 1-month survival was 60.6%, and the 6-month survival was 20%. There was no significant relationship between OS and age (p=0.401; correlation coefficient: -282) or primary diagnosis (p=0.638). The median OS in women was 5.3 (range 2.7–9.8) months; the median OS in men was 1 month (range 1–5.5; p=0.059). The median OS of those who completed treatment was 4.5 months (range 1–9.8), while that of those who did not complete the treatment was 1.1 months (range 1–4; p=0.037).

Conclusion: Approximately 60% of the patients who were hospitalized in the ICU and indicated for RT were able to complete treatment. A significantly higher OS was achieved in patients who completed the RT protocol. Criteria must be developed when determining the indications for radiotherapy of cancer patients hospitalized in intensive care.

Keywords: Radiotherapy, intensive care unit, palliative

ÖZ

Amaç: Radyasyon onkolojisi kliniğinde yoğun bakım ünitesi (YBÜ) yatışı sırasında radyoterapi endikasyonu konulan hastaların tedavi tamamlama durumunu ve sağkalım sonuçlarını değerlendirmek amaçlanmıştır.

Gereç ve Yöntem: Ankara Şehir Hastanesi Radyasyon Onkolojisi Kliniği'nde 01.01.2020-30.06.2022 tarihleri arasında RT uygulanmış hastaların verileri retrospektif olarak değerlendirilmiştir. Bu araştırmanın primer sonlanım noktası hastaların tedaviyi tamamlama durumudur ve sekonder sonlanım noktası genel sağkalımdır (GS). Veriler SPSS ver. 26 (İBM Corporation, Armonk, NY, USA) kullanılarak kaydedilmiştir ve analiz edilmiştir.

Bulgular: Araştırmamızda Ankara Şehir Hastanesi Radyasyon Onkolojisi Kliniğinde 20.05.2020 - 30.06.2022 tarihleri arasında radyoterapi alan hastalardan, endikasyonu yoğun bakım yatışı sırasında konulmuş olan 11 hastanın verileri retrospektif incelenmiştir. RT başlangıcından itibaren medyan takip süresi 4.1 (range 1-9.8) aydır. Bu süre içinde 9 (81.8%) hasta ex, 2 (18.2%) hasta hayattadır. Hastaların median yaşı 55 (range 3-70); 4 (36.4%) kadın 7 (63.6%)'sı erkektir. Hastaların 7 (%63.6)' si planlanan radyoterapi şemasını tamamlanmıştır ve 4 (36.4%)'ü ise tedaviyi tamamlayamamıştır. Tedaviyi tamamlayamama ile primer tanı (p=0.545) arasında anlamlı ilişki tespit edilememiştir. Hastaların median GS değeri 4.1 (range 1-9.8) aydır Ayrıca 1 aylık sağkalım 60.6 % ve 6 aylık sağkalım 20%'dır. GS ile yaş (p=0.401; correlation coefficient -282) ve primer tanı (p=0.638) arasında anlamlı ilişki yoktur. Kadınlarda median GS 5.3 (range 2.7-9.8) aydır; erkeklerde median GS 1 (range 1-5.5) aydır (p=0.059). Tedaviyi tamamlayanların median GS değeri 4.5 (aralık 1-9.8) ay iken; tedaviyi tamamlayamayanlar median GS 1.1 (range 1-4) aydır (p=0.037).

Sonuç: YBÜ yatışı olup RT endikasyonu konulan hastaların yaklaşık %60'ı tedaviyi tamamlayabilmiştir. Planlanan RT şemasını tamamlayan hastalarda anlamlı olarak daha yüksek GS elde edilmiştir. Yoğun bakım yatışı olan kanser hastalarının radyoterapi endikasyonlarını belirlerken uygulanacak kriterlerin geliştirilmesi gerekmektedir.

Anahtar Kelimeler: Radyoterapi, yoğun bakım ünitesi, palyatif

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INTRODUCTION

Recent advances in cancer treatment have increased survival rates, while new complications may occur due to new treatment modalities (1,2). With the extension of treatment processes and the introduction of new treatment agents, changes in the need for an intensive care unit (ICU) are also being monitored. It has been reported that ICU hospitalizations are gradually increasing due to the treatment-related toxicity of locally advanced cancer cases (3). These hospitalizations may be due to the underlying primary cancer, comorbid diseases, or treatment toxicity. ICU hospitalization is most common in cases of leukemia-lymphoma cancer diagnoses; among solid tumors, it is most common with lung cancer (4).In the ICU, patients are evaluated not only oncologically but also psychosocially (5,6).

Radiation therapy (RT) is one of the cornerstones of the treatment of cancer patients (7,8). It is used in different stages of cancer treatment as primary, adjuvant, and palliative therapy. To perform RT, the patient must be moved to the radiotherapy unit and immobilized in the treatment room. Alongside the increasing need for ICU care among cancer patients and the growing population of patients needing ICU hospitalization, uncertainties in the RT indications of patients in the ICU have become more important than before. Clinicians' general opinion is that patients in the ICU cannot be mobilized to the RT device, which is necessary to apply RT, and immobilization during RT cannot be achieved. So, ICU patients are not indicated for RT until the clinical necessity or the individual condition of the patient has been assessed. Issues such as the expected benefits and toxicity of treatment and the cost of treatment also factor into whether to indicate RT for patients admitted to the ICU. Each patient must be individually assessed for the risks and benefits that will be achieved with treatment. This is especially true for critical patients who will require daily transportation to the RT room from the treatment environment where important interventions can be applied, such as the intensive care unit. Voight et al. (9) reported that in-hospital transportation of cancer patients with ICU hospitalization leads to an increase in hospital and ICU hospitalization time, vasopressin use, and mortality.

Studies on the treatment and follow-up of cancer patients with indications for intensive care are increasingly being conducted (10,11,12). These studies primarily seek to determine the balance between choosing a treatment that will benefit the patient and providing end-of-life care. Different types of cancer, different treatment modalities, different ICU hospitalization indications, and differences in health system policies make it difficult to reach a consensus among studies. Radiotherapy's utility in this group of patients was investigated, in particular, to treat respiratory failure due to malignant obstruction.

RT is a high-cost oncological treatment (13,14). Developments in the field of radiotherapy and case studies including metastatic disease give hope (15,16,17). To evaluate the effect of RT in patients who have been admitted to the ICU, it is important to consider both the necessity of mobilizing patients from the ICU and the regulation of oncological treatment costs. If RT contributes to the health of this group of patients, they should not be deprived of effective treatment only because of ICU hospitalization; if it is ineffective, high-cost treatment should not be forced, although it may reduce patients' comfort. This research topic, which is not yet well represented in the literature, will be examined retrospectively with data from a single center. This study aims to report the characteristics of patients who were prescribed radiotherapy during ICU hospitalization in the radiation oncology clinic, their treatment completion status, and treatment and survival results.

MATERIAL AND METHOD

Data from patients who underwent RT between January 1, 2020, and June 30, 2022, in the Radiation Oncology Clinic of Ankara City Hospital were retrospectively evaluated. The study was initiated with the approval by the Ankara City Hospital Hospital Clinical Research Ethics Committee (Date: 27.07.2022, Decision No: 2787). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient interview information, patient files, and electronic system data were used for the study. Patient age, gender, primary disease, pathological data, disease stage and treatment details, performance status, presence of comorbid disease, other simultaneous medical treatments administered during RT, RT dose and fraction details, RT completion status, RT-related acute side effects, and final patient status were noted.

Patient Selection

Patients who were directed to our clinic during hospitalization in the Ankara City Hospital ICU, diagnosed with cancer with pathological evidence and indicated for RT, and whose file data were complete were included in the study. The main goal of the research is the indication of RT in patients with ICU hospitalization. Therefore, patients with ICU hospitalization were examined at the stage when the RT decision was made. Patients who were not in intensive care at the beginning of RT and were admitted to the ICU during treatment or who had missing file data were excluded.

Primary and Secondary Endpoints of the Study

The primary endpoint of the study is the status of patients' completion of the planned radiotherapy schedule. The secondary endpoint of the study is general survival (OS).

The RT end date was considered the start date for the OS. The endpoint for the OS is the last control date for living patients and the exitus date for deceased patients.

Statistical Analysis

The data were recorded and analyzed using SPSS version 26 (IBM Corporation, Armonk, NY, USA). The categorical demographic characteristics of the patients were calculated with chi-squared and Fisher's exact tests. Kolmogorov–Smirnov and Shapiro–Wilk tests were used to check the suitability of the data for normal distribution. Nonparametric tests were used because the data did not seem to fit the normal distribution.

Spearman's correlation test was used to evaluate the correlation between the numerical variables. Kaplan–Meier was used in the univariate survey analyses and comparisons were made with the log-rank test. In the multivariate analyses, a Cox regression test was used and the significance limit was accepted as ≤ 0.05.

RESULTS

In our study, the data of 11 patients whose radiotherapy indication was placed during intensive care hospitalization between May 20, 2020, and June 30, 2022, at Ankara City Hospital Radiation Oncology Clinic were retrospectively analyzed. The causes of patients' ICU hospitalization include intracranial hematoma, pulmonary thromboembolism, vaginal bleeding, sepsis, status epilepticus, hypoxia, and general condition disorders.

The median follow-up period from the onset of RT was 4.1 months (range 1–9.8). During this period, nine (81.8%) patients had deceased and two (18.2%) were alive. The median age of the patients was 55 years (range 3–70); four (36.4%) were female and seven (63.6%) were male. Five (45.5%) of the patients received palliative RT due to brain metastasis. The patients' demographic data, disease details, and treatment details are summarized in **Table 1** and **Table 2**.

Seven (63.6%) of the patients completed the treatment and four (36.4%) did not. The reasons for the inability to continue treatment were the need for mechanical ventilation. There was no significant relationship between the inability to complete treatment and the primary diagnosis (p=0.545). The median OS value of the patients during the follow-up period was 4.1 months (range 1–9.8) (**Figure 1**). In addition, the 1-month survival is 60.6%; the 2-month survival is 50.5%; the 3-month survival is 40.4%, and the 6-month survival is 20%.

Table 1. Patient and treatment details

Parameters		
Age	55 (3-70)	
Gender		
Female	4	(36.4%)
Male	7	(63.6%)
Primary		
BM	5	(45.5%)
Others	6	(54.5%)
RT indication		
BM	6	(54.5%)
Vaginal bleeding	2	(18.2%)
Hypoxia	2	(18.2%)
Adjuvant	1	(9.1%)
ICU indication		
Intracranial hemorrhage	3	(27.3%)
Pulmonary thromboembolism	2	(18.2%)
Hypoxia	2	(18.2%)
Vaginal bleeding	1	(9.1%)
Status epilepticus	1	(9.1%)
Sepsis	1	(9.1%)
Postoperative	1	(9.1%)
Completion of treatment		
Treatment completed	7	(63.6%)
Treatment not completed	4	(36.4%)
Last status		
Exitus	9	(81.8%)
Alive	2	(18.2%)

Abbreviations: BM=Brain Metastasis

Table 2. Patients and treatment characteristics

Patient	Diagnose	Palliative treatment intent	Prescribed dose	Given fraction number	Last status
Male, 3 yo	Neuroblastoma	Brain metastasis	150 cGyx10 frc	3	Ex
Female, 55 yo	Renal cell cancer, lung metastasis	Hemoptysis	500cGyx4 frc	4	Ex
Male, 10 yo	High grade B cell lymphoma, brain involvement	Brain involvement	180 cGY x 13 frc	1	Ex
Male, 70 yo	Unknown primary with brain metastasis	Brain metastasis	400 cGY x 5 frc	0	Ex
Male, 63 yo	Metastatic lung cancer	Shortness of breath	400 cGy x 5 frc	5	Ex
Female, 49 yo	Metastatic thyroid cancer	Shortness of breath	300cGy x 18 frc	18	Alive
Male, 66 yo	Endometrial cancer with lung metastasis	Vaginal bleeding	400 cGyx 5 frc	5	Ex
Female, 47 yo	Lung cancer with brain metastasis	Brain metastasis	800cGy x 1 frc	1	Ex
Male, 56 yo	Glioblastom	Inoperable mass	300 cGy x 10 frc	2	Ex
Female, 57 yo	Recurrent endometrial cancer	Vaginal bleeding	500 cGy x 5 frc	5	Ex
Male, 52 yo	Lung cancer with bone and brain metastasis	Brain metastasis	400 cGy x 5 frc	5	Alive

Abbreviations: yo: years old; cGy: santigray; frc: fractions; ex:exitus

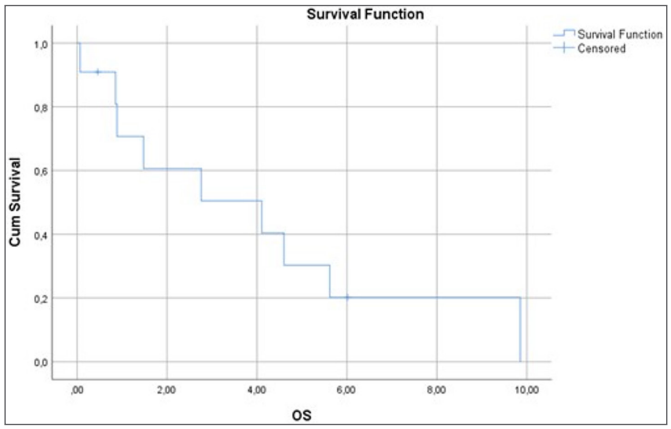

Figure 1. Results of Kaplan-Meier analysis of overall survival of patients

When OS-influencing factors were evaluated, there was no significant correlation between the age of the patients and OS (p=0.401; correlation coefficient: -282). There was also no statistically significant relationship between the patients' primary diagnoses and OS (p=0.638). When compared by gender; the median OS in females was 5.3 months (range 2.7–9.8), and the median OS in males was 1 month (range 1–5.5; p=0.059). A median OS of approximately 4.5 months more was obtained in women than in men, and the difference is close to the significance limit (**Figure 2,3**). With an increased number of patients, this difference may become significant.

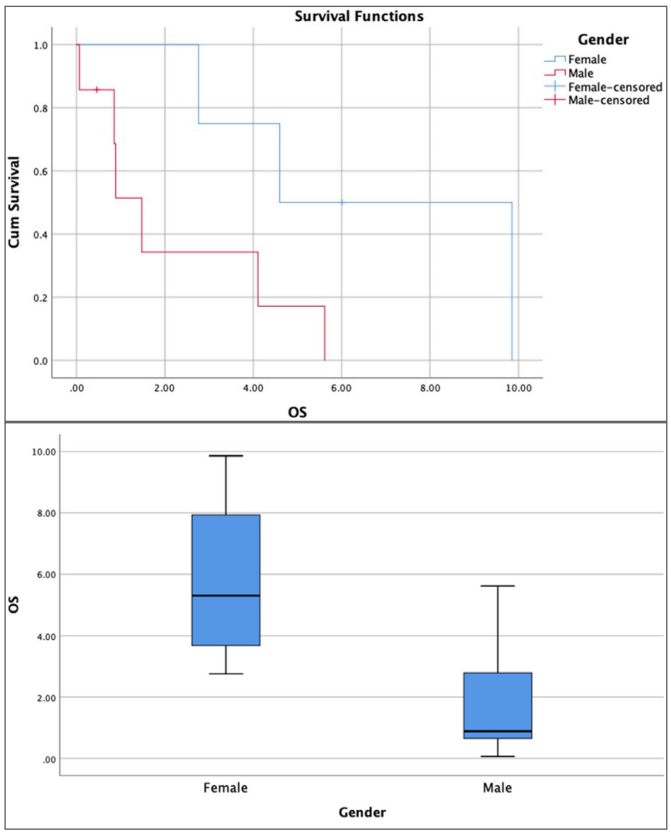

Figure 2,3. The Relationship between gender and OS

When those who completed the treatment and those who could not complete it were examined; the median OS of those who completed the treatment was 4.5 months (range 1–9.8); those who did not complete treatment had a median OS of 1.1 months (range 1–4). Those who completed the treatment lived significantly longer. All of the patients who could not complete the treatment had deceased within 1–4 months; the remaining two patients were in the group that completed treatment (p=0.037) (**Figure 4,5**).

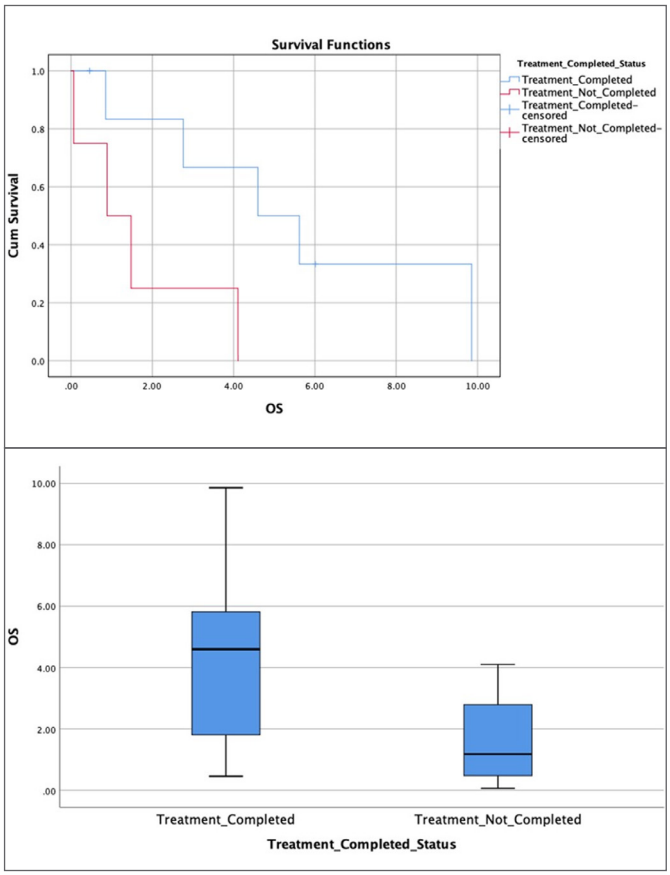

Figure 4,5. The Relationship between status of treatment completion and OS

DISCUSSION

This study aimed to examine the completion of the planned treatment and the overall survival rates of cancer patients who were indicated for radiotherapy during ICU hospitalization. According to the study findings, 63.6% of the patients were able to complete the treatment. The median survival of patients was 4 months, and the 6-month survival was 20%. The median OS in women is 4 months greater than in men (5.8 months vs. 1 month), and this difference is close to the significance limit. A significantly higher OS was obtained in those patients who completed treatment (p=0.037).

With the new developments in cancer treatment, changes in the ICU admission patterns of these patients have been observed over time.

The main important factors in this change are increased survival times and the new toxic complications that develop with new treatments. In Vigneron et al.'s study, the ICU admission of cases with solid malignancies was reported (3). The ICU admission status of 1,525 patients with solid tumor diagnoses was evaluated in a single-center study, and the lungs and gastrointestinal system were reported as the most common primary tumor sites. Another important point reported is a recent increase in the ICU admissions of metastatic patients, and this increase is generally due to drug and treatment-related toxicity. In this study, the 1-year OS rate was 33.2% in patients whose follow-up was completed.

Although there is an increase in ICU admissions of cancer cases, the mortality of these patients is reportedly two times higher than that of non-cancer patients (18). Recent studies and guidelines have advanced toward correctly evaluating which cancer patients are suitable for ICU admission (19). Two main elements are involved in the decision to admit patients to the ICU and apply the treatment: The first is whether the treatment that is planned for a cancer patient in the intensive care unit will prolong life at an acceptable level or contribute to the patient's symptom palliation, and the second is whether the planned treatment and ICU hospitalization will make the time until death more distressing. The balance between these two factors should be calculated carefully when deciding on the hospitalization and treatment of the patient.

As mentioned above, current studies are moving toward determining which patients will benefit from ICU admission. In a review published by the European Society for Medical Oncology, patients who are recommended for admittance to the ICU are cases in remission, newly diagnosed cancer cases with a life expectancy of more than 1 year, patients requiring ICU admission due to OCT complications, and cases of locally advanced solid tumors with a life expectancy of more than 1 year (19). The development of these and similar criteria for patients who will be treated during ICU hospitalization may prevent unnecessary treatment applications.

Another factor that may be important in establishing a cancer treatment indication among ICU admissions is the chosen treatment modality and purpose of treatment. Radiotherapy is an important component of palliative therapy (20,21). The literature on radiotherapy indication that is relevant to this article generally includes studies evaluating palliative irradiation due to malignant airway obstruction (16,17).

Louie et al. (16), who have published important studies on this subject, report that 26 patients who were offered palliative RT due to malignant obstruction were retrospectively examined. In terms of overall survival and extubation success, the median survival was reported as 0.36 months (range 0–113 months). The 6-month overall survival (OS) was reported as 11%. In our study, which uses a very different patient population and sample size, the reported 6-month OS was 20%. Researchers have reported a relationship between an increase in the applied radiation dose and survival. In Assi et al.'s study, in which the ICU hospitalizations of cancer cases were evaluated in general, the median OS reported was 22 days (12). This suggests that palliative radiotherapy applications may be beneficial in this patient group. In addition, evaluating the subject in terms of patient palliation and the achievement of the palliation target are elements that will be useful in making the treatment decision. Due to the retrospective nature of the study, this evaluation could not be made or reported for these patients.

This study has many limitations in terms of adequate evaluation of the subject. First, this is a retrospective and single-center study with a small number of cases. In our clinic, which is a new center, a common criterion has not yet been determined for these patients and the determination of treatment indications is clinician-dependent. The heterogeneity of the patient group in terms of diagnosis, age, and purpose of RT makes it difficult to reach a consensus. In addition to these limitations, the positive effect of the completion of the planned treatment on survival emphasizes the importance of evaluating patients from this perspective.

CONCLUSION

Despite its shortcomings, this cohort data, which comprised mainly brain metastasis cases, was expected to contribute usefully due to the limited literature data on the subject. Prospective and planned studies with homogeneous patient groups are needed on this subject.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara City Hospital No: 1 Clinical Researches Ethics Committee (Date: 27.07.2022, Decision No: E1-22-2787).

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.

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The effects and differences of kidney transplantation and hemodialysis treatments on quality of life

Böbrek nakli ve hemodiyaliz hastalarında yaşam kalitesini etkileyen faktörler farklılık göstermektedir

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ABSTRACT

Aim: Renal replacement therapies (RRT), including dialysis modalities and renal transplantation (RT), affect patients' quality of life (QoL) differently. This study aimed to determine the factors affecting the QoL in hemodialysis (HD) and RT patients.

Material and Method: One hundred patients in each RT and HD group were included in the study. Socio-demographic data was determined with a questionnaire. Laboratory information and other medical information of the patients were obtained from the medical records. Short Form-36 (SF-36) and Nottingham Health Profile (NHP) scales were used to assess the QoL.

Results: The mean ages in HD and RT patients were 58.28±15.21 and 47.92±12.01 years. Most patients were male (53% HD, 68% RT). RT patients had a higher QoL than HD patients in all components. On the NHP scale, RT patients had higher QoL in all parts except social isolation and emotional reactions. Male gender, non-smoker status, high education level, being employed and living in the city, and some laboratory parameters (hemoglobin, ferritin, sodium, calcium, magnesium, and albumin) positively affected the QoL in the HD group; diabetes and CVD had a negative impact on the QoL. In the RT group, male gender, high education level, being employed; normal potassium, phosphorus, and parathormone levels affect QoL positively while hypertension and CVD negatively affect the QoL.

Conclusion: Factors affecting QoL in patients receiving RRT are different. Efforts to correct laboratory parameters may impact the quality of life in HD patients. Returning to working life could increase the QoL in RT patients.

Keywords: Hemodialysis, quality of life, renal transplantation

ÖZ

Amaç: Diyaliz modalitelerini ve böbrek naklini (BN) içeren renal replasman tedavileri (RRT), hastaların yaşam kalitesini (QoL) farklı şekilde etkiler. Bu çalışmada hemodiyaliz (HD) ve BN hastalarında yaşam kalitesini etkileyen faktörlerin belirlenmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya RT ve HD gruplarının her birinde 100 hasta dahil edildi. Sosyo-demografik veriler anket yolu ile toplandı. Hastaların laboratuvar ve diğer tıbbi bilgileri tıbbi kayıtlarından elde edildi. Yaşam kalitesini değerlendirmek için Kısa Form-36 (SF-36) ve Nottingham Sağlık Profili (NHP) ölçekleri kullanıldı.

Bulgular: HD ve BN hastalarında ortalama yaşlar sırasıyla 58,28±15,21 ve 47,92±12,01 idi. Hastaların çoğu erkekti (%53 HD, %68 BN). Böbrek nakli hastaları, tüm bileşenlerde HD hastalarından daha yüksek bir yaşam kalitesine sahipti. NHP ölçeğinde, BN hastalarının sosyal izolasyon ve duygusal tepkiler dışında tüm alanlarda yaşam kalitesi daha yüksekti. HD grubunda erkek cinsiyet, sigara içmeme, yüksek eğitim düzeyi, çalışıyor ve şehirde yaşıyor olmak ile bazı laboratuvar parametreleri (hemoglobin, ferritin, sodyum, kalsiyum, magnezyum ve albümin düzeyleri) yaşam kalitesini olumlu yönde etkilerken; diyabet ve kardiyovasküler hastalık (KVH) yaşam kalitesi üzerinde olumsuz bir etkiye sahipti. BN grubunda erkek cinsiyet, yüksek eğitim düzeyi, çalışıyor olmak; normal potasyum, fosfor ve parathormon seviyeleri QoL'yi olumlu etkilerken, KVH ve hipertansiyon QoL'yi olumsuz etkilemekteydi.

Sonuç: Farklı RRT alan hastalarda yaşam kalitesini etkileyen faktörler farklıdır. HD hastalarında laboratuvar parametrelerini düzeltmek için çaba göstermek yaşam kalitesi üzerinde etkili olabilir. Çalışma hayatına dönüş, BN hastalarında yaşam kalitesini artırabilir.

Anahtar Kelimeler: Böbrek nakli, hemodiyaliz, yaşam kalitesi

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INTRODUCTION

Chronic kidney disease is a common public health problem (1). Renal replacement therapies (RRT) have prolonged the life expectancy in patients with end-stage renal disease and indirectly increased the number of patients. Increasing the survival of patients has brought with it efforts to improve the quality of life (QoL) in patients.

Improvement of QoL is as significant as survival in patients with end-stage renal disease. In addition to the presence of factors such as anemia and depression that affect the general population and affect the QoL in patients receiving RRT, there are various factors specific to these patients. RRT, including dialysis modalities and renal transplantation (RT), affect patients' QoL differently (2). Renal transplant patients offer better QoL compared to dialysis modalities. On the other hand, when all patient groups are evaluated separately, serious differences are observed in the quality of life of the patients. We have limited information about the factors affecting the QoL in patients treated with given treatments, apart from the RRT modality. This study aimed to determine the factors affecting the QoL in hemodialysis (HD) and RT patients.

MATERIAL AND METHOD

The study was initiated with the approval of the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.06.2020, Decision No: 2020/417), and the study was conducted under the ethical standards specified in the Helsinki Declaration. One hundred RT and one hundred HD patients who were followed up at Ondokuz Mayıs University Medical Faculty Hospital between June 1, 2020, and June 30, 2021, met the study criteria. Patients aged 18 years and older who had been on hemodialysis treatment for at least one year and patients with RT followed for more than six months without any rejection were included in the study. HD patients younger than 18 years of age or with mental/psychological disease or under HD treatment for less than one year were not included in the study. Patients with transplantation duration of fewer than six months or RT patients with concomitant malignancy or active infection were excluded.

Socio-demographic data was determined with a questionnaire. Laboratory information and other medical information of the patients were obtained from the medical records. Short Form-36 (SF-36) and Nottingham Health Profile (NHP) scales were used to assess the QoL. SF-36 and NHP are reliable tests for measuring the QoL. Studies showed the validity and reliability of the Turkish versions (3,4).

The SF-36 scale consists of 36 questions under eight titles (Physical Function, Physical Role Restriction, Social Function, Mental Health, Emotional Role Restriction, Energy/Vitality, Pain, General Health Perception), and each title score is evaluated between 0-100. High scores are associated with a higher QoL.

NHP consists of two parts. The first part has 38 questions with 'yes' or 'no' answers. There are questions about pain (8 questions), emotional reactions (9 questions), sleep patterns (5 questions), physical activity (8 questions), social isolation, and energy (6 questions). In the second part, the effects of the participants' health status on their daily lives are questioned. The second part examines whether daily life routines such as work-life, social life, home life, sexual life, hobbies, and holidays are affected. A 'yes' answer on each item represents the most severe complaint and gets the highest score. When the score of all 'yes' responses to a topic is summed up, 100 points are reached. Thus, zero reflects the best health status, while a hundred points reflect the worst health.

We aimed to determine the factors affecting the QoL in HD and RT patients.

Statistical Analysis

In descriptive statistics, numbers and percentages are given for categorical variables. Kolmogorov-Smirnov and Shapiro-Wilk tests were used to determine the conformity of continuous variables to normal distribution. The mean and standard deviation for continuous variables fit the normal distribution; median and minimum-maximum values are given if they do not provide the normal distribution. Median and 25-75 percentile values were used for the SF-36 and NHP scales that did not offer the normal distribution. In analytical analyses, the relationship between categorical variables was evaluated with chi-square and, where appropriate, Fisher's exact chi-square test. In comparing the means, the Student-T test was used for groups with normal distribution, and the Mann-Whitney-U test was used for groups that did not. The statistical significance level was accepted as $p<0.05$. Data entry and statistical analysis were performed with IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

RESULTS

In the patients included in the study, the mean ages were 58.28±15.21 and 47.92±12.01 years in HD and RT patients, respectively. Most patients were male (53% HD, 68% RT). **Table 1** shows the demographic and clinical characteristics of the patients.

When the two types of RRT were compared, there was no difference between the groups regarding gender, educational status, marital status, and survival. Age, smoking, employment status, residence, type of dialysis, and comorbidity differed between the groups (**Table 1**).

Table 1. Demographic and epidemiological characteristics of patients according to renal replacement therapy type

	HD (n=100)	RT (n=100)	p
Age (years)	58.28±15.21	47.92±12.01	<0.001
Gender (n)			0.108
Male	57	68	
Female	43	32	
Smoking			0.011
Non-smoker	52	54	
Smoker	18	5	
Ex-smoker	30	41	
Education status			0.120
Not graduated	6	7	
Primary school	71	60	
High school	18	21	
Associate degree	0	6	
License	5	6	
Marital status			0.432
Single	23	21	
Married	77	79	
Home situation			0.470
Single	3	5	
With family	97	95	
Employment status			0.001
Unemployed	91	73	
Employed	9	27	
Living place			<0.001
Village	13	30	
Town	23	38	
City center	64	32	
HD vascular access			<0.001
Catheter	18	9	
Fistula	82	63	
No (Pre-emptive)	0	28	
Hypertension (yes)	80	58	0.001
Diabetes mellitus (yes)	43	24	0.004
Cardiovascular disease (yes)	34	21	0.040
Co-morbid disease (n)	2 (0-3)	1 (0-3)	<0.001

HD: Hemodialysis, RT: Renal transplantation

When RT patients and HD patients were compared according to the SF-36 scale, RT patients had a higher QoL in all components. On the NHP scale, RT patients had higher QoL in all parts except social isolation and emotional reactions (**Table 2**).

When the effect of demographic characteristics on the QoL was examined (**Table 3**), the QoL was better in the male gender, and the difference in the QoL due to gender was more pronounced in RT patients. Active smoking affected the general health perception component of SF-36 in HD patients. There was no effect of active smoking on QoL in RT patients.

Table 2. Short Form-36 and Nottingham Health Profile scores by type of renal replacement therapy

	HD	RT	p
SF-36			
Physical function	62.50 (35-85)	90.00 (81.25-95)	<0.001
Physical role restriction	75 (25-100)	100 (75-100)	<0.001
Social function	87.50 (53,13-100)	100 (90.62-100)	<0.001
Mental health	68 (56-80)	76 (64-88)	0.004
Emotional role restriction	66.66 (33.33-100)	100 (66.66-100)	0.012
Energy/vitality	50 (30-70)	67.50 (55-85)	<0.001
Pain	67.50 (35-100)	90 (71.88-100)	<0.001
General health perception	45 (30-60)	70 (41.25-80)	<0.001
NHP			
NHP total score	122.78 (69.91-253.36)	50.58 (22.01-92.91)	<0.001
Pain NHP	20.33 (0-48.54)	0 (0-10.49)	<0.001
Emotional reactions	10.47 (0-35.30)	10.47 (0-23.71)	0.380
Sleep	28.67 (12.57-60.13)	12.57 (0-39.83)	<0.001
Social isolation	0 (0-22.53)	0 (0-21.54)	0.066
Physical activity	21.88 (0-52.67)	0 (0-0)	<0.001
Energy	24 (0-100)	0 (0-124)	<0.001

HD: Hemodialysis, RT: Renal transplantation, SF-36: Short Form-36, NHP: Nottingham Health Profile

Higher education was associated with better QoL. Educational status affected the physical function component of SF-36 in HD patients and the physical function and Energy/Vitality components of SF-36 in RT patients. Marital status was not effective on QoL in RT and HD patients. Home status didn't affect the patients' QoL (**Table 3**).

Employed was associated with a higher QoL. Employment status affected the physical function component in the SF-36 scale and the total score, emotional reaction, sleep, and energy components in the NHP scale of HD patients. Physical function, energy/vitality components on the SF-36 scale, and total score and parts in the NHP scale of RT patients were affected by working status. The most affected component was the physical function component of SF-36 in RT patients (p<0.001).

Vascular access (catheter or fistula) did not affect the QoL in HD patients and donor status (cadaver or living donor) in RT patients. Living in the city caused a significant difference in the emotional role restriction component of the SF-36 scale in HD patients. RT did not affect the QoL in patients. Hemoglobin, ferritin, sodium, calcium, magnesium, and albumin levels affected the QoL in HD patients. Potassium, phosphorus, and parathormone levels in the normal range in RT patients positively impact the QoL.

When all patients were evaluated together, comorbidity negatively affected the QoL. Physical function, physical role restriction, and energy components of the SF-36 scale were more affected. The presence of comorbidity decreased the HD group's QoL. The co-morbid condition that most affected the QoL was the presence of cardiovascular disease (CVD). In the SF-36 scale, comorbidity more significantly affected the results.

Table 3. Comparison of the effects of demographic characteristics on quality of life in hemodialysis and renal transplant patients

	Gender		Active smoker		Education		Marital status		Home situation		Employment		Vascular access/ Donor type		Living place	
	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	Fistula/ catheter	Living/ cadaveric	HD	RT
SF-36																
Physical function	✓	✓✓			✓	✓					✓	✓✓				
Physical role restriction		✓✓														
Social function																
Mental health																
Emotional role restriction		✓													✓	
Energy/Vitality						✓										
Pain		✓										✓				
General health perception		✓	✓													
NHP																
NHP total score	✓	✓									✓	✓				
Pain NHP		✓										✓				
Emotional reactions		✓									✓					
Sleep											✓✓					
Social isolation																
Physical activity	✓	✓✓														
Energy											✓					

✓ : p<0.05; ✓✓: p<0.001, HD: Hemodialysis, RT: Renal transplantation, SF-36: Short Form-36, NHP: Nottingham Health Profile

Table 4. Comparison of the effects of laboratory parameters on the quality of life in hemodialysis and kidney transplant patients

	Hb (11,9-14,6)		Ferritin (100-400)		Na (135-145)		K (3,5-5,5)		Ca (8,8-10,2)		P (2,3-4,7)		Mg (0,66-0,99)		PTH (150-650)		Albumin (3,5-5,5)	
	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT	HD	RT
SF-36																		
Physical function			✓		✓				✓								✓	
Physical role restriction	✓											✓					✓	
Social function					✓				✓✓								✓	
Mental health	✓		✓						✓				✓					
Emotional role restriction			✓		✓			✓	✓								✓	
Energy/Vitality	✓		✓✓		✓											✓	✓	
Pain													✓					
General health perception			✓													✓	✓	
NHP																		
NHP total score			✓						✓								✓	
Pain NHP																		
Emotional reactions																	✓	
Sleep													✓				✓	
Social isolation																	✓	
Physical activity									✓			✓						
Energy			✓✓		✓				✓								✓	

Hb: Hemoglobin, Na: Sodium, K: Potassium, Ca: Calcium, P: Phosphorus, Mg: Magnesium, PTH: Parathormone, HD: Hemodialysis, RT: Renal transplantation, SF-36: Short Form-36, NHP: Nottingham Health Profile, ✓ : p<0.05 ✓✓: p<0.001. Note: Our central laboratory's normal serum level ranges are in parentheses. The comparison was made between patients with and without serum levels in the normal range.

Table 5. The effect of co-morbid diseases on SF-36 and NHP scores

	Hypertension			Diabetes mellitus			Cardiovascular disease		
	All patients	HD	RT	All patients	HD	RT	All patients	HD	RT
SF-36									
Physical function	✓✓			✓✓	✓		✓✓		✓✓
Physical role restriction	✓		✓				✓	✓	
Social function							✓		
Mental health							✓	✓	
Emotional role restriction							✓	✓	
Energy/Vitality	✓			✓	✓		✓✓	✓	
Pain	✓						✓	✓	
General health perception							✓✓	✓	
NHP									
NHP total score							✓	✓	
Pain NHP									
Emotional reactions							✓	✓✓	
Sleep							✓	✓	
Social isolation							✓		
Physical activity	✓			✓			✓		
Energy	✓			✓					

✓: p<0.05, ✓✓: p<0.001, HD: Hemodialysis, RT: Renal transplantation, SF-36: Short Form-36, NHP: Nottingham Health Profile

Male gender, non-smoker, high education level, being employed and living in the city, and some laboratory parameters (hemoglobin, ferritin, sodium, calcium, magnesium, and albumin levels) positively affected the QoL in the HD group; diabetes and CVD had a negative impact. In the RT group, male gender, high education level, being employed; normal potassium, phosphorus, and parathormone levels affect the QoL positively, while hypertension and CVD negatively affect the QoL (**Table 6**).

Table 6. Effects of demographic characteristics, laboratory values, and co-morbid diseases on quality of life in hemodialysis and renal transplantation patients

Factors	Hemodialysis		Renal transplantation	
	SF-36	NHP	SF-36	NSP
Genders	✓	✓	✓✓	✓✓
Active smoker	✓	-	-	-
Education	✓	-	✓	-
Marital status	-	-	-	-
Home situation	-	-	-	-
Employment	✓	✓✓	✓✓	✓
HD vascular access	-	-		
Donor type			-	-
Living place	✓	-	-	-
Hemoglobin	✓	-	-	-
Ferritin	✓✓	✓✓	-	-
Sodium	✓	✓	-	-
Potassium	-	-	✓	-
Calcium	✓	✓	-	-
Phosphorus	-	-	✓	✓
Magnesium	✓	✓	-	-
Parathormone	-	-	✓	✓
Albumin	✓	✓	-	-
Hypertension	-	-	✓	-
Diabetes Mellitus	✓	-	-	-
CVD	✓	✓	✓	-

✓: p<0.05, ✓✓: p<0.001, SF-36: Short Form-36, NHP: Nottingham Health Profile, HD: Hemodialysis, CVD: Cardiovascular disease

DISCUSSION

Many studies have evaluated the QoL of CKD patients receiving different RRT modalities. In these studies, RT was superior to HD in terms of QoL (4). Our study found that RT patients had a better QoL than HD patients. Biochemical parameters such as hemoglobin, ferritin, sodium, calcium, magnesium, and albumin affected the QoL more in the HD group, and social factors such as high education level and being an employee were more effective in the RT group, as well as the male gender.

Our study showed that the QoL in RT patients was better than in HD patients, in line with the literature. A large meta-analysis showed that RT patients had better QoL than HD patients (4). A study showed no difference between the groups regarding anxiety and depression in HD and RT patients and QoL was better in RT patients (5). In another study conducted with The Kidney Disease Quality of Life (KDQOL) and EuroQOL scales, the QoL of RT patients was better than HD patients on both scales (6).

Different parameters affect the results of the QoL differently. The first of these is gender. In a study investigating the effects of gender and race on the QoL in RT patients, the results were significantly lower in the female gender group on all scales (7). Similarly, in a study using the SF-36 scale, the scores were lower in females (8). In another study, patients with chronic kidney disease at different stages were compared using the KDQOL scale, and women had a lower QoL (9). In our study, we found that the female gender negatively affected the results in both HD and RT patients.

Employment status affects the QoL. The QoL of employed patients after transplantation is better in RT patients (10,11). In our study, the employed position positively impacted the results of both HD and RT patients. While this is easier to explain in renal transplant patients, it may be more difficult in HD patients. However, although it is speculative, the QoL of patients who have better physical performance and can work may be responsible for this result.

Our study found no statistically significant difference when marital status was compared to RRT and gender. There are inconsistent results in the literature (12-14). In a meta-analysis of 34 randomized controlled studies, marriage did not affect the QoL of patients receiving RRT (15). In this respect, our study is compatible with the meta-analysis results.

A study in our country showed that 98.7% of RT patients and 91.8% of HD patients live with their families. The same researchers stated that this situation did not affect the QoL (3). Our study found that marital and social status at home did not affect the test results in either HD or RT patients.

Many previous studies have shown a correlation between education level and QoL (16,17). In our study, we found that higher education level was associated with increased QoL, consistent with the literature. This result may be related to patients with higher education levels having better drug compliance and heightened awareness of possible complications.

Donor status affects the QoL in RT patients. One study showed that patients with RT from a living donor of fewer than five years had a better QoL. After more than five years, this effect disappeared (18). However, some studies, as our study, also show that donor type has no effect (19).

Diabetes mellitus adversely affects the QoL in patients under RRT (20,21). In comparing peritoneal dialysis patients with SF-36, the QoL of the group without diabetes was found to be better (22). Another study used the Swedish health-related quality of life scale (SwedHRQOL). People with diabetes have lower scores except for social isolation (23). We also found that the QoL improved in HD patients without diabetes. However, diabetes did not cause any harmful results in RT patients.

Previous studies have shown cardiovascular disease (CVD) adversely affects the QoL (24-27). Our study showed that CVD adversely affected the test results in both HD and RT patients, but this effect was more significant in the HD group. Studies have shown that those with CVD and those with CVD risk factors have worse results (25,28). This data may explain why the HD group's QoL is more affected, which has more CVD risk factors.

Previous studies have shown that the QoL in RT patients is better than in other RRT modalities. In addition to the literature, our study showed that the factors affecting the results of HD and RT patients differ. While gender, education, and employment status are more effective on RT patients, laboratory characteristics are more effective on the QoL of HD patients. However, phosphorus and parathormone levels within normal ranges in RT patients are also associated with improved results.

Our study has some limitations. The most important limitation is that it was performed in a single center with a small number of patients. Another limitation is that the HD patient group has a higher mean age and has more co-morbid diseases. On the other hand, the cross-sectional study may be insufficient to show real-life data. However, determining the factors affecting the QoL of patients receiving RRT with two different QoL scales emerges as the strength of our study.

CONCLUSION

As a result, factors affecting QoL in patients receiving different RRT are different. Avoiding electrolyte imbalance and controlling comorbidities are more critical for HD patients. Rehabilitative efforts for returning to working life after transplantation will increase the QoL in RT patients.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.06.2020, Decision No: 2020/417).

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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The knowledge level and attitude of the parents about COVID-19 vaccination in children: a single-center survey study

Ebeveynlerin çocuklarda COVID-19 aşısı konusundaki bilgi düzeyi ve tutumu: tek merkezli bir anket çalışması

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ABSTRACT

Aim: The primary method of prevention for children involves vaccination. The generally accepted approach in the world is the vaccination of eligible children for COVID-19 (Coronavirus Disease 2019). In the field of COVID-19 vaccines, hesitation and vaccine denial are anticipated concurrently with the rise in the incidence of vaccine instability and rejection around the world. The aim of this study is to find out what parents think about the COVID-19 vaccination program for children and what factors may cause anti-vaccination.

Material and Method: 208 parents with children aged 0-18 who applied to the University of Health and Sciences, Ankara Keçiören Training and Research Hospital's pediatrics clinics between April-June 2021 were included in the study. A questionnaire consisting of 26 questions developed by public health experts for COVID-19, the COVID-19 Phobia Scale (C19P-S), and the Short Form of COVID-19 Anxiety Scale were administered to the participants.

Results: 58.2% of participants believed that vaccines could only partially protect against the virus, while 19.2% disagreed and 22.6% were unsure of their position on this. While 67.3% of individuals said they would be willing to receive the COVID-19 vaccine, 36.1% said they would be willing to immunize their children ($p< 0.001$). Participants who refused to receive their own vaccinations did not consider vaccinating their children ($p<0.001$). With a rate of 76.5%, parents cited the possibility of vaccine side effects as their main objection to immunizing their children. Parents who have never been vaccinated or under-vaccinated their children according to the national vaccination program, did not intend to vaccinate their children with the COVID-19 vaccine at a higher rate. Parents who did not intend to vaccinate their children with the COVID-19 vaccine had significantly lower overall scores on the COVID-19 Phobia Scale, psychological sub-dimension, somatic sub-dimension, and social sub-dimension than parents who did ($p<0.05$).

Conclusion: The majority of parents were hesitant to vaccinate their children. The vaccine side effects were the main objection to immunizing children. Therefore understanding the attitudes and perspectives of parents toward COVID-19 vaccines may shed light on the pediatric COVID-19 vaccination programs that will be implemented in the future.

Keywords: COVID-19, vaccination, children, parents, survey

ÖZ

Amaç: Çocuklar için birincil korunma yöntemi aşılamadır. Dünyada genel kabul görmüş yaklaşım uygun görülen çocukların Koronavirüs Hastalığı 2019 (COVID-19) için aşılanması yönündedir. Tüm dünyadaki aşı kararsızlığı ve reddi insidansındaki artışla paralel olarak COVID-19 aşıları için de tereddüt ve aşı reddi beklenmektedir. Bu çalışmanın amacı, ebeveynlerin çocuklara yönelik COVID-19 aşı programı hakkındaki düşüncelerini ve aşı karşıtlığına hangi faktörlerin neden olabileceğini ortaya çıkarmaktır.

Gereç ve Yöntem: Sağlık Bilimleri Üniversitesi, Ankara Keçiören Eğitim ve Araştırma Hastanesi çocuk hastalıkları kliniklerine Nisan-Haziran 2021 tarihleri arasında başvuran, 0-18 yaş arası çocuğu olan 208 ebeveyn araştırmaya dahil edildi. Katılımcılara (COVID-19) için halk sağlığı uzmanları tarafından geliştirilen 26 sorudan oluşan anket, COVID-19 Fobi Ölçeği (C19P-S) ve COVID-19 Kısa Form Anksiyete Ölçeği uygulandı.

Bulgular: Katılımcıların %58,2'si aşıların virüse karşı yalnızca kısmen koruyabileceğine inanırken, %19,2'si aynı fikirde değildi ve %22,6'sı bu konudaki tutumlarından emin değildi. Bireylerin %67,3'ü COVID-19 aşısını yaptırmaya istekli olacağını belirtirken, %36,1'sı çocuklarını aşılamaya istekli olacağını belirtti ($p<0,001$). Kendi aşılarını yaptırmayı reddeden katılımcılar çocuklarına aşı yaptırmayı düşünmüyordular ($p<0,001$). Ebeveynler, %76,5' lik bir oranla, çocuklarına aşı yaptırma konusundaki temel itirazları olarak aşı yan etkileri olasılığını belirttiler. Ulusal aşı programına göre çocuklarına hiç aşı yaptırmamış veya eksik aşı yaptırmamış olan ebeveynler, çocuklarına daha yüksek oranda COVID-19 aşısı yaptırmayı düşünmemişlerdi. Çocuklarına COVID-19 aşısı yaptırmayı düşünmeyen anne babaların COVID-19 Fobi Ölçeği, psikolojik alt boyut, somatik alt boyut ve sosyal alt boyut toplam puanları, yaptıran ebeveynlere göre anlamlı olarak daha düşüktü ($p<0.05$).

Sonuç: Ebeveynlerin çoğunluğu çocuklarına aşı yaptırmakta tereddüt etmektedir ve bunun en sık sebebi aşının yan etkileri olabileceği düşüncesidir. Bu nedenle ebeveynlerin COVID-19 aşılarına yönelik tutum ve bakış açılarının anlaşılması, gelecekte uygulanacak pediatrik COVID-19 aşılama programlarına ışık tutabilir.

Anahtar Kelimeler: COVID-19, aşılama, çocuklar, ebeveynler, anket

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INTRODUCTION

In children, Coronavirus Disease 2019 (COVID-19) typically results in a mild recovery; serious infection is uncommon. Approximately 1%–8% of confirmed COVID-19 patients are children, according to data from the World Health Organization (WHO). Hospitalization rates range from 5.7%–20%, with a rate of 0.58% 2% in pediatric intensive care units (1,2). However, some fatal conditions can appear in some kid's weeks after infection (3).

Numerous medications have been used against the disease since the outbreak's inception (3). Since there is no treatment that has been categorically proven effective for COVID-19, vaccine development studies are crucial for preventing morbidity and mortality from the disease. Inactivated virus, attenuated live virus, recombinant protein-based vaccines, DNA, RNA, and viral vector-based vaccines have all been developed against COVID-19 (4,5).

The primary method of prevention for children involves vaccination. The generally accepted approach in the world; vaccination of eligible children for COVID-19 (6). For children between the ages of 5 and 15 years, the United States has approved BNTb162b (Pfizer COVID-19 vaccine) (7). Children over the age of 12 in Turkey are immunized, in accordance with Centers for Disease Control and Prevention (CDC) recommendations. Since kids can't make informed decisions for themselves, parental consent is necessary.

It has been identified by World Health Organization (WHO) as one of the 10 major global health issues of 2019, in part because of the rise in vaccine hesitancy and the decline in vaccination rates. If the incidence of a disease that is preventable by vaccination declines, vaccination rates may also decline as disease-related anxiety declines (6). Thanks to blogs, websites, and articles describing the dangers of vaccines in the internet environment where there is no truthfulness about vaccines, parents who believe that vaccine-related side effects and the substances in vaccines may harm the body in the long term have increased reservations about vaccination (6-9). It has been observed in our country that the rate of vaccine rejection has risen over time. The number of parents who refused to vaccinate their children grew from 183 in 2011 to 23.000 in 2018. Measles was diagnosed in 85 children across the Turkey in 2017, with 44 cases reported in the first three months of 2018. As a result, the incidence of measles increased tenfold in 2018, rising to 0.10/100.000 from 0.01/100.000 in 2016. If the number of vaccine refusal cases reaches 50.000, the possibility of an epidemic increases significantly (10, 11).

A serious threat to the public health is posed by the rise in the proportion of parents who refuse to vaccinate their kids. Refusing vaccination increases the risk of getting sick, and interruptions in vaccination programs give the infectious disease agent a chance to spread and start epidemics. The medical and economic effects of these epidemics on nations are unavoidable (12). In the field of COVID-19 vaccines, hesitation and vaccine rejection are anticipated concurrently with the rise in the incidence of vaccine instability and rejection around the world. Since the disease's discovery, there have almost always been conspiracy theories about COVID-19, and it is thought that these claims may have a negative effect on people's perceptions of these vaccines (13).

It is well known that COVID-19 vaccine hesitancy rates differ from country to country. This vaccine hesitancy may be brought on by a number of things, such as existing uncertainty, mistrust of medical professionals, financial worries, and a lack of awareness (14). Hesitancy rates have gradually decreased as a result of the introduction and use of COVID-19 vaccines. Right now, it's critical to understand how people feel about COVID-19 vaccines in order to predict its causes, combat the pandemic, and pinpoint potential contributing factors. It will be advantageous to maintain public confidence in COVID-19 vaccines if development processes, mechanisms of action, contents, results, and efficacy of studies, as well as potential risks and side effects of vaccines, are openly shared with the public (15).

Not only do infectious diseases make people afraid of getting sick or dying, but they also make people depressed and anxious (16). In addition to the fear of losing their health or their relatives, this process can also cause psychological mediators. Epidemic-related issues include social isolation, quarantine, and social isolation (17). Corona phobia is a brand-new phobia that has emerged as a result of the detrimental economic, social, and psychological effects of the COVID-19 pandemic period. The fear of losing loved ones, self-health anxiety, and increased social media use are thought to be related to corona phobia (18).

In this context, the goal of our research is to find out what parents think about the COVID-19 vaccination program for children, where they get their information, how many parents are anti-vaccine, and what factors may cause anti-vaccination. The study's findings are expected to be useful in combating the COVID-19 pandemic and may shed light on the COVID-19 vaccination program that will be implemented in the future.

MATERIAL AND METHOD

All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study was carried out with the permission of University of Health and Sciences Ankara Keçiören

Training and Research Hospital Clinical Research Ethics Committee (Date: 23.03.2021, Decision No: 2012-KAEK-15/2281). With the ethics committee approval, the data were scanned retrospectively using the Hospital Information Management System.

This study included 204 parents who came to the University of Health and Sciences Ankara Keçiören Training and Research Hospital's pediatric clinic for any reason between 15.04.2021 and 15.06.2021, agreed to participate in the study, and had the cognitive ability to answer the questions. The research was conducted both prospectively and cross-sectional. In line with the number of patients expected to apply during the research period, it was calculated that at least 170 participants should be included in the study, with the assumption percentage frequency of the outcome factor in the population 14.5±5% and the confidence level of 95%. It was planned to include at least 204 people in the study based on the assumption that 20% of the cases could be excluded from the study due to missing data or deciding to drop out of the study. During this time, the questionnaire was distributed to 311 parents via face-to-face interviews, with verbal and written consent obtained. 103 parents were excluded from the evaluation for a variety of reasons, including incomplete questionnaire completion and contradictory responses. As a result, the study included 208 parents.

Scales and Questionnaires

Questionnaire form: In the study, the socio-demographic characteristics of the parents (age, gender, income level, education level, and occupation), vaccination information resources, compliance with the ministry of health's national vaccination program, attitude toward the COVID-19 vaccine, COVID-19 vaccine according to the age of the children, were prepared by a public health expert. A questionnaire with 26 questions was used to assess individuals' attitudes, chronic disease in themselves and their family members, and previous COVID-19 history. In addition to this questionnaire, individuals' corona phobia and coronavirus anxiety were assessed using scales developed in this field.

COVID-19 phobia scale (C19P-S): C19P-S is a 5-point likert-type self-assessment scale comprised of 20 items developed by Arpacı et al. (19) to assess the corona virus phobia. High scores indicate a high level of height in both sub-dimensions as well as general corona phobia.

Short form of the coronavirus anxiety scale: The Short Form of the Coronavirus Anxiety Scale, the validity and reliability of which were investigated by Biçer et al. (20), was used to assess coronavirus anxiety. Each item on the scale is worth 0-4 points. A score of 9 and above indicates a high level of anxiety.

Statistical Analysis

For statistical analysis, IBM SPSS Statistics software for Windows (Version 25.0, Armonk, NY: IBM Corp.) was used. The variables' conformity to the normal distribution was assessed using the Kolmogorov-Smirnov test, histograms, and probability graphs. For continuous variables, descriptive statistics were presented as mean (standard deviation) or median (25-75th percentile), and numbers (percent) for nominal and ordinal variables. The Mann-Whitney U test was used to determine the difference in continuous variables between groups. The chi-square test (Fisher's exact test when necessary) was used to compare differences in nominal and ordinal variables between groups. If the difference between more than two variables was found to be significant, the Bonferroni correction was used as a post hoc test.

RESULTS

The study included 208 participants; 78.4% of whom were mothers and 21.6% of whom were fathers. The mean age of the mothers was 35.2±7.5 years, and the mean age of the fathers was 38.5±8.4 years. The mean age of mothers and fathers who did not plan to have their children vaccinated was found to be lower than that of those who did ($p<0.05$). The mother's educational level was also related to her vaccination attitude ($p=0.005$). Mothers with a doctorate were more likely to have their children immunized (($p<0.05$). There was no significant relationship between the other socio-demographic characteristics and the participants' attitudes toward getting their children vaccinated ($p>0.05$) (**Table 1**).

People with whom 63.7% of the participants shared the same house had chronic diseases. Participants who lived in the same house as people with chronic diseases were found to be more likely to consider getting the COVID-19 vaccine ($p=0.021$) (**Table 1**).

Participants who refused to be vaccinated against COVID-19 also refused to vaccinate their children ($p<0.001$). Seventy-four participants had one reason not to vaccinate their children against COVID-19, 34 had two reasons, 14 had three, eight had four, and one had five. The most common reason for refusing to be vaccinated was that 76.5% believed there would be side effects, 25.7% believed COVID-19 was milder in children, 22.1% believed the vaccine would not be protective, and 14.4% believed the vaccines were from a foreign country. The number of children under the age of 18 was higher among those who did not intend to have their children vaccinated ($p=0.020$). It was discovered that the state of mind about having a child vaccinated was unrelated to the total number of children or the children's mean age ($p>0.05$). Participants who believed that the developed

COVID-19 vaccines could not defeat the virus did not want the COVID-19 vaccine to be administered to their children at a higher rate (p<0.001). Participants who believed that COVID-19 vaccines would cause serious side effects that would harm human health did not consider vaccinating their children at a higher rate (p<0.001). Participants who believed that the COVID-19 epidemic would resolve on its own, even without the vaccine, did not want their children to be vaccinated at a higher rate (p=0.002). Parents who adhered to the National Vaccination Schedule on a regular basis desired their child to be vaccinated against COVID-19 at a higher rate (p=0.004) (**Table 1**).

Table 1. Comparison of socio-demographic and vaccination attitudes of participants

	Participants do not intend to vaccinate their children (n=133)	Participants intend to vaccinate their children (n=75)	p
Role in the family (%)			0.534
Mother	108 (65.0)	57 (35.0)	
Father	27 (60.0)	18 (40.0)	
Age (years) (median (25p-75p))			
Mother	34 (30.0-38.0)	37 (30.0-42.0)	0.013**
Father	38 (31.0-41.5)	40 (32.0-45.3)	0.023**
Marital status (%)			0.734
Married	124 (64.6)	68 (35.4)	
Divorced	7 (53.8)	6 (46.2)	
Widow	2 (66.7)	1 (33.3)	
Place of live (%)			0.704
Ankara	129 (64.2)	72 (35.8)	
Others	4 (57.1)	3 (42.9)	
Mother' job (%)			0.646
White color	41 (60.3)	27 (39.7)	
Housewife	78 (65.5)	41 (34.5)	
Worker	12 (63.2)	7 (36.8)	
Jobless	2 (100.0)	0 (0)	
Father' job (%)			0.846
White color	50 (64.1)	29 (35.9)	
Worker	71 (63.4)	41 (36.6)	
Jobless	12 (70.6)	5 (29.4)	
Mother' education (%)			0.005*
Illiterate	3 (60.0)	2 (40.0)	
Literate	3 (33.3)	6 (66.7)	
Primary school	44 (68.8)	20 (31.2)	
High school	33 (64.7)	18 (35.3)	
University (associate degree)	8 (72.7)	3 (27.3)	
University (undergraduate)	36 (73.5)	13 (26.5)	
Master's degree	6 (50.0)	6 (50.0)	
PhD	0 (0.0)	7 (100.0)	
Father' education (%)			0.176
Literate	4 (57.1)	3 (42.9)	
Primary school	29 (67.4)	14 (32.6)	
High school	43 (68.3)	20 (31.7)	
University (associate degree)	18 (78.3)	5 (21.7)	
University (undergraduate)	25 (56.8)	19 (43.2)	
Master's degree	6 (42.9)	8 (57.1)	
PhD	2 (33.3)	4 (66.7)	
Income situation (%)			0.353
Low	42 (70.0)	18 (30.0)	
Moderate	56 (59.9)	39 (41.1)	
High	35 (66.0)	18 (34.0)	
Number of children in the family (%)			0.143
1	45 (64.3)	25 (35.7)	
2	55 (72.4)	21 (27.6)	
3	25 (53.2)	22 (46.8)	
≥4	8 (53.3)	7 (46.7)	
Number of people living in the house (%)			0.101
1	0 (0)	1 (100.0)	
2	3 (75.0)	1 (25.0)	
3	33 (55.9)	26 (44.1)	
4	56 (73.7)	20 (26.3)	
5	27 (55.1)	22 (44.9)	
≥ 6	14 (73.7)	5 (26.3)	
Presence of chronic diseases in people living in the same house (%)	36 (52.9)	32 (47.1)	0.021*
Presence of unemployment in the family during the pandemic (%)	51 (61.4)	32 (38.6)	0.541
Number of children (median (25p-75p))	2 (1-2.5)	2 (1-3)	0.224
Number of children under the age of 18 (median (25p-75p))	2 (1-3)	2 (1-2)	0.020**
The mean age of children under the age of 18 years (median (25p-75p))	6.7 (3-10.8)	8.5 (3-12.5)	0.212
Wish to be immunized against COVID-19 (%)	66 (47.1)	74 (52.9)	<0.001*
Believe that the COVID-19 vaccine will cause serious side effects (%)	52 (86.7)	8 (13.3)	<0.001*
Reasons for refusing the COVID -19 vaccine (%)			
Considered the side effects	76.5		
The possibility of not being protective	22.1		
Vaccine originating from a foreign country	22.9		
The child has had COVID-19	15.3		
Mild course of COVID-19 in children	26		
Others	5.3		
Views on the effect of COVID-19 vaccines on the virus (%)			
Partially defeat the virus	63 (52.1)	58 (47.9)	<0.001*
No idea	32 (68.1)	15 (31.9)	
Participation in the national vaccination program (%)			
Have never been vaccinated or under-vaccinated	21 (91.3)	2 (8.7)	0.004*
Have regular vaccinations	112 (63.9)	75 (36.1)	
Sources of vaccine information (%)			
Form a tight circle	16 (80.0)	4 (20.0)	0.116
Television/radio/newspapers	7 (41.2)	10 (58.8)	0.041*
Internet	24 (64.9)	13 (35.1)	0.897
Nurse/midwife	92 (70.8)	38 (29.2)	0.008*
Doctor	59 (56.2)	46 (43.8)	0.019*
Cases of COVID-19 in the family (%)			
A family member died as a result of COVID-19	18 (47.4)	20 (52.6)	0.019*
A family member was infected with COVID-19	47 (60.3)	31 (39.7)	0.391
COVID-19 Phobia Scale (median (25p-75p))			
Psychological sub-dimension	15 (11-20)	17 (13-23)	0.013**
Somatic sub-dimension	6 (5-10)	8 (6-13)	0.021**
Social sub-dimension	12 (9-15)	13 (10.8-17.3)	0.009**
Economic sub-dimension	6 (4-9)	7 (4-10)	0.120
Total score	42.5 (31.3-52.8)	49 (36-59.5)	0.005**
COVID-19 Anxiety Scale (median (25p-75p))	0 (0-2)	0 (0-3)	0.207

*p<0.05, chi-square test, ** p<0.05, Mann-Whitney U test

Participants who received vaccine information from TV/radio/newspaper were significantly more likely to have their children vaccinated (p=0.041). Nurses/midwives and doctors were the most common sources of vaccine information, accounting for 62.5% and 50.5%, respectively. Participants who did not receive vaccine information from doctors were found to be less likely to consider having their children vaccinated (p=0.019) (**Table 1**).

While 18.3% of the participants had a family member who had COVID-19 disease, 37.5% had a family member who had COVID-19 disease. Participants who did not have a history of death due to COVID-19 in their immediate vicinity did not want their children to be vaccinated against COVID-19 at a higher rate (p=0.019). The presence of a person with COVID-19 in the family was found to be unrelated to parents' attitudes toward administering the COVID-19 vaccine to their child (p>0.05) (**Table 1**).

The total COVID-19 Phobia Scale as well as the psychological, somatic, and social sub-dimension scores of those who did not want their child to be vaccinated against COVID-19 were significantly lower than those who did (p<0.05). The economic sub-dimension scores of the COVID-19 Phobia Scale and the Coronavirus Anxiety Scale did not differ significantly between the two groups (p>0.05) (**Table 1**).

Individuals who believed their child would not be vaccinated against COVID-19 had significantly lower scores on the COVID -19 Phobia Scale in all sub-dimensions and total scores (p<0.005). Only the COVID -19 Phobia Scale Psychological sub-dimension score of participants who refused to be vaccinated against COVID-19 due to vaccine originating from a foreign country was significantly lower (p=0.010). Those who stated other reasons for not getting vaccinated scored significantly lower on the COVID-19 Phobia Scale somatic, social, economic, and total (p<0.05) (**Table 2**). The presence of more than one reason for not wanting to receive the COVID-19 vaccine was found to have a significant correlation with a low COVID-19 Phobia Scale Psychological sub-dimension, Somatic sub-dimension, Social sub-dimension, Economic sub-dimension, and Total score (p<0.005) (**Table 3**).

There was a significant difference in the COVID-19 Phobia Scale Psychological sub-dimension, Somatic lower neck, Social sub-dimension, and total score scores of participants who held different beliefs about the potential serious side effects of COVID-19 vaccines (p<0.05). According to the post hoc analyses, the scores of participants who expected to have side effects were significantly lower than those who expected to have no side effects (p<0.05) (**Table 4**).

Table2. Comparison of coronavirus phobia and anxiety levels among parents who do not want to vaccinate their children against COVID-19 (n=131¶)

	Considered the side effects			The possibility of not being protective			Vaccine originating from a foreign country		
	Yes (n=101)	No (n=30)	p	Yes (n=29)	No (n=102)	p	Yes (n=30)	No (n=101)	p
COVID-19 phobia scale									
*Psychological sub-dimension	15 (11-20)	15.5 (10.8-21)	0.989	11 (7-16)	16 (13-20.3)	<0.001*	13 (8-18)	16 (12-21)	0.010*
*Somatic sub-dimension	6 (5-10)	7 (6-10)	0.248	5 (5-9)	7 (5-10)	0.022*	6 (5-9.3)	7 (5-10)	0.707
*Social sub-dimension	12 (9-15.8)	12 (9-15)	0.890	10 (5-12.5)	13 (10-16)	0.003*	10 (15-7)	12 (9-15.5)	0.131
*Economic sub-dimension	6 (4-9)	7 (4.8-8.3)	0.361	4 (4-7)	6 (4-9)	0.016*	5 (4-8.3)	6 (4-9)	0.394
*Total score	41.5 (31-53)	44 (34.8-51.3)	0.834	31 (21-45.5)	44 (36-53.5)	0.001*	39 (26-50)	43 (34.5-53.5)	0.092
COVID-19 anxiety scale	0 (0-2.5)	0 (0-1)	0.594	0 (0-4.5)	0 (0-2)	0.321	0 (0-3)	0 (0-2)	0.977
	The child has had COVID-19			Mild course of COVID-19 in children			Others		
	Yes (n=20)	No (n=111)	p	Yes (n=34)	No (n=97)	p	Yes (n=7)	No (n=124)	p
COVID-19 phobia scale									
*Psychological sub-dimension	12 (10-18)	15 (12-21)	0.120	13 (9.8-18)	16 (12-21)	0.050	7 (6-20)	15 (12-20)	0.067
*Somatic sub-dimension	6 (5.3-9)	7 (5-10)	0.883	6 (5-9)	7 (5-10)	0.302	5 (5-5)	7 (5-10)	0.021*
*Social sub-dimension	10.5 (8-15.8)	12 (9-12)	0.554	10.5 (8-15)	13 (9-15.8)	0.188	5 (5-14)	12 (9-16)	0.049*
*Economic sub-dimension	7 (5-8)	6 (4-9)	0.636	5 (4-8)	6 (4-9)	0.208	4 (4-4)	6 (4-9)	0.030*
*Total score	39 (28.3-51)	43 (32.8-53)	0.399	41 (28-46)	43.5 (33.3-53.8)	0.079	21 (20-41)	43 (33-53)	0.024*
COVID-19 anxiety scale	0 (0-4)	0 (0-2)	0.767	0 (0-1.3)	0 (0-2.5)	0.512	0 (0-09	0 (0-2)	0.288

*p<0.05; Mann-Whitney U test ¶2 people did not report why.

Table3. Correlations between the number of reasons for not wanting their child to be vaccinated against COVID-19 and the levels of coronavirus phobia and anxiety

		Number of reasons for not wanting their child to be vaccinated against COVID-19	COVID-19 phobia scale psychological sub-dimension	COVID-19 phobia scale somatic sub-dimension	COVID-19 phobia scale social sub-dimension	COVID-19 phobia scale economic sub-dimension	COVID-19 phobia scale	COVID-19 anxiety scale
Number of reasons for not wanting their child to be vaccinated against COVID-19	rho	1						
	p	-						
COVID-19 phobia scale psychological sub-dimension	rho	-0.357	1					
	p	<0.001*	-					
COVID-19 phobia scale somatic sub-dimension	rho	-0.254	0.546	1				
	p	0.003*	<0.001*	-				
COVID-19 phobia scale social sub-dimension	rho	-0.25	0.784	0.553	1			
	p	0.004*	<0.001*	<0.001*	-			
COVID-19 phobia scale economic sub-dimension	rho	-0.253	0.456	0.708	0.404	1		
	p	0.004*	<0.001*	<0.001*	<0.001*	-		
COVID-19 phobia scale total score	rho	-0.33	0.892	0.793	0.869	0.695	1	
	p	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	-	
COVID-19 anxiety scale	rho	0.017	0.474	0.506	0.484	0.382	0.561	1
	P	0.846	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	-

*p<0,05; Spearman correlation analysis

Table4. Relationship between thoughts about possible serious side effects of COVID-19 vaccines and coronavirus phobia and anxiety (n=208)

	Considered the side effects (n=60)	Undecided (n=107)	Not considered the side effects (n=41)	p¶	Post hoc analysis§		
					pa	pb	pc
COVID-19 Phobia Scale							
Psychological sub-dimension	14 (10-18)	16 (13-21)	20 (12.5-23.5)	0.003*	0.056	0.003*	0.369
Somatic subdimension	6 (5-9)	7 (5-10.3)	10 (5.5-12)	0.034*	0.135	0.043*	>0.999
Social sub-dimension	11 (9-16)	12 (10-16)	14.5 (10.5-17.8)	0.055	-	-	-
Economic sub-dimension	5 (4-8.8)	6 (4-9)	7 (5-10)	0.038*	0.141	0.049*	>0.999
Total score	40 (29-49)	45 (36-55)	53.5 (35-62.75)	0.008*	0.118	0.006*	0.337
COVID-19 Anxiety Scale	0 (0-2.8)	0 (0-2)	0 (0-3)	0.659	-	-	-

*p<0.05, ¶ Kruskal-Wallis test, §Mann-Whitney U test (Bonferroni correction applied). a Considered side effects -undecided, b Considered side effects –Not considered side effects, c Undecided –Not considered side effects. Data are presented as median (25th -75th percentile).

The mother's educational status was related to her refusal to have her child vaccinated against COVID-19 (p=0.043). High school graduate mothers predicted a higher rate of side effects (p<0.05). The other reasons for refusing COVID-19 vaccine were unrelated to the mother's educational level (p>0.05).

DISCUSSION

In this study, parents' knowledge and attitudes toward COVID-19 vaccines were examined in order to provide preliminary information about the future COVID-19 vaccination plan for children. Even if various measures slow the current pandemic's spread, it does not appear possible to reduce and end its severity unless sufficient herd immunity is provided. To achieve herd immunity, 55%-82% of the population must be vaccinated (21).

Vaccinating children is important for ensuring herd immunity as well as protecting against serious pediatric COVID-19 cases and complications such as MIS-C (3, 22).

In our study, we discovered that the ages of those who do not consider vaccinating their children are significantly lower than those who do. It was discovered that the mother's education level was related to her vaccination attitude, with mothers with a doctorate being more likely to consider having their children vaccinated. In a study from Turkey (2021 February), similar to ours, the desire to allow their children to be vaccinated against COVID-19 was found to be higher among parents aged 40 and over than among those aged 18-29, and the desire to vaccinate children increased as education level increased (23).

In contrast, two studies conducted in France (April 2020) and Australia (November 2020) found that parents' education level had no effect on their desire to have their children vaccinated (24, 25).The differences between the studies are thought to be due to sociocultural differences between countries, as well as the fact that these studies were conducted at different times during the pandemic.

In our study, it was discovered that living in the same house with someone who a chronic disease has resulted in a higher rate of parents considering having their child vaccinated. This moderate viewpoint may be due to the fact that those with chronic diseases are familiar with the health system and have previously received vaccinations such as pneumococcal and influenza. In another study, parents of children with chronic diseases were found to be less accepting of the COVID-19 vaccine for their children (21). The reason for this disparity could be that we did not question the presence of chronic disease in the form of parent or child in our study or parents' concerns about live vaccines for their immune-compromised children (26).

It was discovered in our study that those who did not want to be vaccinated did not want their children to be vaccinated at a higher rate. Similar to previous studies conducted in Turkey, 67.3% of participants were willing to vaccinate themselves against COVID-19, while 36.1% were unwilling to have their children (23, 26). Participants were more reluctant to have their children vaccinated rather than themselves. In contrast to our study, rates in England were 89%, New Zealand was 80%, China was 73%, the United States was 65%, and New York was 61.9% (24, 28, 29, and 30). This could be due to the fact that vaccine willingness varies across countries, depending on the availability of different types of COVID-19 vaccines, the time and speed of vaccination, and other factors.

Similar to other studies, the most common reasons given by parents in our study for not wanting the COVID-19 vaccine administered to their children were: the vaccine may have a side effect, COVID-19 is milder in children, and the vaccine will not be protective (23, 28, 31).

It was discovered that the mother's fear of side effects increased as her education level decreased. Because approximately 60% of those who participated in our study as "mothers" are housewives, they spend less time outdoors than working mothers, are less afraid of contracting the virus, and are more exposed to mass media (such as television, social media). The fact that they were more exposed to speculations about side effects may have helped.

Similar to studies conducted in Turkey, we discovered that vaccine acceptability was not related to the average age of children in our study; however, a Chinese study found that vaccine acceptability was lower for young children of parents (23, 29). The difference in Turkey may be due to the fact that education has continued online since the beginning of the pandemic in our country.

In our study, 11% of parents had previously refused vaccination, which is consistent with the literature and willingness to allow vaccination was found to be related to current vaccination program compliance (21, 30-32). Vaccine rejection has been observed in Turkey for the past ten years and is gradually increasing (10). In order to solve this problem, it is necessary to thoroughly address the issue of vaccine hesitancy.

Similar to previous reports in our study, participants who received vaccine information from TV/radio/newspaper wanted their child to be vaccinated with COVID-19 at a significantly higher rate than those who did not (33). Understanding the sources of information on COVID-19 vaccines that people trust the most is critical to the success of any future national immunization campaign, as these sources of information can shape people's acceptance or rejection of COVID-19 vaccines (34). According to a study conducted in France, those who received vaccine information from doctors wanted their children to be vaccinated with COVID-19 at a higher rate (35). These findings indicate that doctors, as the most trustworthy source of vaccination information, are in a unique position to combat parental vaccination hesitancy.

In our study, participants with a family history of COVID-19 death desired to have their children vaccinated at a higher rate. Unlike our study, a study discovered no significant difference (31). The reason for this could be an increase in the number of deaths caused by virus mutation between the two studies. In our study, those who do not plan to have their child vaccinated had significantly lower total COVID-19 Phobia Scale and sub-dimensions than those who planned to have their child vaccinated. These findings support previous findings that COVID-19 and its effects are significantly positively correlated with vaccine acceptance (23, 32). It should not be assumed that the positive correlation between vaccine acceptance and COVID-19-related anxiety and health fears would be beneficial in raising these fears in the general population, thereby increasing vaccine acceptance. An exaggerated fear of the pandemic is a risk factor for serious mental health problems caused by the pandemic, and it can lead to a failure to take proper and harmonious preventive measures (36). As a result, our findings emphasize the importance of improving risk communication strategies and dealing more effectively with various fears in the context of a pandemic.

When coronavirus phobia and anxiety levels were examined, it was discovered that all sub-dimensions and total scores of the COVID-19 Phobia Scale were significantly lower for people who believed the vaccine would not be protective. This finding suggests that a large number of people underestimate this disease.

The limitations of our study are that it was single-centered, conducted in a hospital setting, and face-to-face, based on the parents' own statements and the person who administered the questionnaire was a 'Doctor.' A larger sample size for future studies will result in a more accurate analysis.

CONCLUSION

While the majority of parents are willing to vaccinate themselves with the COVID-19 vaccine, the majority are hesitant to vaccinate their children, owing to concerns about vaccine side effects. In the future, administering the COVID-19 vaccine to the parents' children and fighting the pandemic will require identifying parents who are incompatible with the national vaccination program and who refuse vaccination, as well as providing accurate and effective information using media tools and health professionals. Understanding the attitudes and perspectives of parents toward COVID-19 vaccines in our study is important in terms of shedding light on the COVID-19 vaccine application and the difficulties that may be encountered in children in the future.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health and Sciences Ankara Keçiören Training and Research Hospital Clinical Research Ethics Committee (Date: 23.03.2021, Decision No: 2012-KAEK-15/2281).

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.

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The relationship between anti mullerian hormone level and endometrial polyp frequency in patients with polycystic ovary syndrome

Polikistik over sendromlu hastalarda anti müllerian hormon düzeyi ile endometrial polip sıklığı arasındaki ilişki

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ABSTRACT

Aim: This study aimed to conduct a case-control study to determine the relationship between serum anti mullerian hormone (AMH) levels and frequency of endometrial polyp in women with polycystic ovary syndrome (PCOS).

Material and Method: Patients with endometrial polyps (n=55) were included in the study group. The control group was selected from women without endometrial polyps (n=49). The relationship between the case and control groups was studied using the chi-square test to check the AMH levels and endometrial polyps.

Results: The participants' age and body mass index (BMI) were 28.20±3.08 and 25.45±2.25, respectively. There was a statistically significant association between AMH levels and endometrial polyp (p-value <0.001). There was no significant difference between the endometrial polyps group and the control group in terms of age, BMI, prolactin, follicle-stimulating hormone (FSH), luteinizing hormone (LH), dehydroepiandrosterone sulphate (DHEA-SO4), total testosterone, estradiol, thyroid-stimulating hormone (TSH) and thyroxine (T4) (p-value >0.05).

Conclusion: This research showed that the frequency of endometrial polyps increases with higher AMH levels in PCOS patients.

Keywords: Anti mullerian hormone, endometrial polyp, polycystic ovary syndrome

ÖZ

Amaç: Bu çalışmada polikistik over sendromlu (PKOS) kadınlarda serum anti mullerian hormon (AMH) düzeyleri ile endometrial polip sıklığı arasındaki ilişkiyi belirlemeyi amaçladık.

Gereç ve Yöntem: Çalışma grubuna endometrial polipli hastalar (n=55) dahil edildi. Kontrol grubu endometrial polip olmayan kadınlardan (n=49) seçildi. Olgu ve kontrol grupları arasındaki ilişki, AMH düzeylerini ve endometriyal polipleri kontrol etmek için ki-kare testi kullanılarak araştırıldı.

Bulgular: Katılımcıların yaş ve vücut kitle indeksi (VKİ) sırasıyla 28,20±3,08 ve 25,45±2,25 idi. AMH seviyeleri ile endometrial polip arasında istatistiksel olarak anlamlı bir ilişki saptandı (p değeri <0,001). Endometriyal polip grubu ile kontrol grubu arasında yaş, VKI, prolaktin, folikül uyarıcı hormon (FSH), luteinize edici hormon (LH), dehidroepiandrosteron sülfat (DHEA-SO4), total testosteron, östradiol, tiroid uyarıcı hormon (TSH) ve tiroksin (T4) değerleri açısından anlamlı farklılık saptanmadı (p değeri >0,05).

Sonuç: Bu araştırma, PKOS hastalarında yüksek AMH seviyeleri ile endometrial polip sıklığının arttığını göstermiştir.

Anahtar Kelimeler: Anti müllerian hormone, endometrial polip, polikistik over sendromu

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INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women, which is manifested in 5-8% of women of reproductive age and is one of the most important causes of infertility (1). Chronic anovulation and clinical or laboratory signs of hyperandrogenism are symptoms of PCOS (2). Among the subcriteria for diagnosing this syndrome are insulin resistance, the onset of obesity and premenarche hirsutism, the luteinizing hormone (LH) to follicle-stimulating hormone (FSH) ratio above, and sonography evidence of PCOS (3).

One of the causes contributing to the diagnosis of this disease is anti mullerian hormone (AMH) (4). AMH is a member of the large TGF_B beta factor family, secreted by the granulosa cells of small follicles to regulate the initial stages of follicle growth. AMH is used to predict and determine ovarian reserve and the quality of remaining oocytes (5,6).

AMH is a hormone produced by the growing follicles (containing ovum). For this reason, it is regarded as an indicator of the number and quality of ovum produced in the menstrual cycle. Few studies have been conducted on the relationship between serum levels and the incidence of endometrial polyps in PCOS women (7). Excessive growth of cells in the endometrial inner lining leads to the formation of uterine polyps, which are also called endometrial polyps. The incidence of endometrial polyps in infertile women of reproductive age is about 15% (8).

Endometrial polyps play an important role in infertility, implantation failure and recurrent miscarriages (9). Uterine polyps prevent the transfer of sperm, and for this reason, they have a direct effect on the pregnancy trend. Identification of markers in the manifestation of endometrial polyps plays a vital role in providing diagnosis and effective treatment methods.

Considering the complications caused by PCOS disease and the heavy economic burden of this disease for treatment of infertility, the lost years of life and its mental burden on the family, and the lack of sufficient information in this field in the country, one should conduct the study of the relationship between AMH serum level as a diagnostic marker of the probability of uterine polyps among the PCOS women.

This study aimed to conduct a case-control study to determine the relationship between AMH serum level and endometrial polyps in PCOS women to give the results for future actions in this field.

MATERIAL AND METHOD

This study was started after the ethical approval of the study was obtained from Beykoz University Clinical Researches Ethics Committee (Date: 21.01.2021, Decision No: 2). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective study evaluated patients who had endometrial polyps at Medistate Hospital Gynecology and Obstetrics clinic between January 2019 and December 2020.

Patients with endometrial polyps (n=55) were included in the study group. The control group was selected from women without endometrial polyps (n=49). All the participants had PCOS disease. Endometrial polyps were detected by ultrasound. According to 2003 Rotterdam consensus, the criteria for the diagnosis of PCOS are having two of the following: 1) oligoovulation, 2) hyperandrogenism and 3) polycystic ovaries (≥ 12 follicles measuring 2-9 mm in diameter and/or an ovarian volume > 10 mL in at least one ovary).

Information about the serum AMH levels were collected from medical records. AMH enzyme immunoassay (Instrumentation Laboratory and Beckman-Coulter, Vienna, Austria) was used to specify serum AMH (ng/ml).

The inclusion criteria were: (1) the woman between the ages of 20 and 45. The exclusion criteria were: (1) pregnant women and women in the breastfeeding period; (2) absence of diabetes, thyroid dysfunction, and systemic diseases.

Statistical Analysis

The Kolmogorov-Smirnov test was performed to check the normality, and the nonparametric tests were performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) were measured to check each continuous variable, including age, body mass index (BMI), infertility period, AMH, FSH, LH, Prolactin, dehydroepiandrosterone sulphate (DHEA-SO4), total testosterone, estradiol, thyroid-stimulating hormone (TSH) and thyroxine (T4) . The relationship between the AMH levels and endometrial polyps was compared using the chi-square test. The Mann-Whitney test is performed to study the difference between the two groups. SPSS v20 was used for statistical analyses. A value of p-value < 0.05 was accepted as statistically significant.

RESULTS

The study included 104 women (mean age±SD: 28.20±3.08). The participants' BMI were 25.45±2.25. **Table 1** shows descriptive statistics of study parameters. **Table 2** shows the relationship between AMH level and endometrial polyp.

Table 1. Descriptive statistics of study parameters in women (n=104).

Study parameters	median (range)	mean±SD
Patients characteristics		
Age	28 (22-36)	28.2±3.08
BMI	25 (20-33)	25.45±2.26
Infertility Period(years)	3 (0-5)	3±1.35
Laboratory values		
AMH (ng/ml)	5.8 (2.3-14.5)	6.22±2.57
FSH	5.68 (1.79-9.66)	5.65±1.81
LH	6.14 (2.73-22.8)	7.48±4.32
Prolactin	20.41 (2.57-143)	26.53±20.33
TSH	2.48 (0.46-7.98)	2.71±1.42
T4	1.24 (0.95-2.75)	1.27±0.26
DHEA-SO4	265.15 (33.8-671)	288.92±118.07
Total testosterone	32.5 (3-141)	37.05±22.7
Estradiol	50.02 (6.98-330.9)	70.56±60.95

SD, standard deviation.

Table 2. The relationship between AMH level and endometrial polyp

Variable level	Endometrial Polyps (n=55) n (%)	No Endometrial Polyps (n=49) n (%)	p
AMH levels			<0.001*
AMH≤5	†10 (18.20)	24 (49)	
5<AMH <7	21(38.20)	17 (34.7)	
AMH≥ 7	24(43.60)	†8 (16.3)	

*A chi-square test † Pairwise Z-Tests

As stated in Table 2, a chi-square test found a statistically significant association between AMH levels and endometrial polyp (p-value < 0.05). Data in **Table 1** are presented as numbers (percentages). The number of polyps increases with the increase of AMH. The prevalence of endometrial polyp in women with AMH≤5 was (18.20%), 5<AMH<7 (38.20%), and AMH≥7 (43.60%). **Figure** shows the frequency of endometrial polyps at different AMH levels.

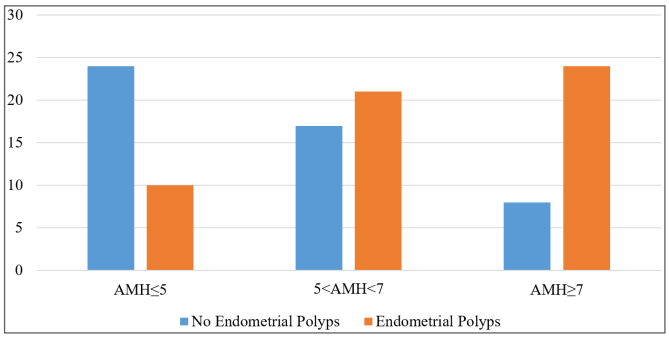

Figure. Frequency of endometrial polyps in different AMH levels

The Pairwise Z-Tests found that the percentage of women who had the endometrial polyps was significantly higher for those who had AMH < 5 ng/ml than for those who had AMH > 5 ng/ml. Also AMH > 7 ng/ml decreased the endometrial polyps risk.

Table 3 shows the hormonal characteristics of the study groups. There was not a statistically significant difference between endometrial polyps group and control in terms of age (p=0.063), BMI (p=0.819), infertility period (p=0.136), FSH (p=0.749), LH (p=0.686), prolaktin (p=0.076), TSH (p=0.525), T4 (p=0.062).DHEASO4 (p=0.212), total testosterone (p=0.564), and Estradiol (p=0.297).

There was a statistically significant difference between endometrial polyps group and control in terms of AMH levels (p < 0.05).

Table 3. Average of study parameters according to the endometrial polyps result

Study parameters	Endometrial Polyps (n=55)	Mean±SD	No Endometrial Polyps (n=49)	Mean±SD	p
Age (years)	29(22-36)	28.91±3.41	27(22-32)	27.41±2.47	0.063*
BMI	25(20-33)	25.6±2.7	25(22-29)	25.29±1.63	0.819*
Infertility Period(years)	3(0-5)	2.78±1.42	3(1-5)	3.24±1.23	0.136*
AMH (ng/ml)	6.5(3.2-14.5)	7.16±2.63	5.1(2.3-11)	5.17±2.05	<0.001*
FSH	5.76(1.79-9.66)	5.71±1.87	5.66(2.4-9.51)	5.59±1.74	0.749**
LH	6.32(2.73-22.8)	7.63±4.61	5.8(2.73-19.36)	7.31±4.01	0.686*
Prolactin	22.59(5.08-143)	32.33±25.14	18.45(2.57-46.73)	20.03±9.7	0.076*
TSH	2.42(0.46-7.98)	2.71±1.58	2.57(0.54-6.7)	2.7±1.24	0.525*
T4	1.21(0.95-2.75)	1.24±0.26	1.28(0.95-2.75)	1.31±0.27	0.062*
DHEA-SO4	268.7(125.7-671)	306.81±129.29	262.8(33.8-545.6)	268.84±101.65	0.212*
Total testosterone	32(3-141)	36.8±25.54	34(5-84)	37.34±19.27	0.564*
Estradiol	47.12(21-330.9)	68.76±63.82	55(6.98-275.6)	72.58±58.17	0.297*

* Mann-Whitney test **The independent t-test, BMI, body mass index ; AMH, anti-Mullerian hormone; FSH, follicle-stimulating hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; T4, Thyroxine; DHEA-SO4, dehydroepiandrosterone sulphate.

DISCUSSION

This study aimed to conduct a case-control study to determine the relationship between AMH serum levels and endometrial polyps in women with PCOS. AMH is helpful in evaluating women at risk of decreased ovarian reserve, including women with a family history of ovarian failure (10), women with early menopause (11), women with a history of severe endometriosis (12), chemotherapy or previous surgery on the ovaries (13), women with autoimmune diseases (14), pelvic infections (15), and women using vegetarian diets (16).

This retrospective study showed that in women with PCOS, the endometrial polyps increase the level of AMH levels. In various studies, the relationship between AMH and PCOS has been discussed. It has been shown that androgens cause the proliferation of the inner theca and granulosa layer, which can increase AMH (10-16). Also, the level of AMH can be highly related to the number of antral follicles and oocytes (17). Therefore, there is an increase in the serum level of AMH in PCOS patients with endometrial polyps (14,17,18).

Although the serum AMH level cannot accurately predict the risk level of endometrial polyps in women with PCOS, different studies have found different threshold levels (from AMH 3.8 to 5 ng/cc) to be sensitive for diagnosis (16,19,20). In a study conducted by Munro (20) on 60 PCOS cases and a control group, there was a significant difference in the average AMH level in patients with 14.7 and 3.14 in the control group. In another study, it was concluded that androgens could increase AMH (20). But the important thing to note in this study was the investigation of other factors that could affect the AMH level. Our study argued that the level of AMH is higher in PCOS women with endometrial polyps than in the control group, independently of other factors such as androgens and testosterone.

In the current study, the average AMH in the endometrial polyp group was 7.16 and in the control group was 5.17. The difference in hormone levels between the two groups was significant with $p > 0.001$, which shows a significant difference in the AMH level of the two groups. Other studies have concluded that AMH and PCOS can be a good differentiator between endometrial polyp sufferers and non-affected people (16,19). As in this research, a clear difference was seen between the level of this hormone in endometrial polyp and healthy subjects. Zhang et al. (21) studied 104 women with PCOS and found no relationship between AMH and BMI in patients, which is consistent with the findings of our study.

Considering that the patients' race in this study differs from other studies, there will be expected differences in the obtained results. The difference in the level of AMH, along with the difference in LH level and the ratio of LH to FSH in patients, can help in the early diagnosis of the disease (22,23). An important point is the low average age of patients without endometrial polyps in this study. As a result, it is possible to reduce the burden of the disease in the early stages of infertility by correctly diagnosing and treating it. Despite extensive and growing research in the field of PCOS and AMH, unfortunately, very few studies have been conducted on the effect of other factors, including endometrial polyps, on AMH in PCOS sufferers.

The study's retrospective nature and the subsequent lack of data due to file reading and the low accuracy of paraclinical results are the limitations of this study. Prospective studies and high measurement accuracy can help solve this limitation for future research.

CONCLUSION

This research, by examining AMH in two groups with endometrial polyps and non-endometrial polyps, showed that the frequency of endometrial polyps increases with higher AMH levels in PCOS patients and this result can be a platform for future research. Due to the study's retrospective nature and the impossibility of a detailed investigation of the effects of various other factors, a prospective study is recommended for future studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Beykoz University Ethics Committee (Date: 21.01.2021, Decision No:2).

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.

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Original Article / Özgün Makale

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Can PCO_2 be a mortality predictor in COVID-19 patients?

PCO_2, COVID-19 hastalarında mortalite belirteci olabilir mi?

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ABSTRACT

Aim: The clinical course of Corona Virus Disease 2019 (COVID-19) infection is ranging from asymptomatic to moderate and severe disease with low survival rates. Therefore, reliable prediction of COVID-19 mortality and identification of contributing factors would allow targeted therapies for high-risk individuals. We aimed to determine whether partial carbon dioxide (PCO_2) concentrations could predict mortality in patients treated in the intensive care unit (ICU).

Material and Method: Acute Physiology and Chronic Health Evaluation (APACHE -2) scores, ferritin, lymphocyte count, neutrophil lymphocyte ratio (NLR), PCO_2, partial oxygen concentration to inspired oxygen fraction (P/F) ratio were retrospectively determined and were compared between survivors and non-survivors.

Results: The mean APACHE-2 value was higher in Group Non-survivors than in Group Survivors. Patients in Group Non-survivors were significantly older than those in Group Survivors (p=0,012). From day 7, low baseline lymphocyte counts were significant for mortality (p=0,046). NLR was also high at ICU admission, and it was significant for mortality from the 7^{th} day (p=0.022). From day 10, PCO_2 and ferritin levels increased in Group Non-survivors. The P/F ratio increased with treatment in both groups during the first 10 days, and after day 13, the increase continued in Group Survivors, whereas the values decreased in Group Non-survivors. We found that PCO_2 concentrations in patients at ICU admission were as expected and that the increase in PCO_2 could predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio.

Conclusion: This study showed that in patients with COVID -19, an increase in PCO_2 concentration can predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio.

Keywords: COVID-19, mortality, pneumonia, PCO_2

ÖZ

Amaç: Corona Virüs Hastalığı 2019 (COVID-19) enfeksiyonunun klinik seyri, asemptomatikten düşük sağkalım oranlarına sahip orta ve şiddetli hastalığa kadar değişmektedir. Bu nedenle, COVID-19 mortalitesinin güvenilir bir şekilde tahmin edilmesi ve katkıda bulunan faktörlerin belirlenmesi, yüksek riskli bireyler için hedefe yönelik tedavilere olanak sağlayacaktır. Yoğun bakım ünitesinde (YBÜ) tedavi edilen COVID-19 hastalarında kısmi karbon dioksit (PCO_2) konsantrasyonlarının mortaliteyi tahmin edip edemeyeceğini belirlemeyi amaçladık.

Gereç ve Yöntem: Akut fizyoloji ve kronik sağlık değerlendirmesi (APACHE -2) skorları, ferritin, lenfosit sayısı, nötrofil lenfosit oranı (NLR), PCO_2, kısmi oksijen konsantrasyonu/inspire edilen oksijen fraksiyon oranı (P/F) hasta dosyaları taranarak belirlendi ve hayatta kalanlarla ölen hastalar karşılaştırıldı.

Bulgular: Ortalama APACHE-2 değeri ölen grupta sağ kalanlardan daha yüksekti. Ölen hastalar, sağ kalanlardan anlamlı olarak daha yaşlıydı (p=0,012). 7. günden itibaren, düşük bazal lenfosit sayıları mortalite için önemliydi (p=0,046). NLR, yoğun bakıma yatışta da yüksekti ve 7. günden itibaren mortalite açısından anlamlıydı (p=0,022). 10. günden itibaren, ölen grubunda PCO_2 ve ferritin seviyeleri arttı. İlk 10 gün boyunca her iki grupta da tedavi ile P/F oranı arttı ve 13. günden sonra artış sağ kalanlarda devam ederken, ölen grubunda değerler azaldı.

Sonuç: Bu çalışma, COVID-19 hastalarında PCO_2 konsantrasyonundaki artışın, yüksek ferritin seviyesi, ileri yaş, yüksek APACHE skorları, düşük lenfosit sayısı, yüksek NLR ve yüksek P/F oranı ile birlikte mortaliteyi öngörebileceğini göstermiştir.

Anahtar Kelimeler: COVID-19, PCO_2, mortalite, pnömoni

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INTRODUCTION

Severe acute respiratory syndrome-Corona virus-2 (SARS-CoV-2), a member of the coronavirus family, causes Corona virus disease 2019 (COVID-19). World Health Organization (WHO) declared COVID-19 a pandemic on 11 March 2020. The COVID-19 pandemic affected over 400 million people worldwide and caused close to 6 million deaths (1). The disease's spread is worrisome because it has been linked to respiratory illnesses. Fever, cold, cough, shortness of breath, and diarrhea are among the symptoms. In severe circumstances, pneumonia can cause death. Because the disease is rapidly spreading, it is urgently required to predict its fatality rate and assess the related hazards. The growth of such an epidemic has also produced issues for healthcare personnel and public health communities because of the disease's uncertainties, including transmission medium, treatment, recovery rates, and risk prediction (2).

The clinical course of SARS-CoV-2 infection has revealed significant heterogeneity, ranging from asymptomatic to moderate and severe disease types with low survival rates. In particular, it is difficult to predict clinical outcomes for patients with a wide range of symptoms. This issue complicates prognostication and management of COVID-19 patients, especially in disease epicenters with high patient volumes. Therefore, reliable prediction of COVID-19 mortality and identification of contributory factors would allow focused treatments in high-risk individuals (3). Predicting patient mortality helps with the classification and allocation of resources. Commonly used scores for mortality and morbidity, Modified Early Warning Score (MEWS), Acute Physiology and Chronic Health Evaluation (APACHE II), Simplified Acute Physiology Score (SAPS II), sequential organ failure assessment score (SOFA), and quick SOFA (qSOFA), provide a rough estimate. However, the specificity and sensitivity of these tools are limited for patients with COVID-19 (4). In a large-scale study in Wuhan, China, epidemiological, clinical, and laboratory characteristics differed significantly between survivors and non-survivors. For example, older age, dyspnea, chest pain and unconsciousness were more common in healed patients who died. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine (Cr), ferritine, creatine kinase (CK), lactate dehydrogenase (LDH), troponin I (TnI), N-terminal pro-brain natriuretic peptide (NT proBNP) and D-dimer concentrations were higher and lymphocyte count lower than those in survivors in patients who died (5).

Although the prognosis of COVID-19 pneumonia can be predicted by various biomarkers and scoring methods described above, a parameter that directly predicts mortality has not yet been demonstrated. In our experience in the intensive care unit (ICU), we have seen that the increase in PCO_2 concentration above a certain level leads to mortality. This study aimed to investigate whether PCO_2 concentration can predict mortality by comparing it with ferritin, lymphocyte count, neutrophil lymphocyte ratio (NLR), and partial oxygen concentration to inspired oxygen fraction (P/F) ratio, in covid-19 patients treated in the ICU.

MATERIAL AND METHOD

After approval of Ethical Committee of the Erzurum Regional Education and Research Hospital, the files of all COVID-19 patients followed in Erzincan Binali Yıldırım University Mengucek Gazi Training and Research Hospital were scanned retrospectively. Patients aged 18-100 years with a diagnosis of COVID -19 were included in the study. Patients with a COPD diagnosis and patients who died within the first 16 days were excluded from the study. The patients were divided into two groups as survivors and non-survivors. The male and female genders were equal. Along with the demographic data of the patients, arterial PCO_2, APACHE II scores, NLR, ferritin levels, arterial partial oxygen concentration (PO_2), fraction of inspired oxygen (FIO_2) , P/F ratio were recorded. The results of the first 16 days of the patients were evaluated.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) version 26 was used for data analyses (IBM Corp., Armonk, NY). The Mann Whitney U-test was used to determine between groups differences. The repeated measures ANOVA was used for determining pairwise comparison and $P<0.05$ was defined as statistically significant. To further evaluate the link between PCO_2, ferritin, lymphocyte count, NLR, P/F ratio and mortality, the receiver operating characteristic curve (ROC) was plotted, and the area under the curve (AUC) was obtained. The cutoff values were designed to be as high as possible while maintaining a consistent mix of sensitivity and specificity. Additionally, a binary logistic regression was utilized to assess the relationship with mortality.

RESULTS

Data from 120 patients were analyzed. Sixty consecutive survivors and non-survivor patients were enrolled in the study (Group Survivors, n=60, Group Non-survivors, n=60). Demographic data are summarized in **Table 1**.

PCO_2 Analyses

Time-dependent variation in PCO_2 concentrations was different in Survivor and Non-survivor Groups (**Figure 1**). A positive correlation was found between PCO_2 concentration and mortality (r= 0.333, P= 0.009), which was observed from the 11th day. The strong correlation value calculated on the 16th day was (r=0.732, p=0.00). As a result of the ROC analysis performed to determine mortality, diagnostic discrimination was found from the 11th day (p=0.013) (**Figure 2**.). ROC curve analysis was used to compare the performance of PCO_2 as predictors of mortality. PCO_2 was a better predictor of mortality with an AUC of 0.91 (95% CI: 0.829-0.996) at day 16, and the optimal cut-off value for predicting mortality was 47 mmHg with a sensitivity of 90% at the expense of a specificity of 83.3%, as shown in **Table 2**.

Table 1. Demographic data

	Survivors	Non-survivors	p-value
Age (Years)			p= 0.012
Mean	66.33	73.83	
Youngest	21	48	
Oldest	81	88	
Gender			
Male	26	32	
Female	34	28	
APACHE-2 Score			p=0.09
Mean	26.93	30.90	
Lowest	15	18	
Highest	42	44	

APACHE-2: Acute Physiology and Chronic Health Evaluation

Ferritin Analyses

Ferritin levels over time were different in the death and survival groups (**Figure 1**.). A positive correlation was found between ferritin and mortality (r= 0.353, P= 0.006), which was observed from the 10th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 10-day measurement (p=0.011) (**Figure 2**.). ROC curve analysis was used to compare the performance of ferritin, as predictors of mortality. Ferritin was a better predictor of mortality with an AUC of 0.81 (95% CI: 0.693-0.927) at day 16, and the optimal cut-off value for predicting mortality was 648,5 ng/mlL with a sensitivity of 76.7% at the expense of a specificity of 66.7%, as shown in **Table 2**.

Lymphocyte Analyses

Lymphocyte count over time were different in the death and survival groups (**Figure 1**.). A negative correlation was found between lymphocyte count and mortality (r= 0.258, P= 0.046), which was observed from the 7th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 7th day measurement (p=0.048) (**Figure 2**.). ROC Curve analysis was used to compare the performance of lymphocyte count as predictors of mortality. Lymphocyte was a better predictor of mortality with an AUC of 0.828 (95% CI: 0.719-0.938) at day 16, and the optimal cut-off value for predicting mortality was $0,65x10^9$/L with a sensitivity of 86% at the expense of a specificity of 66%, as shown in **Table 2**.

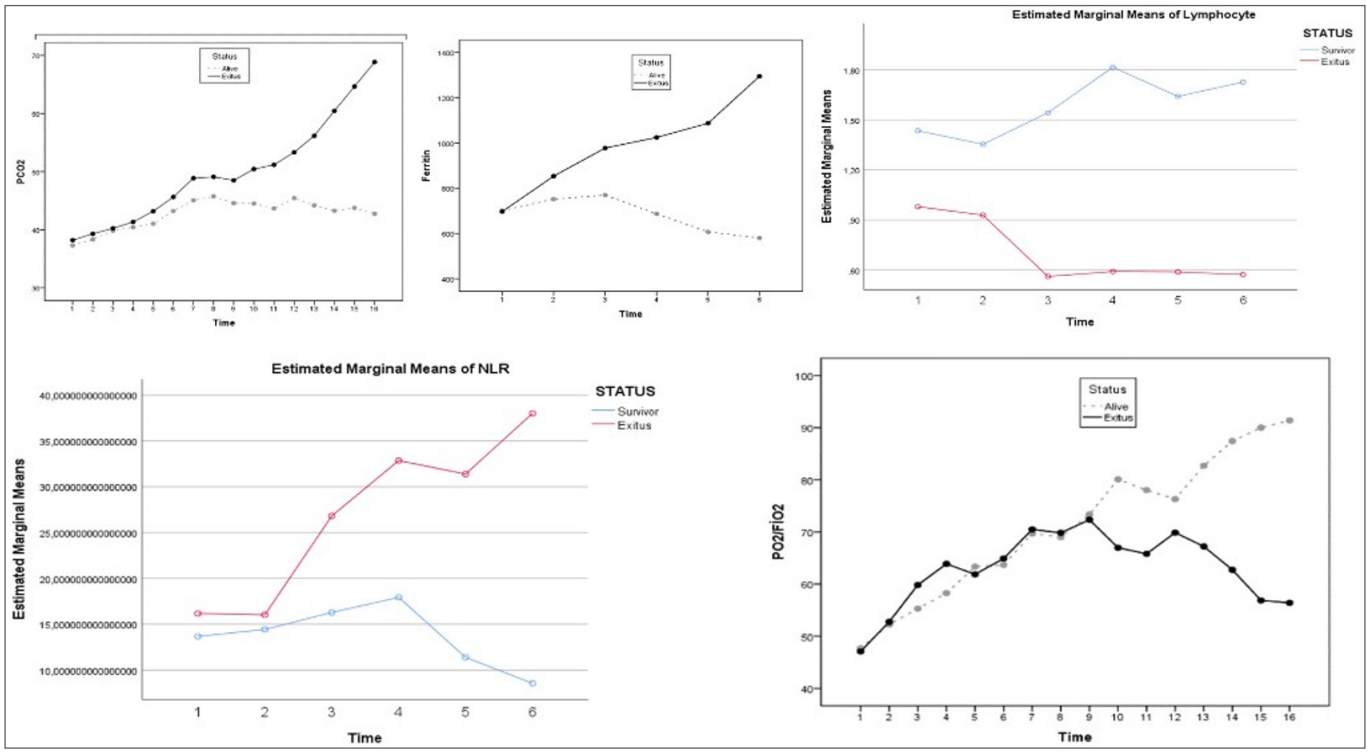

Figure 1. Time-dependent variations

Table 2. Area Under the Curve and Cut-off values

Test Result Variable(s)	Area	Std. Errora	Asymptotic Sig.b	Asymptotic 95% Confidence Interval		Cut-off	Sensitivity %	Specifity %
				Lower Bound	Upper Bound			
PCO_2 11th day	.687	.069	.013	.552	.822	49.5	%73.3	%80
PCO_2 12th day	.715	.071	.004	.576	.854	47.0	%90	%83.3
PCO_2 13th day	.815	.057	.000	.703	.927	54.5	%80	%90
PCO_2 14th day	.869	.053	.000	.766	.973	56.5	%83.3	%93.3
PCO_2 15th day	.887	.047	.000	.795	.979	49.5	%73.3	%80
PCO_2 16th day	.912	.043	.000	.829	.996	47.0	%90	%83.3
Ferritin 10th day	.691	.070	.011	.553	.828	648.5	%76.7	%66.7
Ferritin 13th day	.750	.066	.001	.622	.878	692.5	%76.7	%73.3
Ferritin 16th day	.810	.059	.000	.693	.927	1003	%76.7	%86.7
Lymphocyte 7th day	.649	.071	.048	.510	.788	0.54	%60	%60
Lymphocyte 10th day	.702	.070	.007	.565	.839	0.71	%60	%70
Lymphocyte 13th day	.750	.064	.001	.624	.876	0.72	%60	%80
Lymphocyte 16th day	.828	.056	.000	.719	.938	0.65	%86	%66
NLR 7th day	.670	.071	.024	.532	.808	18.58	%70	%66
NLR 10th day	.709	.068	.005	.576	.842	18.46	%73	%73
NLR 13th day	.862	.051	.000	.763	.961	20.75	%70	%83
NLR 16th day	.884	.047	.000	.793	.976	20.16	%66	%93
P/F 13th day	.734	.065	.002	.606	.862	66.5	%66.7	%76.7
P/F 14th day	.864	.047	.000	.772	.956	67.5	%76.7	%86.7
P/F 15th day	.926	.032	.000	.863	.989	67.75	%86.7	%83.3
P/F 16th day	.941	.028	.000	.887	.996	69.5	%86.7	%86.7

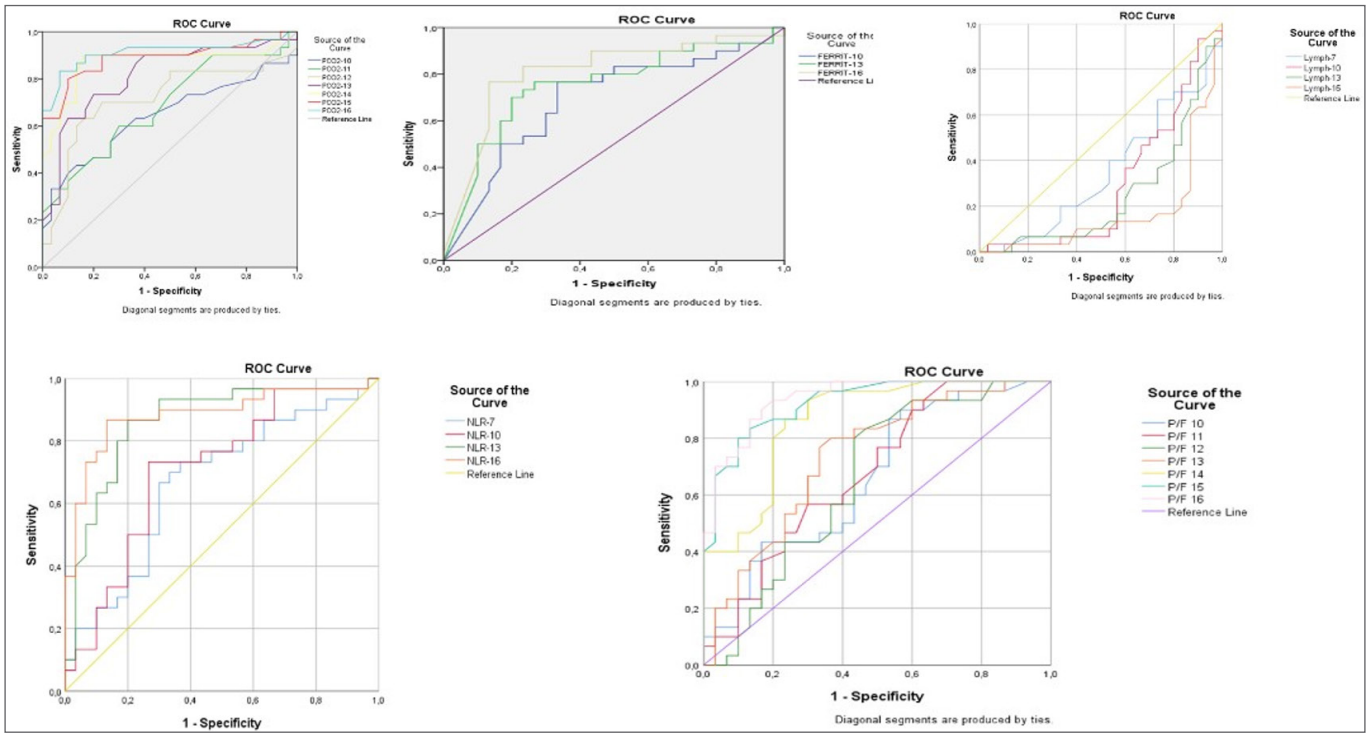

Figure 2. ROC curves

Neutrophil Lymphocyte Ratio (NLR)

NLR over time were different in the death and survival groups (**Figure 1**.). A positive correlation was found between NLR and mortality (r= 0.294, P= 0.022), which was observed from the 7th day. As a result of the ROC analysis performed to determine mortality, diagnostic distinctiveness was found from the 7th day measurement (p=0.024) (**Figure 2**.). ROC curve analysis was used to compare the performance of NLR as predictors of mortality. NLR was a better predictor of mortality with an AUC of 0.884 (95% CI: 0.793-0.976) at day 16, and the optimal cut-off value for predicting mortality was 18,46 with a sensitivity of 73% at the expense of a specificity of 73%, as shown in **Table 2**.

P/F Ratio Analysis

Time-dependent variation in P/F ratio was different in Survivor and Non-survivor Groups (**Figure 1**.). A negative correlation was found between PO_2/FO_2 ratio and mortality (r=0.348, P=0.006), which was observed from the 13th day. As a result of the ROC analysis performed to determine mortality, diagnostic discrimination was found at 10, 11, 13, 14, 15 and 16 time points. This difference became continuous from the 13th-day measurement (p=0.02) (**Figure 2**.). ROC curve analysis was used to compare the performance of P/F ratio as predictors of mortality. P/F ratio was a better predictor of mortality with an AUC of 0.941 (95% CI: 0.887-0.996) at day 16, and the optimal cut-off value for predicting mortality was 69.75 with a sensitivity of 86.7% at the expense of a specificity of 86.7%, as shown in **Table 2**.

We performed a logistic regression model to analyze PCO_2 concentration, Lymphocyte count, serum ferritin level, NLR and P/F ratio as independent predictors of mortality (**Table 3**). Age (OR: 1.098; 95% CI: 1.014-1.190; p=0.021), ferritin (OR: 1.004; 95% CI=1.000-1.008; p=0.037), PCO_2 concentration (OR: 1.335; 95% CI: 1.03-1.729; p=0.029), lymphocyte count (OR: 1.068; 95% CI: 1.01-1.464; p=0.006), NLR (OR: 1.151; 95% CI=1.064-1.246; p=0.00), P/F ratio (OR: 1.083; 95% CI=1.000-1.172; p=0.05) remained independently associated with mortality.

DISCUSSION

COVID-19 is leading to mortality since the day it started. Although many different treatment protocols have been tried worldwide, the rate of severe morbidity and mortality has not been sufficiently reduced. Most of the patients in the ICU are hospitalized due to respiratory failure and hypoxia. All studies on COVID-19 report that age is a risk factor. Parallel to this, in our study, the mortality rate was statistically higher in elderly patients. The process that starts with hypoxia progresses to ventilation disorder when there is no response to treatment, which increases the PCO_2 values. In our intensive care experience, we found that the patients entered an arduous process to reverse with increased PCO_2 values. Unfortunately, most of these patients died.

This study was based on the hypothesis that the PCO_2 value measured in arterial blood gas could be a mortality indicator, and our hypothesis was confirmed. The PCO_2 values of the patients who died increased on the 11th day of ICU hospitalization, and the optimal cut-off value for predicting mortality was 47 mmHg with a sensitivity of 90% at the expense of a specificity of 83.3%. In the literature review, we have not yet seen any comment on the contribution of PCO_2 value to mortality. This study in 120 ICU patients will be the first in this regard. Wang et al. (6) found a mean PCO_2 concentration of 34 mmHg in 138 patients. In contrast to our study, only 36 (26.1%) of the patients in their study were ICU patients. Vélez-Paez et al. (7) found that a PCO_2 concentration of 49.34 mmHg and above was associated with mortality, which is close to our value (p=0.026).

The cut-off values for lymphopenia ranged from 0.5 to 1.5×10^9/L in a meta-analysis by Brandon et al. (8) that included twenty-one studies reporting the rate of lymphopenia by disease severity. The presence of lymphopenia at diagnosis was associated with a greater than 4-fold increased likelihood of progression to severe disease. The same meta-analysis reported that the presence of lymphopenia increased mortality by up to 4-fold and by up to 12 times in severe lymphopenia ($< 0.5\times10^9$/L). In our study, lymphopenia was associated with mortality, similar to the meta-analysis, and the cutoff value was 0.65×10^9/L with a sensitivity of 86% and a specificity of 66%.

According to recent research, inflammatory cytokines, chemokines, and NLR are related to disease severity and are indicators of cytokine storm intensity. NLR, which primarily represents the extent of systemic inflammation, has been associated with pathogenicity in COVID -19 patients. High NLR has been associated with severe clinical symptoms as well as hospitalization in the intensive care unit, recovery, and situations such as discharge and mechanical ventilation (9). In their study, Asghar et al. (10) calculated the AUC value of NLR in deceased patients to be 0.860 and found it to be a strong predictor of mortality. Similarly, the AUC value in our study was 0.884 and the optimal cut-off value for predicting mortality was 18,46 with a sensitivity of 73% at the expense of a specificity of 73%.

Table 3. Analysis of independent predictors of mortality in COVID-19 patients in ICU using a logistic regression model

Parameters	B	SE	Wald	p value	Odds ratio	Lower 95% CI	Upper 95% CI
Age	0.094	0.041	5.311	0.021	1.098	1,014	1,190
Ferritin	0.004	0.002	4.366	0.037	1.004	1,000	1,007
PCO_2	0.289	0.132	4.781	0.029	1.335	1,030	1,729
Lymphocyte	-2.690	0.981	7.515	0.006	1.068	1,010	1,464
NLR	0.141	0.040	12.129	0.000	1.151	1,064	1,246
P/F ratio	0.79	0.041	3.834	0.050	1.083	1,000	1,172

The inflammatory cytokine storm, characterized by a sudden and excessive production of proinflammatory cytokines, notably interleukins (IL-6,IL-10), and tumor necrosis factor (TNF-), has been linked to severity and mortality (11). With this in mind, the biochemical examination of plasma inflammatory markers and positive acute phase reactants, including ferritin, may be beneficial in predicting disease development (12). Ahmed et al. (13) found the optimal cutoff value of ferritin 574 ng/mL for predicting mortality in COVID-19 patients. In our study, the cutoff for the prediction of mortality was 648.5 ng/mL, with a sensitivity of 66.7% at the cost of specificity 76.7%. In our study, the ferritin value, which was high in all groups, increased to higher levels (>1000 ng/mL) in the deceased group. Ferritin concentrations in COVID-19 patients were typically within the normal range of less than 400 ng/ml in patients with nonsevere illness, according to Pastora et al. (12) in a systematic study. Hyperferritinemia (ferritin level > 400 g/L) was observed in patients with severe illness at admission, ranging from 1.5 to 5.3 times higher. According to Pastora et al. (12), nonsurvivors had ferritin levels on admission of approximately 1400 ng/mL, which is between 3 and 4 times greater than those reported in survivors.

P/F ratio is the de facto standard for ARDS severity classification since it corresponds to death estimates (14). However, the PaO_2/FIO_2 ratio has limitations: it is not linearly linked to FIO_2 (i.e., the same patient may have varying PaO_2/FIO_2 at various FIO_2) (15). Alfonso et al. (16) found that a P/F ratio below 100 in the ICU was strongly associated with mortality. This study is in parallel with our findings. Although the P/F ratio is used more frequently in ICU admission, we observed that this ratio is meagre and cannot be treated with mechanical ventilation, which may be associated with mortality. Bellan et al. (17) found that the P/F ratio was significantly lower in patients who died than in survivors, indicating more severe respiratory failure at baseline (246 [184-300] vs. 126 [100-202]; <0.001). We found that the P/F ratio AUC was 0.994 and P/F values below 69.75 could be a strong indicator of mortality.

This study has many limitations. Because the hypothesis was based on critical care experience, a retrospective method was used. This limited control in patient selection. Due to the nature of COVID -19 pneumonia, this situation could not be included in the study because different mechanical ventilator settings were used throughout the process.

CONCLUSION

This study showed that in patients with COVID -19, an increase in PCO_2 concentration can predict mortality along with increased ferritin levels, older age, high APACHE scores, low lymphocyte count, elevated NLR and high P/F ratio. The treatment protocols and mortality assessment of COVID -19 patients in the ICU are still not fully elucidated. We hope to shed light on this problem from a different perspective.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Erzurum Regional Education and Research Hospital Clinical Research Ethics Committee (Date: 20.06.2022, Decision No: 2022/08-96).

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.

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Evaluation of real-life data in patients with severe eosinophilic asthma treated with mepolizumab

Mepolizumab ile tedavi edilen ağır eozinofilik astımlı hastalarda gerçek yaşam verilerinin değerlendirilmesi

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ABSTRACT

Aim: We aimed to evaluate the efficacy of mepolizumab on asthma exacerbations, blood eosinophils, oral steroid dependence, and asthma control.

Material and Method: This study is a clinical observational study created from real-life data obtained by retrospective analysis. Patients who were initiated subcutaneous mepolizumab at a dose of 100 mg every four weeks in our clinic and received treatment for at least 16 weeks were included in the study.

Result: Thirty-four patients with severe eosinophilic asthma were included in the study. We found that mepolizumab treatment resulted in a decrease in the number of asthma exacerbations, the need for maintenance oral corticosteroid, blood eosinophil counts, and improvement in lung functions and asthma control test scores in patients with severe eosinophilic asthma. At 6 months the rate of responders and super responders to mepolizumab treatment was 75% and 17.9%, respectively, and the overall response rate was 92.9% as a result. In the first year of treatment, the rate of super-responders increased to 58.3%, and the overall response rate was 91.7%. The rate of second-year responders and super-responders was 7.7% and 84.6%, respectively, and the overall response rate was 92.3%. At 3 years, the overall response rate had increased to 100%.

Conclusion: The results of our single-center study, in which we evaluated the results of mepolizumab treatment in patients with severe eosinophilic asthma, confirmed the clinical, hematological and functional findings published by previous studies in a real-life setting.

Keywords: Asthma control test, blood eosinophil counts, corticosteroid, interleukin – 5

ÖZ

Amaç: Mepolizumabın astım alevlenmeleri, kan eozinofilleri, oral steroid bağımlılığı ve astım kontrolü üzerindeki etkinliğini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışma, retrospektif analiz ile elde edilen gerçek yaşam verilerinden oluşturulmuş klinik gözlemsel bir çalışmadır. Kliniğimizde dört haftada bir 100 mg deri altı mepolizumab başlanan ve en az 16 hafta tedavi gören hastalar çalışmaya alındı.

Bulgular: Ağır eozinofilik astımı olan 34 hasta çalışmaya dahil edildi. Ağır eozinofilik astımı olan hastalarda mepolizumab tedavisinin astım alevlenmelerinin sayısında, oral kortikosteroid idame ihtiyacında, kan eozinofil sayılarında ve akciğer fonksiyonlarında ve astım kontrol testi puanlarında iyileşme ile sonuçlandığını bulduk. 6 ayda mepolizumab tedavisine yanıt verenlerin ve süper yanıt verenlerin oranı sırasıyla %75 ve %17,9'du ve sonuç olarak genel yanıt oranı %92,9'du. Tedavinin ilk yılında, süper yanıt verenlerin oranı %58,3'e yükseldi ve genel yanıt oranı %91,7 oldu. İkinci yılda yanıt verenlerin ve süper yanıt verenlerin oranı sırasıyla %7,7 ve %84,6 ve genel yanıt oranı %92,3'tü. 3 yılda, genel yanıt oranı %100'e yükselmişti.

Sonuç: Ağır eozinofilik astımı olan hastalarda mepolizumab tedavisinin sonuçlarını değerlendirdiğimiz tek merkezli çalışmamızın sonuçları, gerçek yaşam ortamında önceki çalışmalarda yayınlanan klinik, hematolojik ve fonksiyonel bulguları doğruladı.

Anahtar Kelimeler: Astım kontrol testi, interlökin–5, kan eozinofil sayıları, kortikosteroid

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INTRODUCTION

Asthma is a heterogeneous disease characterized by chronic and variable airway inflammation, affecting more than 300 million people worldwide. Asthmatic patients differ not only in clinical features and disease severity, but also in underlying chronic airway inflammation, airway hyperresponsiveness, and airway remodeling. Among the different phenotypes and endotypes of asthma, eosinophilic inflammation is detected in more than 50% of patients, whether atopic or not (1). Severe eosinophilic asthma, which is associated with high numbers of eosinophils in both peripheral blood and airways, severe airflow limitation and recurrent asthma exacerbations, can often be controlled with the use of maintenance systemic corticosteroids (2,3).

Interleukin–5 (IL–5) is the main cytokine responsible for differentiation, maturation, activation and proliferation of eosinophils. Therefore, biological agents targeting IL–5 have been developed in severe eosinophilic asthma. Of these, mepolizumab is an IgG1/k class humanized monoclonal antibody that blocks IL – 5 by preventing its interaction with the α chain of the IL–5 receptor (4,5).

In randomized controlled studies, it has been shown that mepolizumab reduces asthma exacerbations and the dose of oral steroids used, has a significant lowering effect on blood eosinophils, and improves asthma control in severe eosinophilic asthmatics (6-9). The efficacy of mepolizumab in severe eosinophilic asthma has also been demonstrated in real-life studies and is now well established. However, these real-life studies are limited both in our country and worldwide. Therefore, we aimed to evaluate the efficacy of mepolizumab on asthma exacerbations, blood eosinophils, oral steroid dependence, and asthma control.

MATERIAL AND METHOD

The study was carried out with the permission of Health Sciences University Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.03.2021, Decision No: 2021-KAEK-15/2247). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Subject Characteristics and Study Design

This study is a clinical observational study created from real-life data obtained by retrospective analysis of patients in the Allergy and Immunology Clinic of Health Sciences University Ankara Keçiören Training and Research Hospital.

Patients who were initiated subcutaneous mepolizumab at a dose of 100 mg every four weeks in our clinic and received treatment for at least 16 weeks were included in the study. All patients had uncontrolled asthma (at least 2 attacks per year, requiring systemic corticosteroid use for at least 3 days) despite using high-dose inhaled corticosteroids (ICS) (>800 mcg/day budesonide or equivalent) and an inhaler long-acting β2-agonist, along with a third controller drug at least 1 year and/or had controlled or uncontrolled asthma under regular systemic steroids for at least 6 months and had a blood eosinophil count ≥300 cells/μL(for long-term regular systemic steroid users, ≥150 cells/μL under this treatment). All patients met the ATS/ERS criteria for uncontrolled severe asthma and defined conditions for mepolizumab according to the Turkish Social Security Institution (10).

Demographic data of the patients, their asthma diagnosis and follow-up times, information about whether they have been treated with omalizumab before, asthma control test (ACT) score at baseline and after mepolizumab injection, blood eosinophil count, FEV1 and FEV1/FVC values, oral corticosteroid (OCS) use Parameters including dose, asthma treatment step and number of attacks were obtained from the files of the patients. Asthma attack was defined as worsening of asthma symptoms requiring systemic corticosteroid use for at least 3 days. In the specified time periods (1st year, 2nd year and 3rd year); Patients who met one of the criteria for a ≥50% reduction in the number of asthma attacks compared to the previous year in those with a history of frequent exacerbations or a ≥50% reduction in daily OCS dose in continuous OCS users were defined as 'responder', while those who could discontinue OCS and had no exacerbations were defined as 'super-responders' (11).

Statistical Analysis

Predictive analytical software (PASW statistics 18, 2009) was used for the analysis. Descriptive statistics was expressed as numbers and percentages for categorical variables and as mean, standard deviation, median, percentile 25, percentile 75, minimum and maximum for numerical variables.

RESULTS

Baseline Patient Characteristics

Thirty-four patients with severe eosinophilic asthma were included in the study. The mean age of the study population was 49±12 years and 23 participants were female (67.6%). The mean body mass index (BMI) was 29±5 kg/m², and 12 patients (35.3%) were obese (BMI 30 Kg/m²). The median total IgE value of the patients before treatment was 414.98 (37-2500) kU/L. Atopy (26.5%) was detected in 9 patients according to skin test positivity and/or sIgE levels. The mean duration of asthma diagnosis of the patients was 14.24±8.05 years. Seventeen of the patients (50%) had previously received omalizumab treatment and were switched to mepolizumab due to partial response to omalizumab (**Table 1**).

Because the patients had a baseline ACT score of 16.62±4.72, these patients had poor symptom control. A mean of 2.38±1.84 asthma exacerbations occurred in patients in the year prior to the start of mepolizumab. The mean FEV1 values of the patients before mepolizumab treatment were 2375.86±733.22 (580-4340) mL. Of the 34 patients included in the study, 29 were using OCS and the mean OCS dose was 6.38±4.01 mg. Prior to mepolizumab treatment, the mean baseline eosinophil level was 885.47±728.06 /μL (min-max:150-3880).

Table 1. Baseline demographic and clinical characteristics

Variables	Baseline (N=34)
Age. (years)	49±12
Female. n (%)	23 (67.6)
BMI. (kg/m²)	29±5
Smoking story. n (%)	
Activesmoker	3 (8.8)
Never smoked	23 (67.6)
Ex-smoker	8 (23.5)
Asthma duration. (years)	14.24±8.05
Mean follow-up duration. (years)	6.65±3.96
Exacerbations (last 12 months)	2.38±1.84
Patients receiving maintenance OCS at baseline n (%)	29 (85.3)
Methylprednisolone equivalent OCS dose at baseline. (mg)	6.38±4.01
Baseline total IgE levels. (IU/mL)	414.98±556.84
History of treatment with omalizumab. n (%)	7 (50)
Atopy. n (%)	9 (26.5)
Perennial allergen sensitivity n (%)	9 (26.5)
Nasal polyposis. n (%)	20 (58.8)
Chronic eosinophilic pneumonia. n (%)	16 (47.1)

Follow-up Data with Mepolizumab

Six of the patients received mepolizumab for 16 weeks, 4 for 6 months, 11 for 1 year, 8 for 2 years, and 5 for 3 years. It was observed that the ACT score increased from 16.62±4.72 to 21±4.17 at the 4th week of mepolizumab treatment. The ACT score, which was 21.14±3.92 at week 24, increased to 22.5±3.46 at year 1, 24.23±1.17 at year 2, and 24±1.41 at year 3. When we look at the effect of mepolizumab on blood eosinophil values (respectively: absolute value, percent) compared to baseline values (885.47±728.06/μL, 8.69±7.36%), a decrease was achieved at 4 weeks (147.29±141.84/μL, 1.6±1.73%). This decrease in blood eosinophil values continued at other time points; 116.96±120.96/μL, 1.49±1.3% at week 24, 131.76±97.87μL, 1.54±1.14% at 1 year, 97.5±57.23/μL, 1.13±0.66% at Year 2 and 100±58.31/μL, 1.08%±0.63% at year 3. The mean FEV1 values measured to evaluate the improvement in lung functions were 2375.86±733.22 mL at baseline, 2675±658.04 mL at week 4, 2620±535.82 mL at week 24, 2777.78±645,38 mL at year 1, 2820±296.98 mL at year 2. While the patients receiving daily OCS were 29 at baseline, it decreased to 19 at 24 weeks, 7 at 1 year, and 1 at 2 years. In the 3rd year, there were no patients who received daily OCS. While the median daily dose of OCS was 6.38±4.01 mg in the premepolizumab period, it decreased to 2.24±1.81 mg at week 24. The mean number of asthma exacerbations in the year before mepolizumab treatment was 2.38±1.84, compared to 0.79±1.14 in the first year, 0.23±0.6 in the second year, and 0.4±0.89 in the third year after treatment (**Table 2**).

When maintenance asthma treatments were evaluated, 47.1% of the patients were receiving high-dose ICS+ Long-Acting Beta-Agonists (LABA) and 52.9% were receiving medium-dose ICS+LABA at baseline. While the rate of those using high-dose ICS+LABA in the first year with mepolizumab treatment decreased to 33.3%, the rate of those using medium-dose ICS+LABA increased to 62.5%. The remaining patients were receiving low-dose ICS+LABA therapy. In the second year after mepolizumab treatment, the proportion of those using high-dose ICS+LABA decreased to 7.7%, while the proportion of those receiving medium-dose ICS+LABA and low-dose ICS+LABA treatment increased to 76.9% and 15.4%, respectively.

At 6 months the rate of responders and super responders to mepolizumab treatment was 75% and 17.9%, respectively, and the overall response rate was 92.9% as a result. In the first year of treatment, the rate of super-responders increased to 58.3%, and the overall response rate was 91.7%. The rate of second-year responders and super-responders was 7.7% and 84.6%, respectively, and the overall response rate was 92.3%. At 3 years, the overall response rate had increased to 100%.

Table 2. Comparison of clinical. laboratory and functional parameters at baseline 24th weeks and 1st. 2nd. 3rd years

Variables	Pre-mepolizumab n: 4	Mepolizumab 24th week, n: 28	Mepolizumab 1st year, n: 24	Mepolizumab 2nd year, n: 13	Mepolizumab 3rd year, n: 5
ACT score	16.62±4.72	21.14±3.92	22.5±3.46	24.23±1.17	24±1.41
Blood eosinophil count (cell/mm³)(%)	885.47±728.06 8.69±7.36	116.96±120.96 1.49±1.3	131.76±97.87 1.54±1.14	97.5±57.23 1.13±0.66	100±58.31 1.08±0.63
FEV1, (mL)	2375.86±733.22	2620±535.82	2777.78±645.38	2820±296.98	-
OCS dosage. (mg/day)	6.38±4.01	2.24±1.81	2.9±2.44	8	0
Attack number	2.38±1.84	0.25±0.5	0.79±1.14	0.23±0.6	0.4±0.89

Abbreviations: ACT: Asthma control test, FEV: Forced expiratory volume, OCS: Oral corticosteroid

At the sixth month of mepolizumab treatment, the duration of asthma diagnosis was shorter in unresponsive patients compared to responders and superresponsive patients (15.24±8.69, 11.6±6.39, and 8±0 years, respectively). Blood eosinophil counts were also lower in responding and superresponsive patients compared to non-responders (822.1±509.58, 684±493.74, and 2261±2289.61/μL, respectively). The number of patients receiving maintenance OCS treatment was higher in responding and superresponsive patients than in non-responders (90.5%, 80% and 50%, respectively). Baseline total IgE levels were higher in responding and superresponsive patients compared to non-responders (465.13±673.3 IU/mL, 461.4±439.38 IU/mL, and 117 IU/mL, respectively). The presence of nasal polyps with asthma was higher in responding and superresponsive patients than in non-responders (66.7%, 40%, and 0%, respectively).

Blood eosinophil counts were higher in responding and superresponsive patients at 1 year than in nonresponders (1474±1086.45/μL, 800.29±439.36/μL, and 425±35.36/μL, respectively). Baseline total IgE levels were higher in responding and superresponsive patients compared to non-responders (955.02±1130.81 IU/mL, 395.12±357.11 IU/mL, and 08.25±99.35IU/mL, respectively). In the second year, blood eosinophil counts were higher in responding and superresponsive patients than in non-responders (1330 /μL, 942.36±533.49/μL and 740/μL, respectively).

Safety and Tolerability of Mepolizumab

Treatment with mepolizumab was well tolerated and no side effects were reported in our patients.

DISCUSSION

In this study, we found that mepolizumab treatment resulted in a decrease in the number of asthma exacerbations, the need for maintenance OCS, blood eosinophil counts, and improvement in lung functions and ACT scores in patients with severe eosinophilic asthma.

The number of eosinophils is increased in the blood, lung tissue and airway mucosa of patients with severe eosinophilic asthma. Blood eosinophils are associated with sputum eosinophils, and high blood eosinophil counts indicate good specificity for airway eosinophilia. IL-5 is a pro-eosinophilic cytokine responsible for differentiation, maturation, activation and proliferation of eosinophils (12). Mepolizumab, which acts by blocking IL-5, has been shown in randomized controlled trials known as DREAM, MENSA and SIRIUS to provide asthma control, reduce the dose of oral steroids and have a significant lowering effect on blood eosinophils in severe eosinophilic asthmatics (6-8). After mepolizumab's approval for use, studies on its real-life effectiveness were conducted. In our study, we showed that mepolizumab reduced the number of asthma exacerbations, improved ACT scores, decreased blood eosinophil counts, decreased need for maintenance OCS, and improved lung function, similar to the aforementioned randomized controlled trials and real-life studies (1,2,4,11-18).

Regarding asthma symptom control, a rapid improvement in ACT scores was observed in our patients starting from the fourth week. Many previous real-life studies have also used ACT to assess asthma control and mepolizumab has been shown to improve asthma control (15,18-20). In our study, a rapid and striking decrease was observed in blood eosinophil counts along with rapid improvement in asthma control. This data of our study was compatible with the literature (4,11,21,22).

In severe eosinophilic asthma, blood eosinophils are reliable biomarkers both for compliance with mepolizumab therapy and for predicting response to therapy (12,23). In our study, a decrease in blood eosinophil counts was observed from the first 4 weeks of treatment. The decrease in blood eosinophil counts continued throughout the duration of the treatment.

One of the main goals in patients with severe eosinophilic asthma is to reduce the steroid dose. In our study, with the gradual decrease in the maintenance OCS dose used in our patients together with mepolizumab treatment, maintenance OCS intake was discontinued in many patients. In a prospective observational study of 61 patients in Israel, the daily dose of OCS was reduced or discontinued in 68% of patients on continuous OCS before mepolizumab (24). In a retrospective real-life study evaluating 138 patients from 11 centers in Italy, it was observed that 66% of OCS-dependent patients stopped taking OCS at the end of the first year, and the dose of OCS decreased from 10.1±9.4 mg/day to 2 mg/day (14). Mepolizumab treatment also reduced the number of asthma exacerbations in patients. Our data were consistent with studies in the literature evaluating the use of mepolizumab in severe eosinophilic asthma (6,7).

In our study, we did not find any finding that enables us to predict which patients will respond or super-responsive to mepolizumab. However, in randomized controlled studies, it was determined that the higher the eosinophil count before treatment, the better the response to treatment (7,25). In a multicenter Australian study of 309 patients, patients identified as responders had higher blood eosinophil levels and lower maintenance OCS use. The same study found that super-responders were less symptomatic at baseline and required less OCS therapy for exacerbations in the previous year (17).

There are some limitations of our study. The first of these was that our study was a retrospective and single-center study. The second was that the statistical results were limited due to the small number of patients included in the study and the unequal number of patients at the specified time points.

CONCLUSION

The results of our single-center study, in which we evaluated the results of mepolizumab treatment in patients with severe eosinophilic asthma, confirmed the clinical, hematological and functional findings published by previous studies in a real-life setting.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Health Sciences University Ankara Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 09.03.2021, Decision No: 2021-KAEK-15/2247).

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.

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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

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Role of neutrophil-to-lymphocyte, mean platelet volume-to-platelet and platelet-to-lymphocyte ratios as predictors of disease severity in Rotavirus gastroenteritis

Rotavirüs gastroenteritinin şiddetin belirlenmesinde nötrofil lenfosit, ortamala trombosit hacmi trombosit ve trombosit lenfosit oranlarının rolü

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ABSTRACT

Aim: In developing countries, Rotavirus Gastroenteritis (RG) is even now one of the most common causes of death and morbidity. As a result, clinicians must be extremely vigilant in detecting the presence and severity of RG. The goal of this study was to identify predictors of RG severity by analyzing complete blood counts, including neutrophil-to-lymphocyte ratio (NLR), mean platelet volume-to-platelet volume (MPV/P); platelet-to-lymphocyte ratio (PLR).

Material and Method: Data were obtained retrospectively from medical records of 456 children diagnosed with RG and age-matched healthy children from University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital between January 2019 and December 2021. The Vesikari Score was used to categorize disease severity as severe or mild. Variables' prognostic effects on disease severity were equated across groups.

Results: The study included 456 children with RG. Two hundred thirty two of them were severe; 126 males; median age: 1.24 (0.41-2.36 years), 224 of them non-severe; 126 males; median age 1.52 (1.01-2.84 years). The median length of hospitalization was 5 (4-7) days for the severe group and 2 (0-3) days for the non-severe group ($p<0.001$). Neutrophils, monocyte, platelet, red cell distribution width, NLR, and PLR levels in RG patients were statistically significantly higher than in the control group, while hemoglobin, platelet distribution width, MPV, and MPV/P levels were lower ($p<0.001$). The area under the operating characteristic curve (AUC) for NLR, and MPV/P for severe disease was calculated as (0.556; and 0.709, respectively), and was all statistically significant ($p<0.001$). However, PLR was not found statistically significant in ROC analysis ($p>0.001$).

Conclusion: NLR was increased and MPV/P was decreased with the increase in severity of Rotavirus Gastroenteritis. NLR and MPV/P were useful for providing additional severity stratification in RG.

Keywords: Rotavirus, children, severity, neutrophil-to-lymphocyte ratio, mean platelet volume-to -platelet volume, platelet-to-lymphocyte ratio

ÖZ

Amaç: Gelişmekte olan ülkelerde Rotavirus gastroenteriti (RG) günümüzde bile en yaygın ölüm ve morbidite nedenlerinden biridir. Sonuç olarak, klinisyenler RG'nin varlığını ve ciddiyetini tespit etmede son derece uyanık olmalıdır. Bu çalışmanın amacı, nötrofil lenfosit oranı (NLO), ortalama trombosit hacmi trombosit oranı (OTH/T) ve trombosit lenfosit oranı (TLO) dahil olmak üzere tam kan sayımlarını analiz ederek RG şiddetinin öngörücülerini belirlemekti.

Gereç ve Yöntem: Veriler, Ocak 2019 ile Aralık 2021 tarihleri arasında Sağlık Bilimleri Üniversitesi, Ankara Atatürk Sanatoryum Eğitim ve Araştırma Hastanesinde de RG tanısı konan 456 çocuğun tıbbi kayıtlarından ve aynı yaştaki sağlıklı çocukların tıbbi kayıtlarından geriye dönük olarak elde edildi. Hastalık şiddetini; şiddetli veya hafif kategorize etmek için Vesikari skoru kullanıldı. Değişkenlerin hastalık şiddeti üzerindeki prognostik etkileri gruplar arasında karşılaştırıldı.

Bulgular: Çalışmaya RG'lı 456 çocuk dahil edildi. Bunlardan iki yüz otuz ikisi şiddetliydi; 126 erkek; medyan yaş: 1,24 (0,41-2,36) yıl, 224'ü şiddetli değil; 126 erkek; medyan yaş 1,52 (1,01-2,84) yıldı. Hastanede medyan kalış süresi ağır grup için 5 (4-7) gün ve ağır olmayan grup için 2 (0-3) gündü ($p<0,001$). RG hastalarında nötrofil, monosit, trombosit, eritrosit dağılım genişliği, NLO ve TLO düzeyleri kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksek, hemoglobin, trombosit dağılım genişliği, OTH ve OTH/T düzeyleri ise daha düşüktü ($p<0,001$). ROC analizinde; NLO ve OTH/T için operasyon karakteristik eğrisi (AUC) altında kalan alan, şiddetli hastalık için (sırasıyla 0,556 ve 0,709) olarak hesaplandı ve tümü istatistiksel olarak anlamlıydı ($p<0,001$) fakat TLO istatistiksel olarak anlamlı bulunmadı ($p>0,001$).

Sonuç: Rotavirüs Gastroenteritinin şiddetinin artmasıyla NLO artmış ve OTH/T azalmıştır. NLO ve OTH/T, RG'de ek şiddet sınıflandırma sağlamak için faydalı bulunmuştur.

Anahtar Kelimeler: Rotavirüs, çocuklar, şiddet, nötrofil lenfosit oranı, ortalama trombosit hacmi-trombosit oranı, trombosit lenfosit oranı

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INTRODUCTION

Rotavirus is a double-stranded RNA virus. Although humans of all ages can become infected with rotavirus, children aged 3 to 24 months account for the majority of severe infections. The most common reason of serious gastroenteritis in children below the age of five is rotavirus. Rotavirus was responsible for 25 million doctor visits, two million hospital stays, and nearly 400 000 deaths among children under the age of five worldwide (1). Rotavirus can cause viremia despite the fact that it frequently infiltrates the surface epithelium of the small bowel villi, causing local inflammation. Rotavirus can also cause pneumonia, disseminated intravascular coagulation, nephritis, exanthema, elevated transaminase, hemophagocytic lymphohistiocytosis, and neurological manifestations (2-7).

Neutrophils, lymphocytes, platelets and red blood cells (RBC) are important cell types that are counted in a complete blood count (CBC). Red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), mean platelet volume (MPV) and mean platelet volume-to-platelet ratio (MPV/P), platelet distribution width (PDW) are newly defined inflammatory markers from these CBC parameters. The levels of these inflammatory markers have been linked to the severity of a variety of diseases (8-13).

As a result, NLR, PLR, and MPV/P ratios were thought to be indicators of disease severity, based on changes in all CBC parameters due to rotavirus viral pathogenicity in RG. Early detection of severe RG is critical for initiating supportive treatment on time, identifying complications as soon as possible, and referring patients to appropriate centers. We wanted to investigate the relationship of CBC parameters and ratios such as NLR, MPV/P, and PLR with disease severity, so we analyzed the clinical and laboratory characteristics of 456 patients with RG to determine the predictors of severe disease.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2388). 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 Information Management System.

A retrospective, cross-sectional study included children diagnosed with RG at pediatric clinics between January 2019 and December 2021, as well as age-matched healthy children. Healthy children were chosen only those being brought in for regular checks. Children with hematologic, inflammatory, or chronic disease, and also those with a positive microscopy test for parasites and/or bacteria in culture specimens, were not included in the study. Rotavirus antigen test were on all children who had gastroenteritis. The severity of diarrhea in children with gastroenteritis was evaluated utilizing 20-point Vesikari Risk Score (14). After that, we divided the children into groups depending on their Vesikari scores: non-severe <11 or severe ≥11. Demographic characteristics, whole blood count, and other biochemical test results of all children included in the study were evaluated on presentation. The LH-780 system was used for CBC analysis (Beckman Coulter Diagnostics, Image 8000, Brea, CA). The highly sensitive and specific ELISA test was used to detect rotavirus in fresh stool samples (Rota Adeno Antigen Test Device, Cambridge). A standard biochemical analyzer was used to examine serum biochemistry samples (Hitachi 902 Automatic Analyzer, Roche Diagnostics, Germany).

Statistical Analysis

SPSS for Windows, version 22.0, was used to analyze the data (SPSS Inc., Chicago, IL, United States). The Kolmogorov Smirnov test was used to determine whether the distribution of continuous variables was normal or not. The Levene test was used to assess variance homogeneity. For skewed distributions, continuous data were described as median (interquartile range: third quartile - first quartile) unless otherwise specified. The number of cases was used to describe categorical data (percent). The Mann Whitney U test was used to compare differences in not normally distributed variables between two independent groups. The Kruskal-Wallis test was used to compare differences in not normally distributed variables between three independent groups. The Conover-Inman test was used to compare binary comparisons between groups, and the p value was set at < 0.05. Pearson's chi-square test or Fisher's exact test were used to compare categorical variables. The cut off values of the NLR, MPV/P, and PLR associated with the risk of severity were determined using ROC curve analysis. In all statistical analyses, the p-value of < 0.05 was accepted as the significance level.

RESULTS

The study included 456 children with RG. Two hundred thirty two of them were severe; 126 males; median age: 1.24(0.41-2.36 years), 224 of them non-severe; 126 males; median age 1.52 (1.01-2.84) years and 300 healthy controls; 140 males; median age: 1.39(0.75-2.52) years. The groups were well-matched in terms of mean age and gender ($p>0.05$) (**Table 1**).

Table 1. Demographic, and clinical, characteristics of the patients with Rotavirus Gastroenteritis and Controls

	RPAG (n=456) Vesikari Score		Healthy Controls (n:300)	p
	Severe (n:232)	Non-severe (n:224)		
Gender				>0.05
Male	126 (54.3%)	126 (56.3%)	140 (46.7%)	
Female	106 (45.7%)	98 (43.8%)	160 (53.3%)	
Age (Years)	1.24 (0.41-2.36)	1.52 (1.01-2.84)	1.39 (0.75-2.52)	>0.05
Hospitalization length (days)	5 (4-7)	2 (0-3)		<0.001
Intravenous hydration requirement	232 (100%)	153 (68.3%)		<0.001
Diarrhea	232 (100%)	224 (100%)		-
Vomiting	178 (76.7%)	158 (70%)		0.134
Fever	94 (40.5%)	20 (8.9%)		<0.001
Upper respiratory tract infection	18 (7.8%)	6 (2.7%)		0.015
Pneumonia	67 (28.9%)	3 (1.3%)		<0.001
Febrile seizure	14 (6%)	-		<0.001
Otitis media	3 (1.3%)	-		0.249
Skin rash	3 (1.3%)	-		0.249
Lymphadenitis	9 (3.9%)	-		0.004

Continuous variables are expressed as the median (Q1-Q3) and categorical variables are expressed as either frequency (percentage). Continuous variables were compared with Mann-Whitney U test, and categorical variables were compared using Pearson's Chi-square test or Fisher Exact test. Statistically significant p-values are in bold.

The median length of hospitalization was 5 (4-7) days for severe group and 2 (0-3) days for the non-severe group (p<0.001). All patients need intra-venous hydration in the severe group, while 68.3% in the non-severe group (p<0.001). The duration of hospitalization and the need of intra-venous hydration were found to be statistically significantly higher in the severe group compared to the non-severe group (p<0.001) (**Table1**).

While 40.5% of the severe group patients had fever, it was 8.9% in the non-severe group (p<0.001). Upper respiratory tract infection was found in 7.8% of severe group while 2.7% in the non-severe group. Pneumonia was accompanying in 28.9% of severe group, 1.3% in non-severe group (p<0.001).

Febrile seizure was found in 6% of severe group, none of the patients had febrile seizure in non-severe group (p<0.001). Otitis media (1.3%), skin rash (1.3%) and lymphadenitis (3.9%) were the other accompanying findings in severe group. The presence of fever, upper respiratory tract infection, pneumonia, febrile seizure, and lymphadenitis was statistically higher in the severe group compared to the non-severe group (p<0.05) (**Table 1**).

Glucose, albumin, calcium, bicarbonate, lymphocytes, RBC, hemoglobin (HGB), platelets, MPV, MPV/P levels were statistically significantly lower; blood-urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), potassium, neutrophils, eosinophil, basophil, NLR and PLR levels were statistically significantly higher in the severe group compared to the non-severe group (p<0.001) (**Table 2**).

Creatinine, AST, alanine aminotransferase (ALT), leukocytes, monocytes, neutrophils, platelets, RDW, and NLR levels were statistically significantly higher; total protein, albumin, alkaline phosphatase (ALP), sodium, eosinophil, HGB, MPV, PDW and MPV/P levels were statistically significantly lower in both severe and non-severe groups compared to the control group (p<0.001) (**Table 2**).

A ROC curve analysis was used to determine the efficacy of various parameters predicting severe prognosis (**Figure 1**, **Figure 2**). In the ROC analysis, the area under the operation characteristic curve (AUC) for MPV, NLR, and MPV/P for severe disease was calculated as (0.701; 0.556; and 0.709, respectively), and was all statistically significant (p<0.05). AUC for PLR was 0.542 and not found statistically significant (p>0.098). The cut-off value for MPV was accepted as 8.19, the sensitivity was calculated as 73.3%, specificity 63.5%. The cut-off value for NLR was accepted as 2.36, sensitivity was calculated as 34.9%, and specificity 94%. The cut-off value for MPV/P was accepted as 0.027, sensitivity was calculated as 70.3%, and specificity 65.6% (**Table 3**).

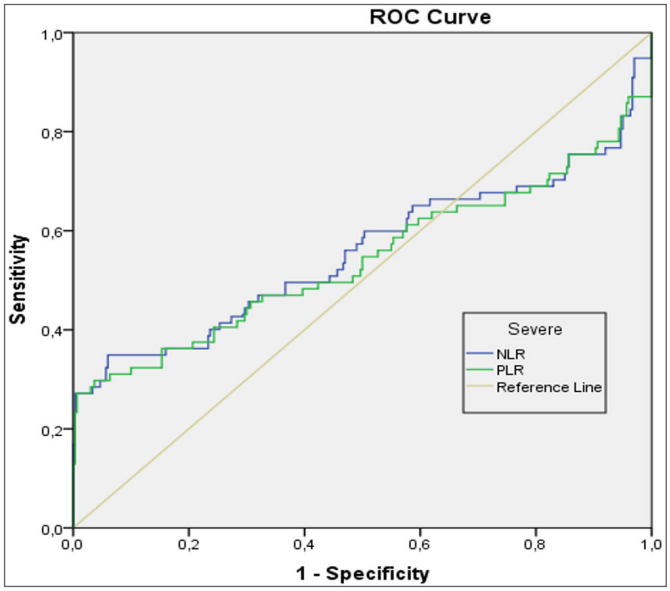

Figure 1. The ROC curves of NLR, PLR in predicting Rotavirus gastroenteritis

Table 2. Baseline blood-routine parameters of the patients with Rotavirus Gastroenteritis

	Severe (n:232)	Non-severe (n:224)	Healthy Control (n:300)	p
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)	
CRP (mg/L)	1.99 (0.49-7.62)	2.22 (0.92-7.79)	-	0.238
Glucose (mg/dL)	82.91 (70.15-97.97)	84.15 (67.00-94.00)	86.24 (81.97-91)	0.023[a,b]
BUN (mg/dL)	23.50 (15.15-31.68)	18.81 (10.10-29.70)	17 (11.64-23)	<0.001[a,b]
Creatinin (mg/dL)	0.57 (0.41-0.55)	0.54 (0.40-0.48)	0.52 (0.48-0.59)	<0.001[a,b,c]
Total Protein(g/dL)	6.63 (6.16-7.00)	6.80 (6.26-7.13)	7.20 (7.00-7.5)	<0.001[b,c]
Albumin (g/dL)	4.20 (3.84-4.46)	4.40 (4.04-4.65)	4.55 (4.40-4.75)	<0.001[a,b,c]
AST (IU/L)	170.85 (36.48-231.83)	145.77 (72.83-216.91)	13 (10.78-16)	0.008[a,b,c]
ALT (IU/L)	29.25 (17.17-39.00)	24.88 (16.16-32.85)	22 (18.00-31)	0.001[b,c]
ALP (IU/L)	45.00 (36.00-54.54)	43.78 (36.36-53.5)	185.64 (133-219.5)	<0.001[b,c]
Calcium (mg/dL)	9.6 (9.3-10.21)	9.9 (9.60-10.3)	10.00 (9.60-10.4)	<0.001[a,b]
Sodium (mmol/L)	137.61 (135-139.59)	137.49 (135.6-140)	138.86 (137-140)	0.002[b,c]
Potassium (mmol/L)	4.33 (4.03-4.76)	4.11 (3.87-4.5)	4.34 (4.07-4.6)	<0.001[a,c]
Magnesium (mg/dL)	2.10 (2.00-2.22)	2.02 (1.92-2.25)	2.00 (1.90-2.2)	0.206
pH	7.33 (7.27-7.40)	7.35 (7.29-7.42)	-	0.026
Bicarbonate(mmol/L)	16.40 (13.46-19.80)	18.71 (15.3-21)	-	<0.001
Lactate	1.59 (1.30-2.18)	1.73 (1.20-2.02)	-	0.621
Leukocytes ($\times10^3$/μL)	9.43 (6.46-12.61)	9.29 (7.51-11.75)	7.10 (6.02-8.61)	<0.001[b,c]
Lymphocytes ($\times10^3$/μL)	2.26 (1.18-3.63))	2.94 (1.92-4.3)	2.87 (2.37-3.57)	<0.001[a,c]
Monocytes ($\times10^3$/μL)	0.84 (0.55-1.1)	0.71 (0.47-1.07)	0.46 (0.37-0.58)	<0.001[b,c]
Neutrophils ($\times10^3$/μL)	5.38 (3.41-8.25)	4.77 (2.85-6.68)	3.64 (2.60-4.69)	<0.001[a,b,c]
Eosinophil ($\times10^3$/μL)	0.04 (0.01-0.14)	0.02 (0.00-0.07)	0.16 (0.08-0.28)	<0.001[a,b,c]
Basophil ($\times10^3$/μL)	0.06 (0.02-0.11)	0.03 (0.02-0.07)	0.04 (0.02-0.06)	0.004[a,b]
RBC ($\times10^6$/μL)	4.55 (4.16-4.95)	4.76 (4.46-5.05)	4.89 (4.60-5.09)	<0.001[a,b]
Hemoglobin (g/dL)	11.92 (11.09-12.77)	12.44 (11.19-13.22)	13.45 (12.74-14.00)	<0.001[a,b,c]
HCT (%)	35.86 (33.33-37.62)	36.88 (33.60-39.55)	39.78 (37.64-41.98)	<0.001[a,b,c]
MCV (fL)	78.48 (47.82-82.97)	78.50 (74.82-81.80)	82.98 (80.00-87)	<0.001[b,c]
MCH (pg)	26.28 (25.17-28.21)	26.58 (24.30-27.61)	28.00 (27.00-29)	<0.001[b,c]
MCHC (g/dL)	33.66 (32.67-34.38)	33.46 (32.57-34.20)	33.60 (32.65-34)	0.320
Platelets ($\times10^3$/μL)	314.1 (242.2-410)	332.6(275.9-451.9)	293 (253.4-332.3)	<0.001[a,b,c]
MPV (fL)	7.52 (6.83-8.41)	8.09 (7.04-9.19)	8.93 (7.21-10)	<0.001[a,b,c]
PDW	15.80 (15.40-16.53)	15.84 (0.32-16.68)	16.19 (15.65-16.9)	<0.001[b,c]
RDW (%)	14.85 (13.55-16.45)	14.00 (13.85-15.95)	13.80 (13-15.19)	<0.001[b,c]
NLR	2.52 (0.98-4.89)	1.34 (0.74-3.35)	1.23 (0.84-1.81)	<0.001[a,b,c]
MPV/P	0.02 (0.01-0.03)	0.02 (0.02-0.04)	0.03 (0.02-0.04)	<0.001[a,b,c]
PLR	140.1 (95.24-236.6)	105.66(76.41-203.16)	102.6 (85.3-129.2)	<0.001[a,b]

Continuous variables are expressed as the median (Q1-Q3. Statistical analysis differences in not normally distributed variables between two independent groups were compared by Mann Whitney U test. Statistical analysis differences in not normally distributed variables between three independent groups were compared by Kruskal Wallis test. Statistically significant p-values are in bold. Conover-Inman test was performed for the binary comparisons among the groups and the p value was set at 0.05. Significant differences were found between; a: Severe vs non severe, b:Severe vs control group, c: Non severe vs control group. Abbreviations: CBC: Complete blood count; CRP: C-reactive protein; BUN: Blood Urea Nitrogen; ALT: Alanine aminotransferase ; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; RBC: Red Blood Cell: HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin: MCHC: Mean Corpuscular Hemoglobin Concentration; MPV: Mean Platelet Volume, PDW: Platelet Distribution Width; RDW: Red Cell Distribution Width; NLR: Neutrophil-to-lymphocyte ratio; MPV/P: Mean platelet volume-to-platelet ratio; PLR: Platelet-to-lymphocyte ratio

Table 3. AUC, optimal cut-off, and sensitivity and specificity values of laboratory parameters

Test Result Variable(s)	AUC	Std. Error	p	95% CI	Cut Off	Sensitivity	Specificity
Severe							
MPV	0.701	0.022	<0.001	(0.657-0.745)	8.19	73.3%	63.5%
NLR	0.556	0.027	0.025	(0.503-0.610)	2.36	34.9%	94.0%
MPV/P	0.709	0.023	<0.001	(0.664-0.754)	0.027	70.3%	65.6%
PLR	0.542	0.027	0.098	(0.488-0.595)	-	-	-

AUC: Area under the ROC Curve. CI: Confidence interval

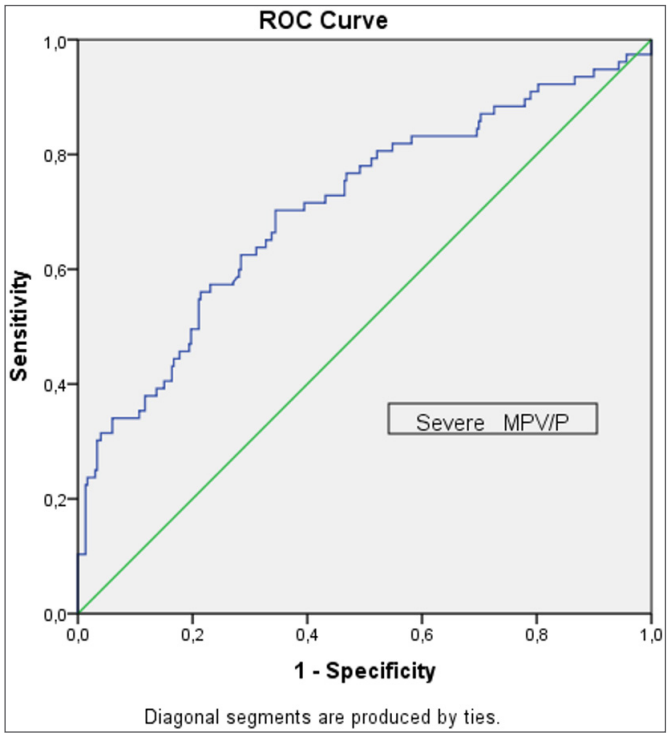

Figure 2. The ROC curve of MPV/P in predicting Rotavirus gastroenteritis

DISCUSSION

It has been reported that RG is more common under the age two and the preponderance of the disease was more in males (15,16). The reasons for the difference in detection rate between males and females are however, not known. The greater sensitivity of children aged below two years to the RG is thought to be due to their greater exposure to contaminated substances. Children in this age group are known to put all in their mouths, and the virus can survive on surfaces, including toys, thus they could become infected quite easily. Natural immunity has also been proposed as a possible explanation for the decrease in incidence with age. By age two, most children have been infected and are protected from subsequent symptomatic re-infection. The majority of children with for RG were under the age of two and in male gender in our study which is consistent with the literature (15,16). Age less than two years was significantly associated with increased diarrheal severity in terms of duration and frequency, as well as a higher modified Vesikari score, compared to age more than two years (15). However, in our study, no statistically significant difference was found for age between the severe and non-severe groups. Considering the older age of non-severe RG cases, children with diarrhea but in good general condition may have been followed at home by families and brought to the hospital less frequently. In addition, the clinician did not consider stool and blood tests necessary for mild cases, which may have caused these cases to be missed. Due to these reasons, the average age of the non-severe age group might have decreased, and there might not have been an age difference between the two groups.

In severe cases, the length of hospital stay was significantly longer and all of these patients required intravenous fluids as their dehydration worsened. Since the severity of the disease was determined based on diarrhea, vomiting duration, degree of dehydration, hospitalization and rehydration in the Vesikari Risk scoring system, it is expected that the length of hospital stay would be longer in severe cases.

There are numerous publications in the literature describing rotavirus infection systemic findings (2-7). Dehydration, electrolyte imbalance, upper respiratory tract infection, otitis media, pneumonia, febrile seizure, skin rash, malnutrition and lymphadenitis were systemic findings that associated with severe RG in our study. While 40.5% of the children in the severe group had high fever, 6% of them developed febrile convulsions due to high fever. Although the presence of pneumonia and rotavirus infection has been reported in previous studies, 28.9% rate in our study was remarkable. Rotavirus infection was not a nosocomial infection in any of these patients, and they were all evaluated at the time of their initial hospitalization.

BUN, creatinine, and blood gases (pH, serum bicarbonate) were discovered to be useful clinical markers to determine dehydration and severity in children with acute gastroenteritis (17-19). Higher levels of creatinine, BUN, potassium, and lower glucose, pH, bicarbonate, albumin levels in severe group were related to the serious dehydration and acidosis. Some studies have found a link between severe rotavirus diarrhea and hypocalcaemia (20). Although the calcium level was not found below the normal limits in RG patients, the calcium level was statistically lower in the children with RG infection compared to the control group, and in the severe group compared to the non-severe group. This could be due to the fact that NSP4-induced disruption of calcium homeostasis plays a critical role in the pathogenesis of diarrhea. It has also been suggested that rotavirus may cause seizures or make people more susceptible to them by altering calcium homeostasis through the same NSP4-induced changes (21).

RG was associated with transaminase elevation, as previously reported in other studies (22-24). Transaminase abnormalities could be caused by virus-induced liver damage, an immune response, or the creation and discharge of a metabolite or toxin during infection (25). Although AST and ALT levels increased in the severe group, only AST elevation was

found to be statistically significant and increased AST levels indicated disease severity, as previously reported (25,26).

Red cell distribution width (RDW) has been shown to rise during a variety of inflammatory events and pathophysiological conditions (8,27,28). Furthermore, numerous studies indicate that RDW can be used as diagnostic markers for disease severity (27,28). RDW and RG have only been studied once, and higher RDW levels were linked to severe rotavirus gastroenteritis (17). Severe and non-severe groups had significantly higher RDW levels than controls in our study however the increase in RDW was not associated with disease severity.

MPV and MPV/P have been identified as inflammatory and prognostic markers, with their role in inflammatory disorders previously demonstrated (9,29). Decreased MPV and increased MPV/P ratio have been found to be a predictor of clinical severity in a variety of diseases (9,29). MPV may rise in minimal inflammation due to the appearance of big platelets in the circulation, and after than MPV may lower with the inflammation severity because of the usage of these big platelets in the inflammation area (30). However, there are only a few studies on MPV's role in RG. MPV levels have been reported to be lower in RG (30,31). Furthermore, no difference in MPV levels was found between disease severity groups in these studies. We discovered that MPV levels were decreased in children with rotavirus gastroenteritis than in healthy controls, and that a decrease in MPV was a predictor for severe disease. There have been few studies on MPV/P and none on rotavirus gastroenteritis (9,29). In a study conducted in adult intensive care unit, patients who diagnosed with bacterial sepsis divided in into two groups as survival and non-survival for evaluating the severity of the sepsis. MPV/P ratio was found to be higher in non-survival patients compared to survival (9). Another study investigated the association between long-term mortality after myocardial infarction and the MPV and MPV/P. Relatively larger MPV with a low platelet count, as well as decreased MPV/P found to be predictor of long-term mortality (29). Low MPV/P, but not high MPV/P, was found to be associated with the presence of severe disease in our study. The reason for this could be that the studies in the literature were conducted on adults, one of them in bacterial sepsis and another in myocardial infection. In addition, these patients had lower platelet levels and higher MPV levels. Our patients had higher platelet levels but lower MPV levels, resulting in a lower MPV/P.

In this study, RG children had lower lymphocytes as well as higher neutrophils and monocytes than controls, and severe group children than non-severe. Neutrophils and lymphocytes are important components of the immune system and inflammatory response. Whereas a reduction in lymphocytes in blood plasma was already discovered in many infectious diseases, only a few studies support the link between rotavirus infection and a reduction in lymphocytes (32-34). In patients with rotavirus infection, a decrease in total lymphocytes is primarily caused by a marked reduce in T-cells. Virus infections can suppress the expression of important molecules required for T-cell survival, resulting in lower lymphocyte levels (33).

Rotavirus infection was reported to activate genes coding for chemokine's, and the inflammatory mediators were implicated in the chemo-taxis of neutrophils. Virus infections can cause neutrophils and monocytes to migrate to circulatory pools (33). Decreased lymphocytes as well as increased neutrophils resulted in a significant increase in NLR. It has been reported that NLR is a prognostic marker in many diseases and increasing NLR has a negative impact on disease prognosis (10,35). In our study, RG children had an elevated NLR levels than controls, and the severe group had a higher NLR levels than the non-severe group. There has only been one previous study (36) on the effect of NLR on rotavirus gastroenteritis, which supports our findings.

Patients with increased PDW value were linked to a more serious illness (11, 37). RG patients had lower PDW levels than controls in our study while we have not found that RDW was a predictor of the disease severity.

PLR is an inflammatory marker, and an increase in PLR levels indicates the severity of a variety of diseases (33,34). PLR was found to be increased in severe group than non-severe and controls in our study, but not statistically significant in ROC analysis.

Our study's limitation was that it was a retrospective, single-center study. To confirm this evidence, large-scale multicenter clinical trials are required.

CONCLUSION

Clinicians must be extremely vigilant in detecting the presence and severity of RG. NLR was increased and MPV/P was decreased with the increase in severity of RG. NLR and MPV/P were useful for providing additional severity stratification in RG and monitoring this severity predictors during treatment planning and following up on patients who are at a higher risk of progression, as well as lead a better understanding of the risk of complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health and Sciences, Ankara Atatürk Sanatorium Training and Research Hospital Clinical Research Ethics Committee (Date: 12.10.2021, Decision No: 2012-KAEK-15/2388).

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.

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Case Report / Olgu Sunumu

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COVID-19 pnömonisi ile birlikte akciğerde kaviter lezyonla seyreden *Klebsiella pneumoniae* pnömoni olgusu

A case of *Klebsiella pneumoniae* pneumonia with a cavitary lesion in the lung with COVID-19 pneumonia

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ÖZ

Hastanede yatan hastalarda COVID-19 pnömonisini ile birlikte veya takiben bakteriyel pnömoni gelişebilir. COVID-19 pnömonisi ile birlikte bakteriyel pnömoni gelişen hastalarda mortalite oranlarının yüksek olduğu bildirilmiştir. Bu yazıda, toraks bilgisayarlı tomografisi ile olası COVID-19 pnömonisi tanısı konulan ve sonrasında *Klebsiella pneumoniae* (*K. pneumoniae*) 'ya bağlı sekonder bakteriyel pnömoni 63 yaşında erkek hasta sunuldu. COVID-19 pnömonisi ve *K. pneumoniae*'ya bağlı uygun antimikrobiyal tedavi sonrasında klinik ve laboratuar bulguları düzelen hasta taburcu edildi. Sonuç olarak, COVID-19 pnömonisi tedavisine rağmen klinik ve laboratuar bulguları düzelmeyen hastalarda klinik tabloya sekonder bakteriyel pnömoni etkenlerinin eklenmiş olabileceği akılda tutulmalıdır.

Anahtar kelimeler: COVID-19, bakteriyel pnömoni, koinfeksiyon, *Klebsiella pneumoniae*

ABSTRACT

Bacterial pneumonia may develop with or following COVID-19 pneumonia in hospitalized patients. It has been reported that mortality rates are high in patients who develop bacterial pneumonia together with COVID-19 pneumonia. In this article, a 63-year-old male patient who was diagnosed with probable COVID-19 pneumonia by thorax computed tomography and then secondary bacterial pneumonia due to *Klebsiella pneumoniae* (*K. pneumoniae*) is presented. The patient, whose clinical and laboratory findings improved after COVID-19 pneumonia and appropriate antimicrobial therapy due to *K. pneumoniae* was discharged. In conclusion, it should be kept in mind that secondary bacterial pneumonia agents may be added to the clinical picture in patients whose clinical and laboratory findings do not improve despite the treatment of COVID-19 pneumonia.

Keywords: COVID-19, bacterial pneumonia, coinfection, *Klebsiella pneumoniae*

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GİRİŞ

Hastanede yatan koronavirüs infeksiyon hastalığı-19 (COVID-19) olgularında bakteriyel ve fungal koinfeksiyonların sıklığına ilişkin yeterli veri yoktur. COVID-19 infeksiyonunda hastanede yatan hastalarda sekonder bakteriyel infeksiyon sıklığı bazı çalışmalarda %15 oranında bildirilmiştir. Sekonder bakteriyel infeksiyon gelişen COVID-19 hastalarında mortalite oranının bakteriyel infeksiyon gelişmeyen hastalara göre daha yüksek olduğu bildirilmiştir (5,6) Bu yazıda, COVID-19 pnömonisi ile birlikte akciğerde kaviter lezyonla seyreden, kan kültüründe *Klebsiella pneumoniae* üremesi nedeniyle sekonder bakteriyel pnömoni gelişen bir olguyu sunduk.

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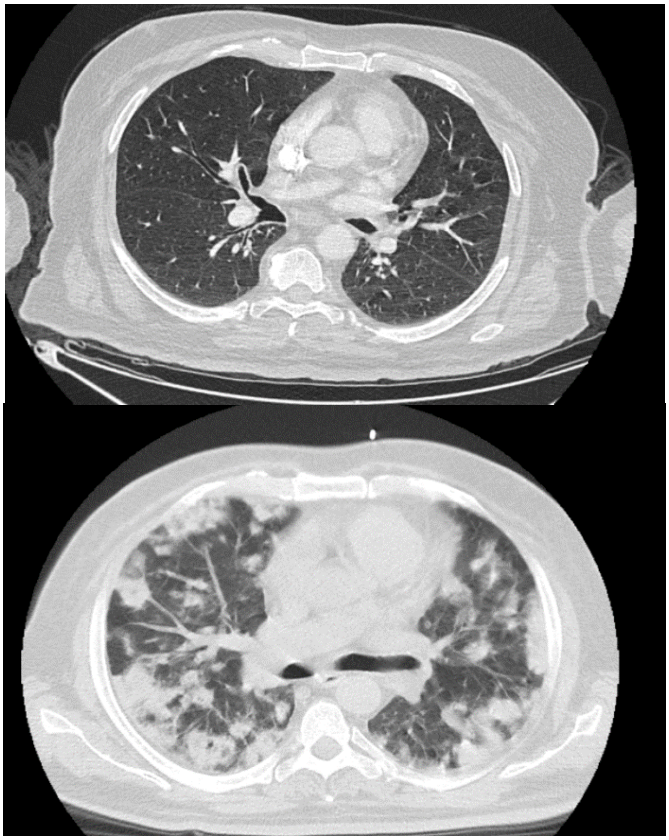
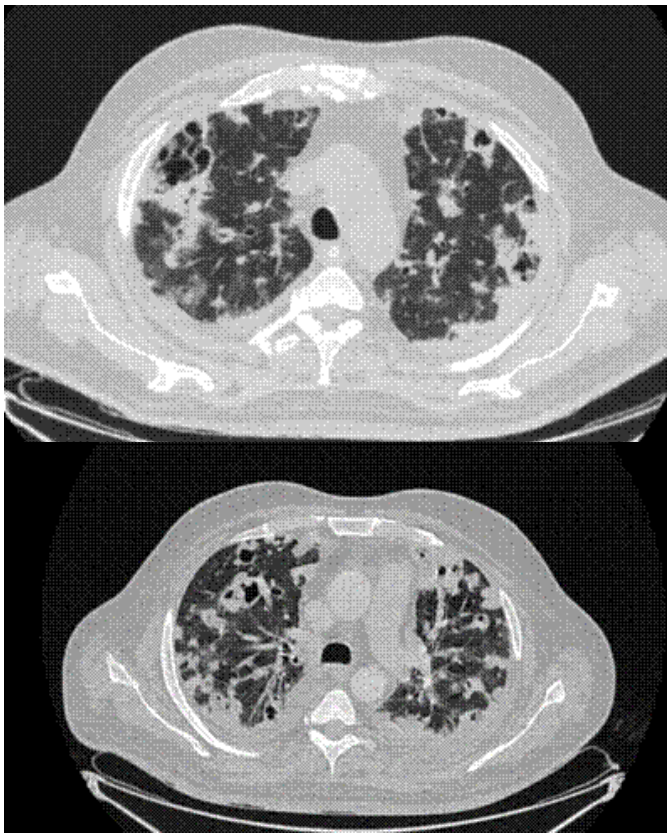
OLGU

Altmış üç yaşında erkek hasta ateş, üşüme, titreme şikayetleri ile acil servise başvurdu. Öz geçmişinde diyabetes mellitus ve hipertansiyon mevcuttu. Anamnezinde öksürük, nefes darlığı ve balgam çıkarma,dizüri ve pollaküri yakınmaları yoktu. Ateşi 38.8°C, TA: 160/80 mm/Hg, SO_2 %92 idi. Fizik muayenede sistem muayeneleri normaldi. Laboratuvar testlerinde; lökosit sayısı 2190/ µL, lenfosit sayısı 210/µL, NLO 9,2, CRP mg/L 282 (0-5 mg/L), prokalsitonin 2,1 µg/L (normali 0,5) , D-dimer 1880 µg/L (normali 500 µg/L) idi. Biyokimyasal testlerinde; AST 40 IU/ml, ALT 27 IU/ml, Cre 1,5 mg/dl idi. Toraks BT'patolojik bulgu saptamadı ancak pandemi döneminde olunması ve ateşi açıklayacak bir infeksiyon odağı olmaması nedeniyle COVID-19 için alınan nazofarenk sürüntü örneğinde polimeraz zincir reaksiyonu testi (Bioeksen Türkiye) istendi. Takiplerinde taşikardisinin ve takipnesinin olması nedeniyle yoğun bakım ünitesine devredildi. Tekrarlanan toraks BT 'si 'Her iki akciğerde yaygın nodüler ve yamasal tarzda konsolidasyonlar izlendi,COVID-19 pnömonisi ile uyumludur' şeklinde raporlandı (**Resim 1**). İlk alınan COVID- 19 polimeraz zincir reaksiyonu (PZR) testinden 48 saat sonra tekrar PZR testi için örnek alındı. Olası COVID-19 tanısı ile Sağlık Bakanlığının tedavi rehberi doğrultusunda hastaya hidroksiklorokin tedavisi 2×200 mg dozda başlandı. Hastadan alınan ikinci COVID-19 PZR testi ve hızlı antikor testi negatif olarak saptandı.Yoğun bakım ünitesinde ventilatöre bağlanmadan takip edilen hastada 38°C ateş ve akut faz proteinlerinde (CRP ve prokalsitonin) artış olması nedeniyle hastaya ampirik olarak meropenem 3×1 gr i.v, linezolid 2×600 mg i.v tedavisi ile birlikte COVID-19 için favipravir 2×1600 mg oral tedavisi başlandı. Ateşinin olduğu dönemde alınan idrar ve kan kültüründe seftriaksona, ertapeneme,imipeneme,meropeneme, piperasilin-tazobaktama duyarlı *Klebsiella pneumoniae* üredi. İnfektif endokardit açısından yapılan transrorasik ekokardiyografide 2 mm nodül izlendi, vejetasyon nodül ayrımı yapılamadı. Yatışının 18. gününde çekilen akciğer BT'de öncelikle septik emboliler lehine değerlendirilen, multipl kaviter nodüller izlendi . Tanımlı kaviter nodül komşuluğundaki akciğer parankim alanlarında yer yer buzlu cam infiltrasyonları izlendi (**Resim 2**). Hasta solunum örneği veremediğinden pnömoni etkenini saptama imkanı olmadı. Kan kültüründe *Klebsiella pneumoniae* üremesi ve akciğerde kaviter lezyonların görülmesi nedeniyle pnömoni etkeninin *K. pneumoniae* olduğu düşünüldü. Takiplerinde akut fazları CRP 72 mg/L'ye,prokalsitonin 0,3 µg/L'ye geriledi yoğunbakım ihtiyacı kalmayan servise nakledildi. Transösofagial ekokardiyografi (TEE) yapıldı ve vejetasyon saptanmadı. Meropenem, linezolid tedavisi 21 güne, favipiravir tedavisi 5 güne tamamlanan hasta taburcu edildi.



Resim 1. Hastanın ilk gün ve 7. gün toraks BT



Resim 2. Hastanın 14. ve 18. günlerdeki toraks BT görüntüsü

TARTIŞMA

Bakteriyel ve viral koinfeksiyonların en sık birlikte görüldüğü hasta grubu influenza infeksiyonu olan hastalardır (3). COVID-19 pandemisiyle birlikte COVID-19 infeksiyonuna bakteriyel infeksiyon etkenlerininin de eşlik ettiği rapor edilmiştir (1-5). Antibiyotiklerin SARS-CoV-2 virüsüne karşı direkt etkinliğinin olmamasına rağmen, viral infeksiyonlar sıklıkla bakteriyel pnömoni ile sonuçlanır. Bu nedenle, bakteriyel koinfeksiyon ve sekonder bakteriyel enfeksiyon COVID-19'un şiddeti ve mortalite oranları için ciddi bir risk faktörü olarak kabul edilir (3). Yapılan çalışmalarda COVID-19 infeksiyonu olan hastaların %5-15'inde sekonder bakteriyel infeksiyonlar görüldüğü bildirilmiştir (2,3)

Sunduğumuz çalışmada toraks BT görüntüsü ile olası COVID-19 tanısı konan hastada yüksek ateş ve akut faz proteinlerinden prokalsitonin düzeyinde artış olması üzerine hastada sekonder bakteriyel infeksiyona bağlı pnömoni ön tanısıyla geniş spektrumlu ampirik antibiyotik tedavisi başlandı. Ampirik antibiyotik tedavisi öncesi alınan kan kültüründe *K. pneumoniae* üremesi ve akciğer BT'deki lezyonların kavitasyon göstermesi nedeniyle hastada bu etkene bağlı bakteriyel pnömoni düşünüldü. Hastadan solunum örneği alınamadığı için solunum örneğinde mikrobiyolojik inceleme yapılamadı.

COVID-19 ile birlikte koinfeksiyona neden olan bakteriyel etkenler; *Staphylococcus aureus*, *Acinetobacter baumannii*, *Klebsiella pneumoniae*, *Enterobacter cloacae* ve *Mycoplasma pneumoniae* olarak rapor edilmiştir. Ayrıca, Candida türleri ve *Aspergillus flavus* mantar enfeksiyonları ile influenza, diğer koronavirüsler, rhinovirüs/enterovirüs, parainfluenza, metapneumovirüs, influenza B virüs ile birlikte koinfeksiyon bildirilmiştir (4).

COVID-19 infeksiyonunda gereksiz ve uygunsuz antibiyotik kullanımı dirençli bakteriyel infeksiyon gelişimine neden olabilir (5). Wuhan'da yapılan bir çalışmada COVID-19 infeksiyonunan en sık eşlik eden bakteriyel infeksiyon etkenleri; *Acinetobacter baumannii*, *Klebsiella pneumoniae* ve *Stenotrophomonas maltophilia* olarak bildirilmiştir. Aynı çalışmada, *Acinetobacter baumannii*, *Klebsiella pneumoniae* suşlarında karbapenem direncinin yüksek olduğuda rapor edilmiştir (5,6).

İtalya'da yoğun bakım ünitelerinde pandemi döbeminde yapılan bir çalışmada COVID-19 hastalarında karbapeneme dirençli *K. pneumoniae* suşları ile nozokomiyal infeksiyon veya kolonizasyon da bildirilmiştir (7).

Literatürde, COVID-19 hastalarında *Pneumocystis jirovecii* ve *Mycobacterium tuberculosis* ile koinfeksiyon gelişen olgular da bildirilmiştir. Yapılan bir çalışmada 191 COVID-19 hastasının 89'unda (%46,5) hızlı moleküler tanı testleri ile bir veya daha fazla koinfeksiyon etkeni bildirilmiştir (8).

COVID-19 hastalarında toplum kaynaklı pnömoni etkenleri olan *Streptococcus pneumoniae*, *Haemophilus influenzae* ve *Moraxella catarrhalis* ile de koinfeksiyon bildirilmiştir (8-11). *Streptococcus pneumoniae* ile koinfeksiyon sıklığı %1,2-3 arasında bildirilirken, bu oranın influenza ile *Streptococcus pneumoniae* koinfeksiyon oranından daha düşük olduğu rapor edilmiştir (11,12).

Yapılan çalışmalarda COVID-19 hastalarında yüksek prokalsitonin düzeylerinin sekonder bakteriyel infeksiyonlarla ilişkili olabileceği rapor edilmiştir (12). Hastanede yatan hastalarda prokalsitonin düzeylerinde yüksekliğin bakteriyel süperinfeksiyon ve bakteriyemi göstergesi olduğuna ilişkin çalışmalar da mevcuttur (13,14) .

SONUÇ

COVID-19 pnömoni tanısı konulan hastalarda tedaviye rağmen klinik, radyolojik bulguları düzelme yoksa ve prokalsitonin düzeyleri yükselme saptanması durumunda *K. pneumoniae* gibi bakteriyel etkenlere bağlı sekonder bakteriyel pnömoninin gelişmiş olabileceği akılda tutulmalıdır.

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References: References should be written according to the order of arrival. If the number of authors in the source is 6 or less, all authors (surname and first name should be the first letter, the names of the authors should be separated by commas) should be specified; ("et al "), the name of the article (only the first letter of the sentence and the first letter of the special names will be capitalized), short journal name, year, volume, short page number (15-8, not 15-18) and a space between the punctuation marks. The format used for the manuscript submission should be as specified in Index Medicus (www.icmje.org). The list of references should only include studies that have been published or accepted for publication or have a Doi number. Journal abbreviations should follow the style used in **Cumulated Index Medicus** (http://www2.bg.am.poznan.pl/czasopisma/medicus.php?lang=eng.). The number of references should be limited to 40 in research articles, 60 in reviews, 20 in case reports and 5 (max. 10) in letter to the editor. References should be given in parentheses at the end of the sentence just before the period. For example (4,5). The author (s) is responsible for the accuracy of the references. Importance should be given to the synthesis of domestic and foreign sources.

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Excerpt from journals;

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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".

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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.